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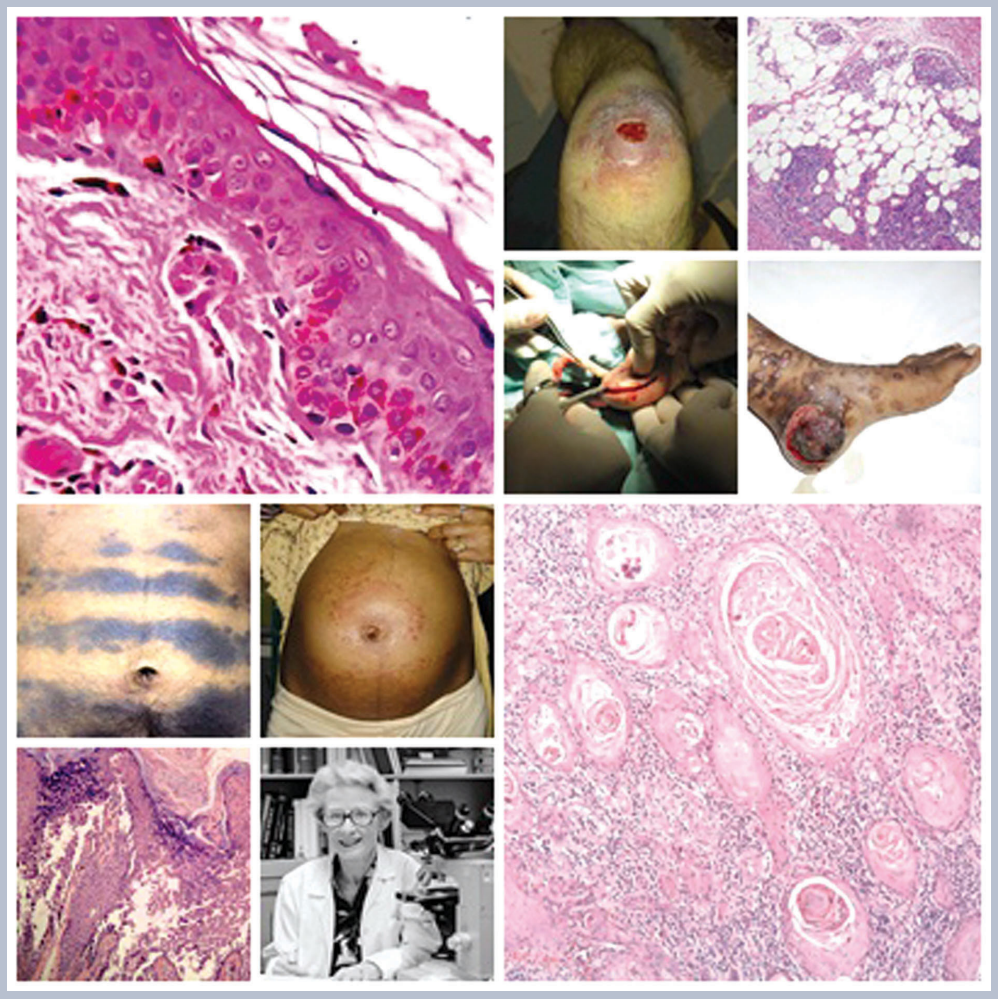

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Editorial Pages

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NASZA DERMATOLOGIA Online
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SOME MODIFICATIONS IN TRANSPLANTATION OF AUTOLOGUS NON-CULTURED MELANOCYTES-KERATINOCYTES SUSPENSION IN TREATMENT OF SEGMENTAL AND FOCAL VITILIGO (EGYPTIAN EXPERIENCE IN ALEXANDRIA UNIVERSITY)

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None

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Abstract
Introduction: Transplantation of Autologous non-cultured melanocytes suspension is a simple yet effective cell-based therapy for vitiligo.
Materials and Methods: 20 patients with stable vitiligo were subjected to epidermal cell suspension transplantation using Osslon's method with some new modifications.
Result: The repigmentation at 7 of the test sites (35.0%) was excellent. It was good for more than half of the test sites (55.0%). Fair repigmentation was encountered among only 2 (10.0%) of the tested sites. None of the tested sites showed poor repigmentation. On the other hand, none of the control sites showed excellent or even good repigmentation. However, repigmentation was fair for nearly 10% and it was poor for 90% of the control sites.
Conclusion: Autologus non cultured basal -enriched epidermal cell suspension transplantation is an effective, simple and safe method for treatment of stable vitiligo.

Key words: autologous; cellular transplantation; non cultured melanocytes; stable; vitiligo

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Nagat Sobhy, Ali Atia, Mahmoud Elramly: Some modifications in transplantation of autologus non-cultured melanocytes-keratinocytes suspension in treatment of segmental and focal vitiligo (Egyptian experience in Alexandria University). Our Dermatol Online. 2013; 4(1): 5-10

Introduction

Vitiligo is an acquired skin disorder caused by the disappearance of pigment cells from the epidermis that gives rise to well defined white patches which are often symmetrically distributed [1,2]. The lack of melanin pigment makes the lesional skin more sensitive to sunburn [3,4]. Vitiligo can be cosmetically disfiguring and it is a stigmatizing condition leading to serious psychological problems in daily life. Stable vitiligo and lesions with depigmented hairs, indicating the depletion of the melanocyte reservoir in the hair follicle, mostly fail to repigment by conservative therapies [5,6]. In these cases, surgical techniques may be indicated but are often time-consuming and lead to undesired effects [7]. For extensive lesions, cell-based techniques offer an alternative option, requiring only a small biopsy. However, the appropriate matrix for delivery and fixation of the cells is still an unsolved question [8].

Aim of the work:

To study the effect of non cultured melanocyte-keratinocyte cell suspension on stable vitiligo.

Material and Methods

Patients

- Twenty patients;10 patients with focal vitiligo and 10 patients with segmental vitiligo.
- 7 male, 13 female.
- Aged between 13 and 33 years.
- 12 patients (60% of cases) are skin type IV and eight patients (40% of cases) skin type III.
- In every patient one area was taken as tested (treated area) and one area taken as control.

Selection criteria

1) Patients should have a realistic expectation.
2) Patients not respond adequately to medical treatment.
3) Patients should be stable for 24 months (no new lesions, no expansion of old ones).

Exclusion criteria

1) Involvement more than 30% body surface area.
2) Patients aged less than 12 years and patients receiving any concomitant medical treatment.

3) Patients who are positive to infectious disease HIV, HCV, HBV.
4) Patients who have a history of koebnerization, Keloid tendency and coagulative disorders.

Methods
All Patients were subjected to the following:
● Personal history.
● History of vitiligo, onset, precipitating factors, duration, course and koebner phenomenon.
● Family history of vitiligo or autoimmune diseases.
● Previous forms of therapy; local or systemic.
● Local examination of vitiligo site, distribution and number of lesions.
● Laboratory examination as CBC, bleeding time, coagulation time, HCV antibodies and HBV antigens.
● Photography.
● Approval by ethical committee was obtained, and a written consent was taken from each participant.

This procedure of transplantation of non-cultured melanocytes-keratinocytes cell suspension has been modified from that of Osslon and Juhlin [9]. CO2 incubator was replaced with an ordinary incubator. Operation theater was modified by adding UV cabin, an incubator and a centrifuge to the existing equipment, so that cell separation could be performed there instead of in a separate laboratory. Single vitiliginous areas is dermabraded and taken as control and exposed to topical PUVA.

Donor site
A donor area of 1/10th of the recipient area was marked on lateral aspect of the gluteal region. The area was then anesthetized with 1% xylocaine. The skin was stretched and a very superficial sample was removed with a skin grafting knife. The superficial wound was then covered with a sterile vaslinated gauze.

Procedure for cell separation
The following procedure was performed in UV cabin kept in our laboratory near the operation theater.

Separation of epidermis from dermis
The thin skin sample was transferred to a Petri dish containing approximately 4 ml of 0.2% trypsin solution. Care was taken to ensure that the sample was properly soaked in the solution. Finally, it was placed epidermis upwards. The sample in the petri dish was incubated for 50 min at 37 °C. After incubation, approximately 2 ml of trypsin inhibitor (Sigma, USA) was added to the petri dish to neutralize the action of the trypsin. The dermis was separated from the epidermis and was transferred to a test tube containing approximately 3 ml of DMEMF12 medium (Sigma, USA) and vortex mixed for 15 Sec.

Preparation of melanocyte cell pellet from epidermis
Epidermis in the petri dish was broken down into multiple small pieces. It was then washed with DMEMF12 medium and then transferred to a test tube containing the same medium. Next it was vortex mixed for 15 sec. The test tube containing the epidermal pieces was then centrifuged for 6 min. The epidermal pieces were discarded and the cell pellet was suspended in DMEMF12 medium in a 1-ml syringe with detachable needle. The quantity of the suspension prepared was approximately 0.5 ml. Hyaluronic acid was added to increase viscosity. One drop of the cell suspension seen under light microscope (magnification100x) had approximately 3-4 melanocytes.

Recipient site
Recipient site was marked out with a marker, cleaned with povidone iodine solution and 70% ethanol and then anesthetized with 1% xylocaine.

Transplantation
The recipient area was abraded down to the dermo-epidermal junction with a high speed dermabrader fitted with diamond fraise wheel. The ideal level was achieved when pinpoint bleeding spots appeared. Denuded area was covered with gauze pieces and moistened with normal saline until the cell suspension was applied. Cell suspension was applied evenly on the denuded area and covered with a vaslinated gauze to help the transplanted cells to remain in place and to provide an optimal environment for cellular growth and vascularization. The patient was allowed to return home 4 hours after dressing. The patient was cautioned against any vigorous activities, which could displace the dressing. Absolute immobilization was however not necessary.

Postoperative care
Prophylactic antibiotics and analgesics are recommended for 1 week. Patients should be instructed not to move the transplanted area. The first 48 hours are crucial to ensure proper embedding of the melanocytes. The dressings are removed after a week. Then topical PUVA was done once weekly for the tested and control area for about six months.

Results
The main parameter to measure the efficacy of the intervention was the percentage of area of repigmentation in the test lesions relative to the baseline depigmented surface area. This percentage was subjectively assessed with area measurements on two week, one month, three months and 6 months after treatment (Tabl. I).
At the 4 observed time points two weeks, 1, 3 and 6 months there were statistical significant differences in repigmentation ($p<0.05$) between actively treated lesions and conventionally (control) treated lesions. At two weeks, 1, 3 and 6 months, the mean percentages of the repigmented areas at the test site for the studied patients were 5.65±3.17, 18.25±8.25, 66.05±13.45, and 66.05±13.45 % respectively). In control sites, at the 4 observed time points, the mean percentages of area of repigmented areas were 1.45±1.57, 4.70±2.89, 12.10±6.49, and 27.25±10.05 % respectively.
Repigmentation in test and control sites was graded as excellent with 95% to 100% pigmentation, good with 65% to 94%, fair with 25% to 64%, and poor with 0% to 24% of the treated area (Fig. 1-3 a, b).

Time of outcome evaluation After treatment	Percentage of area of re-pigmentation in Test lesions (n = 20)	Percentage of area of re-pigmentation in Control lesions (n = 20)	Z of Mann-Whitney U Test (p value)
	Mean ± SD	Mean ± SD	
Two weeks	5.65 ± 3.17	1.45 ± 1.57	4.097 *
One month	18.25 ± 8.25	4.70 ± 2.89	4.718 *
Three months	66.05 ± 13.45	12.10 ± 6.49	5.413 *
Six months	66.05 ± 13.45	27.25 ± 10.05	5.413 *

Table I. Percentage (mean & standard deviation) of area of re-pigmentation in the test and control lesions of the studied cases with vitiligo (n = 20)

Significant at 0.05 level of significance

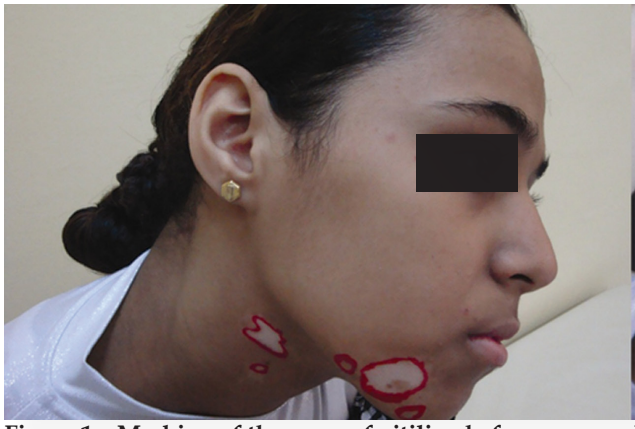

Figure 1a. Marking of the areas of vitiligo before treatment

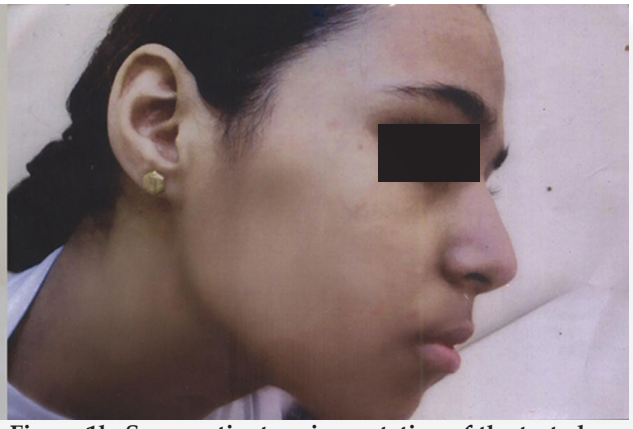

Figure 1b. Same patient repigmentation of the tested area after 6 months (excellent result)

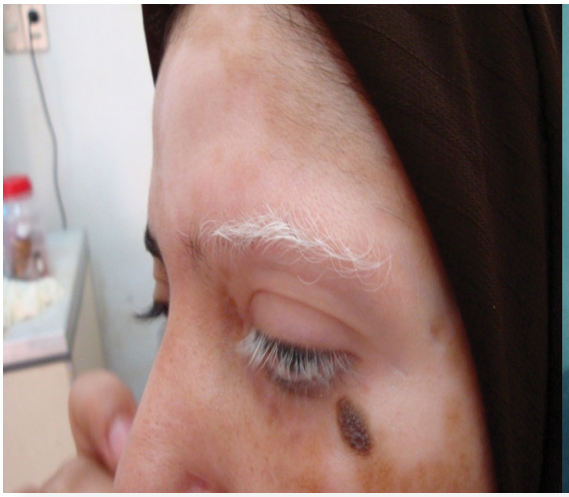

Figure 2a. The depigmented area before transplantation of melanocytes keratinocytes suspension

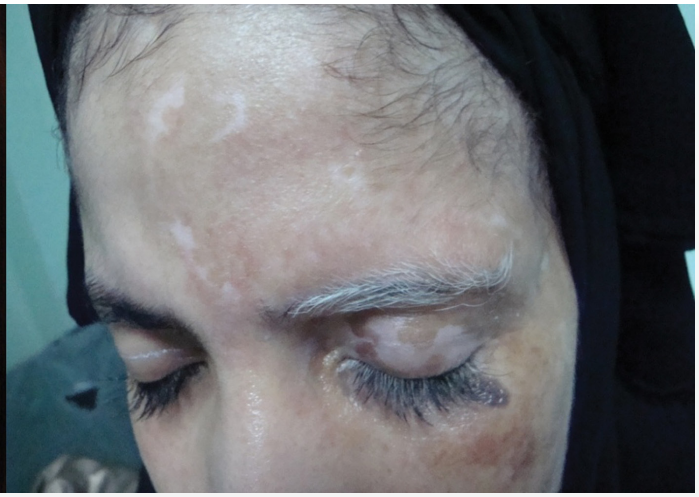

Figure 2b. Excellent result of the same patient after 6 months

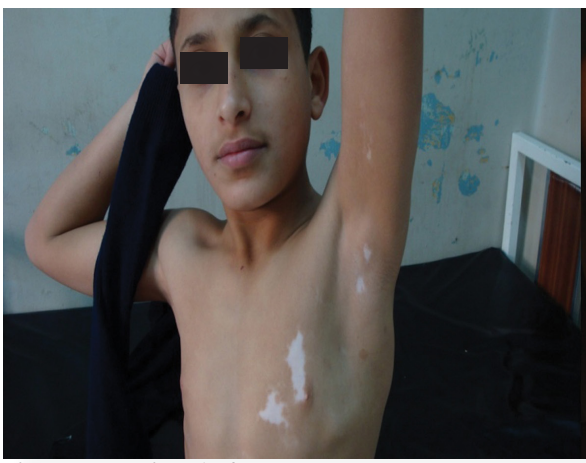

Figure 3a. Patient before

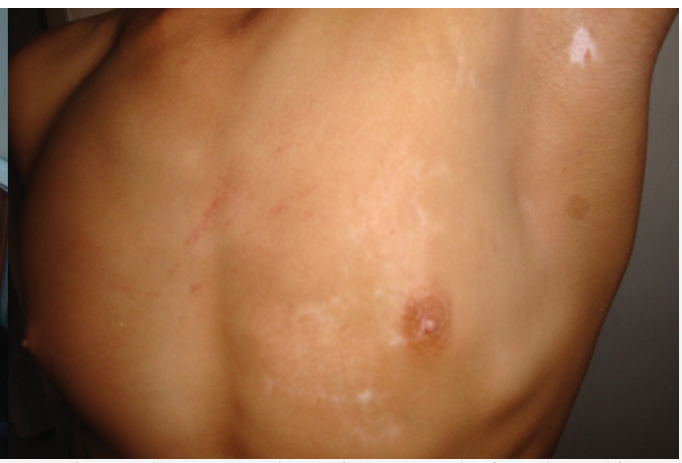

Figure 3b. Same patient after 6 months (good result)

There was a statistical significant difference in the grades of repigmentation (Chi-square test = 33.067, p= 0.000) between test lesions and control lesions. The repigmentation at 7 of the test sites (35.0%) was excellent. It was good for more than half of the test sites (55.0%). Fair repigmentation was encountered among only 2 (10.0%) of the tested sites. None of the tested sites showed poor repigmentation.

On the other hand, none of the control sites showed excellent or even good repigmentation. However, repigmentation was fair for nearly 10% and it was poor for 90% of the control sites (Tabl. II).

Selected parameters of repigmentation of the treated area (Tabl. III)

In the majority of the responding lesions (85.0%), a diffuse repigmentation pattern was observed. This was rather than a typically follicular pattern in 3 patients (15.0%).

In addition, colors of the treated areas in the majority of patients (90.0%) were the same as that of the surrounding normally pigmented skin. However, the color was somewhat darker (hyperpigmentation) in one patient and somewhat lighter in another patient (hypopigmentation).

The time of initial repigmentation for the actively treated areas ranged between 2 and three weeks (a mean, 2.35±0.49 weeks).

The number of topical PUVA sessions required during the whole 6 months follow up period ranged from 20 to 42 sessions (a mean, 29.35±7.17).

Grades of re-pigmentation of the treated area	Test lesions (n = 20)		Control lesions (n = 20)		Chi-square Test (p value)
	No.	%	No.	%	
Excellent	7	35.0	0	0.0	20.067 *(0.000)
Good	11	55.0	0	0.0	
Fair	2	10.0	2	10	
Poor	0	0.0	17	90	

Table II. Grades of repigmentation of the treated area in test lesions and control lesions of the studied cases with vitiligo

Significant at 0.05 level of significance

Parameters of re-pigmentation of the treated area		No. (n = 20)	%
Pattern of re-pigmentation after 1-3 months	Diffuse	17	85.0
	Perifollocular	3	15.0
Color matching	Somewhat darker	1	5.0
	Somewhat lighter	1	5.0
	The same	19	90.0
Time of initial re-pigmentation	Mean ± SD (weeks)	2.35 ± 0.49	
	Minimum – Maximum (weeks)	2 – 3	
Topical PUVA sssions	Mean ± SD (months)	29.35 ± 7.17	
	Minimum – Maximum (session)	20 - 42	

Table III. Distribution of the test lesions (n = 20) according to selected parameters of re-pigmentation of the treated area

Discussion

The age of the twenty studied patients ranged between 13 and 33 years with a mean age of 17.77±6.98 years, that the highest proportion of the studied patients (60.0%) was in the age group less than 15 years and the lower proportion (40.0%) was in the age group of 15 to 33 years, this present study was revealed that the age group below 15 years is earliar in repigmentation and better in prognosis than older age group, this may be due to younger cell age that grows and multiplies rapidly, this is the same in comparison to the study done by Czajkowski [10] who found that the time of proliferation of melanocytes in in-vitro culture conditions depends on the age of patient and, the younger the patient the faster the melanocytes proliferation.

As regard to the skin type in this present study, twelve patients (60% of cases) are skin type IV and eight patients (40% of cases) skin type III and this work did not find any correlation between the skin type and the result of repigmentation, the same result was obtained by Gauthier and Surleve, [11] but different in comparison to Sobhy [12] who injected

the melanocytes suspension obtained from a graft from inner aspect of the thigh to the bullae introduced to vitiliginous area (group II patients) or pouring melanocytes suspention on dermabraded vitiliginous areas (group III patients) and found that skin type IV patients had better prognosis than the skin type III patients, Sobhy [12] found that the higher the skin type the Better the prognosis due to increase the density of melanocytes in donor areas and increasing melanocytic function and melanization of melanosomes in skin type IV patients, this difference from the present study may be due to the small case number in the present study and no patient with higher skin type in this study.

This present study did not find any significant correlation between the type of vitiligo and the response to this procedure, this is different in comparison to what found by Flabella [13] who found that the patients with focal vitiligo have a smaller success rate compared with the patients with segmental vitiligo, and this may be due to small cases number in the present study.

As regards the sex of the patients in this study there were 13 females and 7 males and this study found no correlation to this item and the result of repigmentation, this is the same as what found by the Gauthier result, [11] Sobhy [12] and flabella [13].

In the present study, it was found that the site of the lesions did not significantly affect the result but the mean percentage of repigmentation of the treated area was greater in patients with skin lesions located in the face (89.67±11.76%) compared to those of the patients with skin lesions located in the neck (87.75±13.22%), and those located in the back (86.65±12.53%) and those lesions located in the chest (83.50±14.48%), this is different from the result of Pandya [14] study who found that in the fifty-one sites in 27 patients were chosen for autologous melanocytes transplantation, the most common sites were the feet (45.1%), legs (29.4%), hands (9.8%), knees (3.9%) and the face (3.9%), Pandya [14] results were most favorable on the legs, feet, face and the forearms, and poor on the elbows and the acral areas of the hand. Pandya [14] emphasis that the location of the recipient site was the major determinant of the outcome; acral parts including the dorsal aspects of the hands and feet, and the skin over the joints were less responsive, as 2 patients each with lesions on the hands and feet, and 1 patient with lesions on the elbow had a poor response, Pandya [14] said also that the fingers, the knuckles and the elbows were the most difficult areas to repigment, in part because of the relative uncertainty in controlling the depth of dermabrasion of such heavily cornified areas and also because of the high mobility of the skin covering these joints and so Pandya found also positive correlation with light exposed areas, this difference from the present study may be due to small case number and no acral cases and no cases with joint affection in the present study, but in accordance to Mulkar [15] who found poor response in the sun exposed areas and said that the sun may be a traumatic factor, but Sobhy [12] found that the exposed areas had better prognosis, these differences between the multiple studies may be due to the different degree of sun radiation on the earth and individual variation in melanocytic response to ultraviolet stimulation.

In the present study the face and the neck are cosmetically accepted with good response and rare side effect.

As regard to the duration of stability of the disease in this study, the stability ranged between 2 and 4 years with a mean stability of 2.25±0.55 years, it was found that the duration of stability was not statistically significant in correlation with percentage of repigmentation, this observation was opposite to Van Geel [16] who found positive correlation, this may be due to small difference in duration between the cases in this present study, and this observation is the same found by Sobhy [12] who found that the most important thing that affects the response to treatment is the stability of the disease (2 years or more) rather than the duration of the disease.

In the present study, in the majority of the responding lesions (85.0%), a diffuse repigmentation pattern was observed, but there were rather than a typically follicular pattern in 10.0% or repigmentation from the perilesional margins in only 5.0% this is the same observed by Mulkar study, [15] Sobhy [12] and this observation may be due to spreading of melanocytes rich suspension liquid to all of treated areas giving chance to diffuse spread of transplanted melanocytes and so diffuse repigmentation pattern.

In the present study the transplanted melanocytic cell count per mm^2 ranged between 210-300 cells per mm^2 donner skin graft which were enough to induce repigmentation and this was similar in accordance to GR Tegta et al study [17] that found that the optimal melanocytes count was 210-250 cells per mm^2 donner skin graft and so no great difference in range of these transplanted cells statistically to affect significantly degree of repigmentation.

This study revealed that the time of initial repigmentation for the actively treated areas ranged between one week and three weeks, this was the same in comparison to what is done by Sobhy [12] and Flabella [13].

Every patient was encouraged to topical PUVA irradiation to tested and control areas in a slowly increasing dose to increase the extension of repigmentation and in the tested areas there was progressive increase in the size of pigmented spots until coalescence of pigment has occured,this combination between autologous non-cultured epidermal cellular suspension and topical PUVA reduce the time of complete repigmentation by increasing melanocytes proliferation, function and suppress autoimmunity to transplanted cells.

The lack of pigmentation at the periphery of the transplanted skin observed in two patients was not due to the technical procedure, but probably to residual activity of some melanocyte-destroying factors, [12] another explanation could be an inflow of keratinocytes from the pigmented border which does not allow the transplanted pigment cells to remain where they were seeded, this influx of keratinocytes at the margins appeared as a white rim which could be treated by increasing dermabration beyond lesion boundary during the operation session or performing another session of transplantation of frozen autologous melanocytes not used in first session, this observation was also noted by Osslon et al [9] who found that the white rim decreased more often in the patients treated with the epithelial sheets compared with patients treated with the cells free in suspension.

Conclusion

1. Autologous non-cultured melanocytes transplantation is a rapid method for treating non-progressive vitiligo.

1. This method is simpler than methods involving cell culturing, but is still a quite advanced and requires a laboratory setup.
2. Selection of patients is crucial to the success of the outcome.
3. Segmental vitiligo and focal vitiligo almost always respond with complete repigmentation.
4. Segmental vitiligo and focal vitiligo cases retain all the repigmentation as noted by this study in up to one year of follow-up.

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THE ROLE OF INTERLEUKIN-1ß AND INTERLEUKIN-33 IN ATOPIC DERMATITIS

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Abstract
Introduction: Interleukin-1 super family is a group of cytokines that play a role in the regulation of immune and inflammatory responses. Interleukin-33 is a member of this family and is known to induce expression of the T helper2 cytokines that are important players in atopic dermatitis.
Aim: To evaluate the expression of interleukins-1ß and 33 as T helper2 cytokines inducers in patients with atopic dermatitis.
Materials and Methods: This study included 20 atopic patients and 20 apparently healthy individuals serving as controls. Skin biopsies from all participants will be examined for detection of interleukins-1ß and 33 by ELISA technique.
Results: Both interleukins were statistically higher (P<0.001) in patients than in controls. A statistically significant (P=0.011) highest levels of interleukin-33 was detected in severe cases of atopics when compared to mild and moderate cases. A significant correlation (r=0.632, P=0.003) between both interleukins was detected in atopics.
Conclusions: This is the first study to evaluate both interleukin-1ß and33 together in atopic patients. Both interleukins could play a role in the recruitment of lymphocytes during the inflammatory reaction in atopic dermatitis and could be targeted in the treatment of resistant cases.

Key words: atopic dermatitis; Interleukin-1ß; Interleukin-33

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Introduction

Atopic dermatitis (AD) is a chronic relapsing skin disease, often occurring within the first year of life and affecting up to 20% of children, the majority of whom outgrow the disease within few years. Despite the occurrence of late-onset AD in some adults, the prevalence of AD in the adult population has been estimated to be much lower (2–9%) [1].

Atopic diseases are characterized by IgE sensitization to environmental allergens. The gene-environment interactions leading to the development of AD are only partially understood [2]. Traditionally, two competing hypothesis are presented to explain the pathogenesis of AD. The inside-out hypothesis suggests that an immunological defect predisposes to atopy and that this IgE-mediated sensitization will result in AD, whereas the outside-in hypothesis proposes that disruption of the skin barrier, either resulting from an intrinsic genetic defect in epidermal skin barrier formation or as a result of an environmental alteration, would lead to sensitization and atopic disease [3].

Interleukin (IL) -1 super family is a group of cytokines that play a central role in the regulation of immune and inflammatory responses to infection and tissue injury. IL-1β is the best-studied cytokine of the 11 members of this family. On exposure to pathological stimuli, IL-1β is produced by activated leukocytes, leading to induction and enhancement of inflammatory responses [4].

Interleukin-33 is also a member of the IL-1 family of cytokines [5] and is known to induce expression of the helper (Th)2 cytokines IL-5 and IL-13 in vitro, as well, increased blood eosinophils and serum immunoglobulins when delivered in vivo [6]. IL-33 can also induce the activation and maturation of human mast cells [7,8].

Th2 cells are important players in cutaneous allergic inflammation, an integral part of AD [3]. Th2 cytokines can be secreted by basophils, eosinophils and mast cells. Basophils have recently been detected in AD skin lesions [9] and eosinophils recruitment into the skin is characteristic of AD [3].

In humans, IL-33 mRNA levels are induced almost 10-fold in the skin of AD patients compared to healthy skin [8]. However the role of IL-33 in AD remains to be evaluated.
Our aim is to evaluate the expression of IL-1ß and IL-33 as Th2 cytokines inducers in the patients with AD.

Methods

This study included 20 atopic patients (Group 1) and 20 apparently healthy individuals serving as controls (Group 2). Participants were selected from the outpatient clinic of the Dermatology Department, Faculty of Medicine, Cairo University. A written informed consent was obtained from all participants before initiation of the study.
Atopic patients (Group 1) included twelve males and eight females; each patient was subjected to full history to detect any history of other atopic manifestations like atopic asthma, and the grade of atopic dermatitis severity was evaluated according to Rajka and Langeland [10] as follows; Mild (score:3-4), Moderate (score:4.5-7.5) and Severe (score:8-9). Parameters for scoring the grade of severity included: extent of involvement (as determined by the „rule of 9", as used for burn area), course of the disease and intensity of disease, as determined by itch (considered by the authors to be the basic trait for AD) (Tabl. I).

Assessment of IL-1ß and IL-33:
A portion of the lesional skin tissue was homogenized for testing in IL-33 and IL-1ß ELISA. Homogenization was performed in homogenate buffer [10 mM HEPES (pH 7.9), 10 mM KCL, 0.1 mM EGTA, 1 mM DTT, and 0.5 mM phenylmethanesulfonyl fluoride] using a vertishear tissue homogenizer. Tissue homogenates were centrifuged at 3,000 g for 15 min at 4°C. The supernatants were subsequently stored at –80°C until the ELISA could be performed for IL-33 and IL-1ß.
The ELISA technique was performed by adding 100 µl of each sample to wells in a 96-well plate of a commercially available human ELISA kit (R&D system quantakine USA). The samples were tested in duplicate. The ELISA was performed according to the manufacturer's instructions and final results were expressed as picograms per milliliter.

Statistical analysis:
Data was coded and entered on computer for analysis. A spread sheet on EXCEL was developed for data entry. Data was then transferred to SPSS version 17 for analysis. Simple frequencies were used for data checking. Descriptive statistics (arithmetic mean and standard deviation) were used for summary of quantitative data, while percentages were used for qualitative data. Appropriate statistical tests of significance were used to test the null hypothesis in comparison of the studied groups. A P value < 0.05 was used for detection of statistical significance in all tests.

Parameter	Finding	Points
extent	< 9% of body area	1
	skin involved more than score 1 and less than score 3	2
	> 36% of body area involved	3
course	> 3 months of remission during the year	1
	< 3 months remission during the year	2
	continuous course	3
intensity	mild itch, only exceptionally disturbing night's sleep	1
	itch, evaluated to be more than score 1, less than score 3	2
	severe itch, usually disturbing night's sleep	3

Table I. Parameters for scoring of atopic dermatitis severity

Results

This study included 20 atopic patients; they included 12 males and eight females aged between 10-46 years (mean age 26.75 years). All patients had never received treatment or had stopped therapy six months beforehand. Twenty healthy subjects were included as controls; they included eleven males and nine females aged between 13-45 years (mean age 27.73 years).
Regarding the atopic patients; personal history of other atopic manifestations like asthma were detected in six patients (30%). Family history was positive in six patients` (30%). Grading of disease severity in patients with AD was performed and accordingly, atopic patients were divided into three groups:
- Group of mild cases (score 3-4) included eight patients (40%), four males and four females.
- Group of moderate cases (score 4.5-7.5) included five patients (25%), all of them were males.
- Group of severe cases (score 8-9) included seven patients (35%), three males and four females.

Interleukin-1ß was detected in all atopic patients in the range of 14.5 to 38.2 pg/ml with a mean of 25.9±6.66 pg/ml. IL-33 was also detected in all atopic patients in the range of 194.5 to 516.3 pg/ml with a mean of 292.5±89.68 pg/ml.
Regarding to healthy individuals (Group 2); IL-1ß was detected in the range of 10.2 to 22.3 pg/ml with a mean of 14.75±4.05 pg/ml. IL-33 was also detected in the range of 102.4 to 216.7 pg/ml with a mean of 151.71±38.63 pg/ml.
Statistical analysis revealed a significant difference (P<0.001) between the two studied groups regarding the mean value of both IL-1ß and IL-33 (Tabl. II).

In atopic patients; statistical analysis revealed no significant difference in the mean value of both IL-1ß and IL-33 between the females and males patients (P=0.168 and 0.735 consecutively). Also, there was no statistically significant difference regarding the mean value of both IL1B and IL33 in patients with positive history of asthma and those with negative history (P=0.249 and 0.172 consecutively).

When comparing the mean value of IL-1ß with the severity of atopy in patients group, our results revealed no statistically significant difference (P=0.050) between mild, moderate and severe affection. When comparing the mean value of IL-33 with the severity of atopy in patients group, our results revealed statistically significant difference (P=0.011) between mild, moderate and severe affection with the highest value detected in severe cases (Tabl. III).

Our results revealed no statistically significant correlation between the levels of both IL-1ß and IL-33 in atopics with the age of the patients (P=0.219 and 0.157 consecutively). However there was a statistically significant correlation between both IL-1ß and IL-33 in atopics (r=0.632, P=0.003).

	IL-1ß (pg/ml)		IL-33 (pg/ml)	
	Mean	SD†	Mean	SD
Group1 (n*=20)	25.9	6.66	292.5	89.68
Group2 (n=20)	14.75	4.05	151.71	38.63
P value	<0.001‡		<0.001‡	

Table II. IL-1ß and IL-33 levels in atopic patients and healthy individuals
*** number**
† standard deviation
‡ significant P value

		IL-1B (pg/ml)		IL-33 (pg/ml)	
		Mean	SD*	Mean	SD
Grade of severity (score)	Mild (n†=8)	23.17	6.577	245.57	40.214
	Moderate (n=5)	23.5	4.986	261.5	52.078
	Severe (n=7)	30.73	5.633	368.41	106.356
P value		0.050		0.011‡	

Table III. IL-1ß and IL-33 levels in different clinical severity of atopic patients
*** standard deviation**
† number
‡ significant P value

Discussion

In this study, both IL-1ß and IL-33 are significantly highly expressed in atopics. This could explain a role of both of them in the pathogenesis of atopy and in the trafficking of leucocytes during the inflammation caused by AD.

In this study both IL-1ß and IL-33 were statistically higher (P<0.001) in patients than in healthy individuals. IL-1β is responsible of the acute phase responses to inflammation [4] and this can explain its role as initiator of inflammation in AD. IL-33 is one the IL-1 family and has been described to function as an alarmin. It's expressed in tissues with predominant barrier function, and released upon cell death with activation of several components of the immune system [8].

IL-33 is expressed by human keratinocytes following any insult to the skin causing cell damage of any kind. Dermal immune cells, such as mast cells which express the IL-33 receptor are stimulated by IL-33 and become activated. Mast cells produce cytokines and chemokines which recruit other immune cells, and in the appropriate context inflammation is maintained and lesions develop. IL-33 has been shown to induce the generation of Th2 cytokines producing innate immune cell populations [11]. The IL-33 receptor, consisting of ST2 and IL-1 receptor accessory protein, is also widely expressed, particularly by Th2 cells and mast cells. IL-33 is host-protective against helminth infection by promoting Th2-type immune responses. IL-33 can also promote the pathogenesis of asthma by expanding Th2 cells and mediate joint inflammation, AD and anaphylaxis by mast cell activation. Thus IL-33 could be a new target for therapeutic intervention across a range of diseases [12].

Our results were in accordance with Hakonarson et al. [13] who detected enhanced mRNA expression and release of IL-1beta protein in patients with allergic asthma.

Our findings were also in agreement with Pushparaj et al. [8] who showed that IL-33 is upregulated in AD patients. Matsuda et al. [14] also found IL-33 expression in chronic allergic conjunctivitis but not in the control conjunctivae and that IL-1ß stimulation upregulated IL-33 mRNA expression in conjunctival fibroblasts. The authors also confirmed mature IL-33 protein expression in ocular resident cells by Western blot analysis.

In this study, IL-33 was statistically highly detected in severe cases of AD. This could explain its role in the progression of the disease.

A significant correlation between both IL-1ß and IL-33 was detected in atopics in the current study. This could explain the interrelation of both cytokines to initiate the inflammation in AD. To the best of our knowledge, no previous studies examined these two interleukins together in AD.

As a conclusion, IL-1ß and IL-33 could play a role in the recruitment of lymphocytes during the inflammatory reaction in AD and could be targeted in the treatment of resistant cases; however this finding should be confirmed by further studies with large scales of patients.

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THE ROLE OF INTERLEUKIN-1B AND INTERLEUKIN-33 IN ATOPIC DERMATITIS

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The studies of the pathogenesis of atopic dermatitis are very important not only for investigation of different aspects of chronic allergic inflammation but also for the possible treatment targets. Authors presented interested in vivo study aimed on the detection of expression of two cytokines (IL-1β, IL-33) in the skin of the subjects with moderate to severe atopic dermatitis [1]. Interleukin 33 is one of the newly revealed inflammatory TH2 cytokines which is now studied in relationship with the development of different allergic conditions. The study is of great value, because it examined the production of these two cytokines in vivo in the skin of the dermatitis patients. The role of IL-1β in the chronic inflammation was previously reported, but the finding of increased IL-33 is new. Its association with the severe forms of atopic dermatitis could suggest on one side its role in the progression and exacerbation of the disease, and on the other hand it could be used as possible targeted of aimed biological therapy in the future.

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CLINICAL EVALUATION OF DIFFERENT THERAPEUTIC MODALITIES IN PSORIASIS BY PASI SCORE

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Abstract
Psoriasis is a chronic recurrent papulosquamous disorder characterized by epidermal hyperplasia. The management of psoriasis can be challenging. Although, there are many therapeutic modalities available but still there are no clear cut guidelines regarding the usage of different modalities depending on the severity of psoriasis evaluated by PASI score. Taking this into consideration, a randomized controlled trial was undertaken to clinically evaluate different therapeutic modalities in psoriasis by PASI scoring. We selected fifty clinically diagnosed cases of psoriasis and confirmed by histopathology. The patients were put on different modalities depending on the psoriasis area and severity index score (PASI score) and all the patients were followed up to 24 weeks for any relapse.

Key words: psoriasis; PASI; treatment; diagnosis; methotrexate; retinoids; cyclosporine

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Introduction

Psoriasis [1,2] is a papulosquamous disorder charcterised by increased mitotic activity of the basal cell layer which results in rapid epidermal cell turnover with the 28 day normal epidermal cell cycle reduced to 5 days. Primary treatment goals for patients with psoriasis are: (1) reduce the size, thickness, and extent of plaque, papules, and erythema; and (2) improve quality of life (physical, mental, emotional, and social functioning). The measure of response to therapy (i.e., reduction in symptoms) is generally based on psoriasis area and severity index (PASI) score. A reduction of 50 percent from pretreatment baseline scores is generally accepted as a positive physical response; a reduction of 75 percent or more is generally accepted as a superior response approaching clearance. Though the diagnosis of psoriasis is clinical but still histopathological changes precede the clinical relapse [3].

Several factors influence therapeutic selections for patients with mild-to-moderate disease [4]. First and foremost, the nature of individual lesions (e.g., thick versus thin plaques) as well as the location and extent of distribution of plaques drive treatment decisions. Thereafter, therapeutic success, duration of remission, frequency of relapse, and appearance or desired avoidance of side effects dictate choices [5]. Finally, patient preference must be considered because some therapies are cosmetically inelegant (e.g., topical ointments and creams) or stain skin, clothing, bed linens, and bathtubs (e.g., anthralin); others are time consuming (e.g., broadband ultraviolet A and B phototherapies) or somewhat intolerable (e.g., intralesional injections, especially for nails).

According to treatment guidelines from the American Academy of Dermatology [6] (AAD), therapeutic intervention for localized mild-to-moderate plaque psoriasis should begin with patient education [7] and the use of topical corticosteroids with or without coal tar or calcipotriene. Thereafter, anthralin or tazarotene [8], alone or in combination with steroids, can be used following first-line treatment failure or subsequent loss of response to first-line therapy. Alternatively, if control is difficult to achieve or disease is widespread, phototherapy, with and without drugs such as psoralen or retinoids, may be required. In actual practice, therapies are often rotated [9,10] to take advantage of unique features and benefits, to minimize the development of adverse events, or to avoid tachyphylaxis that may be associated with individual alternatives. More potent systemic therapies, such as methotrexate, cyclosporine, and the biologics, are sometimes required for severe psoriasis.

The course is usually chronic and marked by remissions and relapses.

Although no cure is available, but the disease can be effectively controlled by various topical and systemic treatment modalities alone or in combination. Mainstay of topical therapy includes coal tar, keratolytics, topical steroids, calcipotriol and tazarotene [11]. Most patients can be managed with topical [12] treatment alone. Systemic therapy is indicated in patients with moderate to severe psoriasis, variably having patients with PASI score more than 10.The different modalities available are mrethotrexate, retinoids, systemic PUVA, cyclosporine, hydroxyurea, sulfasalazine and mycophenolic acid.

Aims

To study the therapeutic efficacy of various modalities in psoriasis i.e. topical therapy, methotrexate, PUVA, retinoids and cyclosporine.

1. To do clinical evaluation by PASI scoring in psoriasis.

Material and Methods

For the present study, fifty clinically diagnosed cases of psoriasis were selected from the outpatient department of Dermatology,venereology and leprosy, Guru Gobind Singh Medical College and Hospital, Faridkot. All the patients were subjected to the following investigations:

1. Routine Investigations:

- Haemoglobin assessment, complete blood count, Fasting blood sugar, erythrocyte sedimentation rate and urine complete examination, ASO titre and throat swab for culture.

2. Specialized investigations :

- Biochemical Investigations - These include SGOT, SGPT, Serum Alkaline Phosphatase, Serum Uric acid, Blood urea, Serum creatinine, Total & Differential serum Proteins and Serum calcium.
- Histopathological Investigations - in the form of Skin Biopsy.

The grouping of the patients was done depending on the PASI score. A written informed consent was taken from all the patients before starting the study. Prior approval of hospital ethical committee was taken for the study. PASI score was calculated in all patients at the start of study and then every 2 weekly till the remission phase of the disease. Patients were put on various treatment modalities depending on the PASI score. All patients were subjected to histopathological examination at the start of treatment and the biopsy was repeated at 8 weeks. The patients were evaluated at 0,2,4,6and 8 weeks and all patients were photographed. After 8 weeks, no treatment was given and the patients were asked to come for follow up every 4 weeks upto 24 weeks to see for any relapse.

The psoriasis area and severity index (PASI Score) was recorded in all the patients. The severity of erythema, scaling and induration was recorded on a scale from 0 to 4.

- 0 -- None
- 1 -- Mild
- 2 -- Moderate
- 3 -- Severe
- 4 -- Very Severe

The formula for calculating PASI score is as follows:

PASI score = 0.1 (Eh +I h+D h) x A h + 0.2 (Eu + Iu + Du) x Au + 0.3 (Et+ It + Dt) x At + 0.4 (EL+ IL + DL) x AL

Ah means area of head involved in psoriasis.
Au means area of upper limb involved in psoriasis.
At means area of trunk involved in psoriasis.
AL means area of lower limb involved in psoriasis.

We calculated the area involved by psoriasis as follows:

1 = Less than 10% area involved
2 = 10 - 29% area involved
3 = 30 - 49% area involved
4 = 50 - 69% area involved
5 = 70 – 89% area involved
6 = 90% or more area involved

The grouping of the patients was done depending on the PASI score.

Group I - Patients having PASI score less than 10. These patients were put on topical therapy. Topical therapy included emollients, topical salicylic acid (3%) in Betamethasone valerate (0.12%) and topical calcipotriol.

Group II - Patients having PASI score between 10-20. These patients were put on PUVA therapy alone.

Group III - Patients having PASI score more than 20. These patients were put on methotrexate, cyclosporine or Acitretin, depending on the cost effectiveness, compliance and lipid profile.

Patients were followed up after every 2 weeks. PASI scoring was done at each visit. Complete physical examination, blood pressure recording, haemogram, urine examination,liver function tests and kidney function tests were done at each visit.

Inclusion Criteria

Subjects of both sexes irrespective of their age having psoriasis.

Exclusion criteria

The following patients were excluded from our study:

· Patients with impaired renal function/ preexisting renal disease.
· Patients with acute uncontrolled bacterial, viral or fungal infection.
· Patients on concomitant use of hepatotoxic or nephrotoxic drugs for any other long standing illness.
· Pregnant/ breast feeding females.
· Concurrent immunodeficiency state.
· Uncontrolled hypertension.
· Patients having hepatitis, active or recent
· Patients having severe anaemia, leukopaenia or thrombocytopenia.
· Patients having excessive alcohol consumption.

Results

The data was tabulated and the results were analysed statistically.

I. Age Distribution

The above table shows that maximum number of cases (22 %) were in the age group of 51-60 years. It was followed by 20% in the age group of 31-40 years, 18% in the age group 21-30 years, 16% in the age group 41-50 years, 16% in the age group 11-20 years, 12 % in the age group 0-10 years and 8% of the cases were above 60 years of age. Mean age of psoriasis in our patients was 38.46 + 3.287 (Tabl. I).

Age	Number of patients	Percentage
0-10	2	4%
11-20	6	12%
21-30	9	18%
31-40	10	20%
41-50	8	16%
51-60	11	22%
> 60	4	8%
TOTAL	50	100%

Table I. Incidence of psoriasis among different age groups

II Sex Distribution

The above table shows that out of 50 psoriatics, 31 (62%) were males, while 19 (38%) were females. Male to female ratio was 1.63: 1 (Tabl. II).

Sex	Number of patients	Percentage
Male	31	62%
Female	19	38%
Total	50	100

Table II. Sex incidence in psoriatics

III. Total Duration of Psoriasis

The above table shows that the duration of the psoriasis was less than 5 years was seen in 66% of cases, between 5 and 10 years in 26% of cases, between 11 and 15 years in 6% of cases, between 16 and 20 years in 2% of cases. The mean duration of disease in our study was 4.74 + 14.64 in our study (Tabl. III).

Duration of psoriasis (in years)	Number of cases	Percentage
Less than 5 years	33	66
Between 5-10 years	13	26
Between 11-15 years	3	6
Between 16-20 years	1	2
Total	50	100

Table III. Total duration of psoriasis

IV. Triggering Factors in Psoriasis

The above table shows various triggering factors in psoriasis patients. The commonest triggering factor in psoriasis patients was stress seen in 24 (48%) patients. Trauma as a triggering factor was seen in 10 (20%) patients, drug intake in 18 (36%) patients, alcoholism in 16 (32%) patients and sunlight as a triggering factor was seen in 3 (6%) patients (Tabl. IV).

In our study, the grouping of patients was done depending on the PASI score.

Group I - Group I patients had PASI score less than 10. Group I patients were subdivided into 3 subgroups:

Subgroup (i) - Patients were given only emollients. Number of patients in this group were 2.

Subgroup (ii) - Patients were given topical salicylic acid (3%) in Betamethasone valerate (0.12%). Number of patients in this group were 4.

Subgroup (iii) - Patients were given topical calcipotriol (0.005%) in dose of 50 µgm/gm and was applied twice daily. Number of patients in this group were 3.

Group II - Group II patients had PASI score between 10-20. These patients were put on PUVA therapy. Patients were given 8 methoxypsoralen in a dose of 0.6 mg/kg/day on every alternate day and then patients were exposed to UVA after 2 hours. Number of patients in this group were 12.

Group III - Group III patients had PASI score more than 20. Total number of patients in this group were 29. These patients were subdivided into 3 subgroups:

Subgroup (i) - Patients were put on methotrexate (16 patients). Methotrexate was given in dose of 0.2 mg/kg body weight/ week in 3 divided doses depending upon the severity of psoriasis.

Subgroup (ii) - Patients were put on Acitretin (10 patients). Acitretin was given in dose of 0.5 mg/kg body weight/ day.

Subgroup (iii) - Patients were put on cyclosporine (3 patients). Cyclosporine was given in dose of 3 mg/kg/day.

No	Triggering factors in psoriatics	Number of cases	Percentage
1	Stress	24	48
2	Trauma	10	20
3	Sore throat	18	36
4	Alcoholism	16	32
5	Drug intake	18	36
6	Photo aggravation	3	6

Table IV. Triggering factors in psoriasis patients

V. Grouping of Patients (Tabl. V)

No	Group I (Topical therapy) PASI < 10			Group II (PASI 10-20)	Group III (PASI > 20)		
	Subgroup (i) (Emollients)	Subgroup (ii) topical salicylic acid (3%) in Betamethasone valerate (0.12%)	Subgroup (iii) (Topical calciptriol)	PUVA therapy	Subgroup (i) (Methotrexate)	Subgroup (ii) (Retinoids)	Subgroup (iii) (Cyclosporin)
No. of patients	2	4	3	12	16	10	3

Table V. Grouping of patients depending on PASI score

VI. PASI Score

The above table shows that in all the groups the mean reduction of PASI score was statistically significant (Tabl. VI).

Groups	Mean PASI SCORE						Significance
	AT 0 WKS	AT 2 WKS	AT 4 WKS	AT 6 WKS	AT 8 WKS	Mean % age reduction in PASI	
Gropu I Subgroup (i) (Emollients)	8.2	7.8	6.9	5.1	4.0	PASI 50	t = 4.91 p > 0.05 (S)
Subgroup (ii) (Topical salicylic acid (3%) in Betamethasone valerate (0.12%)	8.7	7.7	6.2	4.4	2.3	PASI 75	t =2.98 p > 0.05 (S)
Subgroup (iii) (Topical calcipotrol)	9.8	8.2	7.3	5.1	2.4	PASI 75	t = 3.14 p > 0.05 (S)
Group II (PUVA)	20	17.2	15.4	12.2	9.2	PASI 50	t =3.68 p > 0.05 (S)
Group III Subgroup (i) (Methotrexate)	42.5	31.7	27.2	18.6	10.4	PASI 75	t = 4.37 p > 0.05 (S)
Subgroup (ii) (Acitretin)	34.8	30.4	25.2	19.1	16.9	PASI 50	t = 3.89 p > 0.05 (S)
Subgroup (iii) (Cyclosporin)	35.6	30.2	24.4	18.1	8.5	PASI 75	t = 3.29 p > 0.05 (S)

Table VI. Reduction in PASI score in different groups (p > 0.05)

(s = significant)

VII. Relapse in Psoriasis

So, from the above table, it is clear that mean 75% reduction in PASI score was achieved with methotrexate (Fig. 1), cyclosporine (Fig. 2), topical corticosteroids and topical calcipotriol, whereas mean 50% reduction in PASI score was achieved with PUVA therapy (Fig. 3), oral retinoids (Fig. 4), and emollients at 8 weeks. During the follow up period upto 24 weeks, relapse was seen in 2% patients. On emollients, topical corticosteroids and PUVA therapy each and 4% patients on retinoids. But no patient on topical calcipotriol, methotrexate or cyclosporin showed any relapse up to 24 weeks (Tabl. VII).

Drug	Total no. of cases	No. of cases showing relapse	% age of patients with relapse
Emollients	2	1	2%
Topical salicylic acid (3%) in Betamethasone valerate (0.12%)	4	1	2%
PUVA	12	1	2%
Acitretin	10	2	4%
Others	26	-	-
Total	50	5	10%

Table VII. Age (%) of patients with relapse.

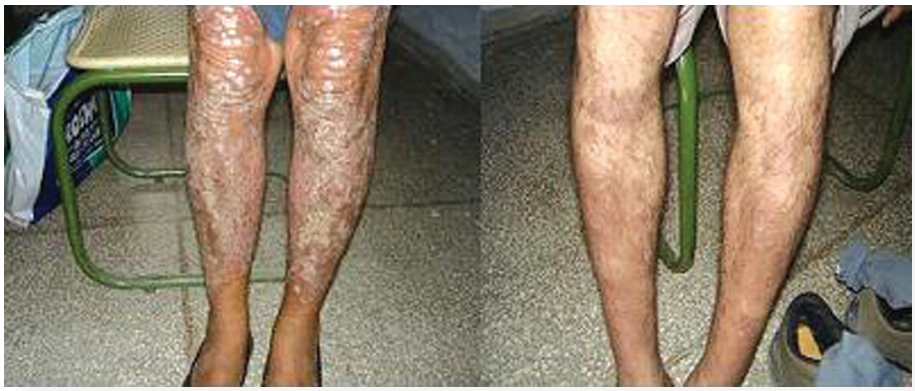

Figure 1. Patient on PUVA therapy before and after treatment

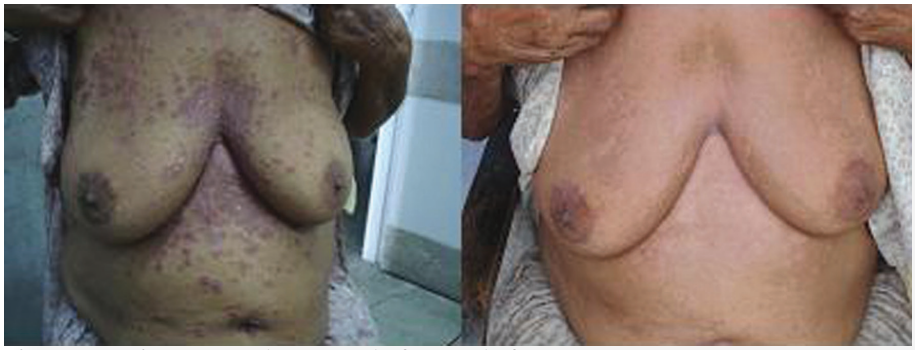

Figure 2. Patient on methotrexate before and after treatment

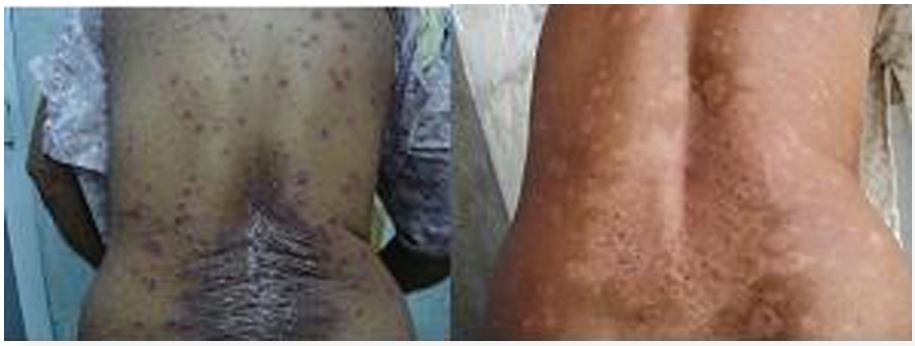

Figure 3. Patient on acitretin before and after treatment

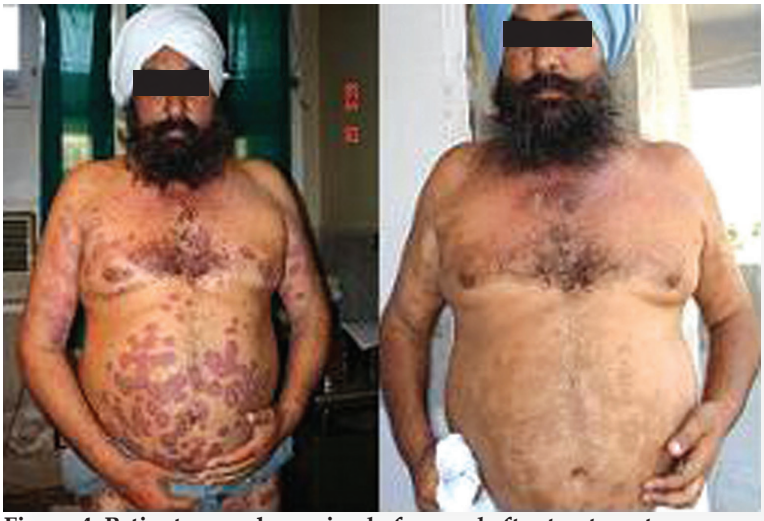

Figure 4. Patient on cyclosporine before and after treatment

Discussion

Although psoriasis is rarely life threatening, it can cause significant morbidity, social embarrassment and financial cost and disruption in patients life; while patients with extensive and severe disease may require systemic therapy, less severe psoriasis is typically treated with topical medications [12]. The management of psoriasis can be challenging on several levels [13]. For patients and providers, resolution of disease is the primary therapeutic objective. Complete and prolonged clearance is the preferred outcome, but one that is elusive in almost all cases. For payers, cost control is vital, so treatment regimens that are less costly or more cost-effective are favored.

For patients with PASI score less than 10, topical corticosteroids [14], with relatively low acquisition costs, are the mainstay of first-line care but can be problematic when used alone. Their onset of action is fast, but exacerbation of disease can also be rapid upon treatment discontinuation. Side effects, such as telangiectasia, striae, epidermal thinning, scar extension, acne, glaucoma, and suppression of hypothalamus-pituitary-adrenal [15] activity are concerns. Moreover, over time effectiveness is lost. For these reasons, the more expensive calcipotriene [16] or possibly tazarotene is commonly combined with a topical corticosteroid for initial disease management. The combination is beneficial for the majority of patients but must be used almost continuously, uninterrupted, or pulsed, to achieve and then maintain a response after successful disease control. Continuous daily or twice-daily applications of one or more creams or ointments can be time consuming, cosmetically inelegant, and objectionable for many patients, especially during work days. Because treatment is continuous, disease control can be prolonged, but treatment-free days are rare. For this reason, cost effectiveness varies according to the outcome that is measured.

Retinoids [17] by themselves, with no additional therapy, are generally ineffective for most forms of psoriasis. Required doses cause significant side effects, such as hair loss, nail thinning, dried and chapped mucous membranes and skin, and hyperlipidemia [18]. The most serious problem associated with retinoid [19] utilization are birth defects in the offspring of women who use these drugs before or during pregnancy. Retinoids can be effective, however, when used judiciously in very low doses in combination with ultraviolet light.

Phototherapies [20], including UVB, UVA plus psoralen (PUVA), are the final options for second-line treatments that are considered in this health economic assessment. According to the American Academy of Dermatology guidelines, these interventions are useful for patients with lesions that are limited but refractory to topical agents, lesions that are widespread, or when disruption of daily activities or employment compromise patient well-being. Logically, UVB and PUVA have more utility when disease is widespread; whereas, the excimer laser is more suitable when disease is more contained. For these reasons, phototherapies are selectively used on different patient populations rather than generally used for all patients who fail first-line care.

Cyclosporine and methotrexate are highly effective drugs in the treatment of severe psoriasis. Methotrexate [21] is a folic acid antagonist which exerts antimitotic action on the epidermis by inhibiting DNA synthesis. Over four decades of experience has established methotrexate as a standard therapy in psoriasis despite its side effects. Methotrexate is indicated in the symptomatic control of patients with moderate to severe psoriasis not responding to topical therapy, patients with erythroderma, palmoplantar pustulosis, generalized pustular psoriasis and psoriatic arthritis. Important contraindications of methotrexate include significant abnormalities in renal and hepatic function, hepatitis (active or recent), cirrhosis, pregnancy, lactation, male or female fertility, immunodeficiency state, excessive alcohol consumption and non compliant patient.

Cyclosporine [22] is a lipophitic cyclic undecapeptide and it inhibits the production of several limphokines including IL-2 bt T cells. Besides extensive severe psoriasis, cyclosporine has also been used in localized, severe and disabling forms of psoriasis like acrodermatitis continua, palmoplantar pustulosis and recalcitrant generalized pustular psoriasis. Its efficacy is somewhat marred by dose related but reversible side effects namely hypertension and renal dysfunction.

In our study, PASI 75 was achieved in patients on methotrexate, cyclosporine, topical corticosteroids (plus emollients and keratolytics) and topical calcipotriol.

PASI 75 is defined as a reduction from baseline PASI score of > 75%. PASI 75 is used as the benchmark of primary end points in assessing therapies for psoriasis. Patients reaching PASI 75 experience very meaningful changes in psoriasis severity. The change in quality of life (QoL) in patients reaching PASI 75 is essentially that of the patient who achieves clear to almost clear status. These days, PASI 50 (or a reduction in PASI score of 75%). These days, PASI 50 [23] is used to assess severity of psoriasis, as many consider PASI 75 as an end point which is too stringent as it places potentially useful therapies at risk of failing to demonstrate efficacy. In our study, PASI 50 was achieved in patients on PUVA therapy, Acitretin and emollients. At the same time, assessment of psoriasis using PASI score has certain drawbacks. An improvement in PASI score [24] does not correlate in a 1:1 ratio with improvement in disease and can underestimate improvement.

In our study it was seen that 5 (10%) patients on PUVA therapy. Acitretin and emollients, showed relapse after stopping the treatment at 8 weeks. Subsequently, it was advised that these patients be put on a combination of drugs in a rotational manner rather than on single drug to increase efficacy, reduce side effects and decreasing the chances of relapse. The patients who went into relapse were put on combination therapy. Hence, it is recommended that all the patients be put on combination therapy on a rotational basis to prolong the remission period. Also, a long term follow up is required to evaluate the exact efficacy of different modalities.

Conclusions

Despite limitations, the PASI score remains the most accepted and widely used measure in clinical trials. PASI, however, is rarely used by dermatologists in clinical practice and most are unaware of its significance or how to interpret changes seen in PASI score in clinical trials. Thus, to interpret the literature and to present results of clinical trials to patients and colleagues, it is imperative that dermatologists, researchers and reviewers understand what level of PASI reduction is clinically meaningful for patients. Also, to reduce side effects, improve efficacy and cost effectiveness, combination therapy on a rotational basis is advised in patients of psoriasis. Further, a large randomized controlled multicentric trial is required to formulate the guidelines for various therapeutic modalities to be used, depending on the severity of psoriasis evaluated by PASI score.

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CLINICAL EVALUATION OF DIFFERENT THERAPEUTIC MODALITIES IN PSORIASIS BY PASI SCORE

by Neerja Puri, Bharat Bhushan Mahajan, Samarjeet Kaur Sandhu

comment:

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Psoriasis is a chronic, intractable disease, and it is difficult to cure completely. Palliative therapy is the mainstay, but there are no general rules. The PASI 75 is considered the gold standard for assessing the effectiveness of each treatment. The results of this study showed that only an approximately 50% reduction in PASI score could be achieved by treating psoriasis with oral retinoids in patients with a PASI score over 20, PUVA therapy in patients with a PASI score between 10-20, and emollients in patients with a PASI score below 10. Therefore, in those patients, dermatologists should select another stronger therapy or a combination therapy. This report is useful for decreasing side effects and exert maximum efficacy. This report can be the indexes for selecting an appropriate therapy in patients with different severities of psoriasis, and thus, it is significant from a cost-effectiveness point of view. Moreover, it is important that dermatologists share these results with patients and discuss the selection of modalities with patients to maintain the patient's motivation for treatment. However, this report did not include results from combination therapy or biologics. In future, studies are required that describe large, randomized controlled multicenter trials and data on treatment with biologics.

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ROLE OF ORAL ZINC SULPHATE IN WARTS-A PLACEBO CONTROLLED, SINGLE-BLINDED STUDY

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Abstract
Verrucae (synonym: warts) are one of the most common viral infections of humans in which the most frequently used modalities of treatment involve destruction of the affected area, which does not prevent recurrences and often results in scarring. In the present study oral zinc sulphate, an immunomodulator was evaluated as a treatment modality for warts. A placebo-controlled, single-blinded study was conducted on one hundred OPD patients with various types of verrucae. Fifty patients were put on oral zinc sulphate at dose of 5mg/kg for six weeks, while an equal number of patients received placebo for the same duration. In the patients who received oral zinc sulphate, 60.97% showed complete response at the end of six weeks in comparison to 6.45% partial response in the placebo group. The resolution of the lesions occurred with restoration of normal epidermal texture with transient alteration in pigmentation.

Key words: verrucae; zinc sulphate; human papillomavirus

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Iffat Hassan, Taseer Bhat, Hinah Altaf, Farah Sameem, Qazi Masood: Role of oral zinc sulphate in warts-a placebo controlled,single-blinded study. Our Dermatol Online. 2013; 4(1): 24-27

Introduction

Verrucae (synonym: warts) are one of the most common viral infections of humans. These are caused by human papillomavirus (HPV). There are approximately 100 genotypes of these DNA viruses. Transmission of HPV occurs most commonly by direct contact with individuals who may be harbouring subclinical or manifesting clinical HPV-associated lesions, or by indirect means such as through contaminated surfaces and objects. Basal keratinocytes of the epidermis which serve as primary targets for HPV infections are exposed to the virus through minor abrasions and infection is promoted by maceration of the epithelia. Recovery from the viral infection is spontaneous in majority of the cases but may take months to years. There is currently no specific antiviral therapy available to cure HPV infection. Existing modalities of treatment including electrocautery, cryotherapy which involve destruction or removal of visible lesions do not prevent recurrences and may even result in scarring.

Zinc, a non-toxic trace element which has been used as an immunomodulator in various dermatological ailments such as leg ulcers, erythema nodosum leprosum (type 2 reaction) and dissecting cellulitis of scalp, has been tried in viral warts with encouraging results [1-3].

Aims and objectives

To assess the efficacy of oral zinc sulphate in the treatment of viral warts.

Material and Methods

A total of 100 patients with warts reporting to the dermatology outpatient department of SMHS Hospital (Associated teaching Hospital of Government Medical College Srinagar) over a period of one year, were recruited into the placebo-controlled, single-blinded study. An informed consent was obtained prior to enrolment in the study. The study group included patients with presence of more than ten warts, not on any concurrent therapy for warts since last two months; patients with immunodeficiency connective tissue disorder, pregnancy, lactation were excluded. The patients were examined for the type of warts and their location on the body. A baseline investigation of complete blood count with erythrocyte sedimentation rate was done in all patients. The serum zinc levels could not be estimated because of non availability of the facility.

The study group was randomized into two groups- Group A and Group B by systemic random sampling. Group A received oral zinc sulphate and group B received placebo. The participants in both groups were kept unaware of the type of treatment.

Fifty patients were given oral zinc sulphate at the dose of 5mg/kg/day in two divided doses for a total duration of six weeks. Another 50 patients were given an oral placebo for the same period. Patients were examined after every two weeks for signs and symptoms of regression of the warts.

The response was graded as:
· Complete response:- all warts disappeared
· Partial response:-50% resolution of warts disappeared
· No response:- none or few warts disappeared

Results (Fig. 1, 2) (Tabl. I-VI)

Of the 50 patients included in Group A, 41 patients (30 females and 11 males) completed the 6 weeks trial of zinc sulphate whereas in Group B only 33 patients (20 females and 13 males) completed the clinical trial.

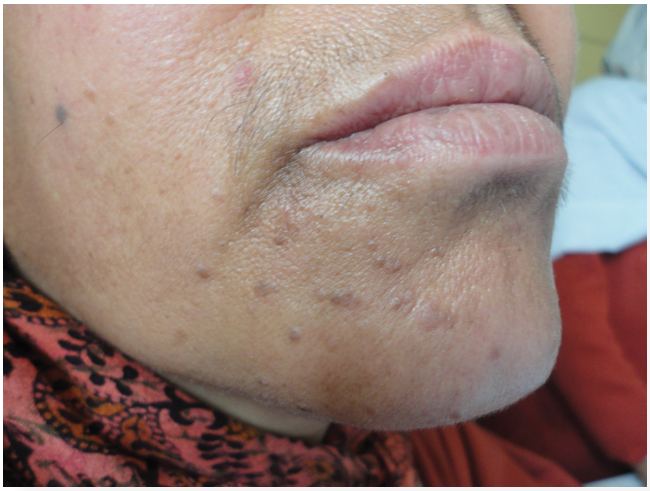

Figure 1. Verruca plana on the chin of a middle aged woman

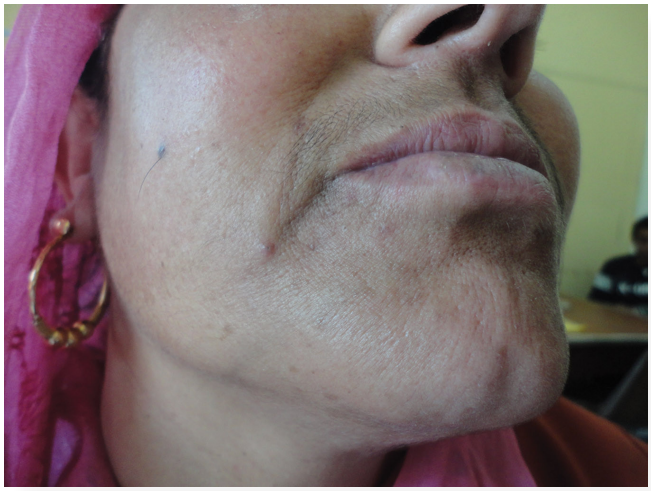

Figure 2. Almost complete clearance at 12 weeks

Clinical description of the study group

Type of warts	Group A(n=41)	Group B (n=33)	p-value
Plane	22 (53.66%)	10 (30.30%)	0.044
Common	20 (48.80%)	19 (57.60%)	0.451
Plantar	1 (2.40%)	4 (12.10%)	0.165
Filiform	2 (4.90%)	3 (9.10%)	0.651
Mucosal	0	0	

Table I. Type of warts in treatment and placebo group

Site	Group A	Group B	p-value
Hands	18 (43.90%)	15 (45.50%)	0.894
Face	26 (63.40)	17 (51.50%)	0.302
Feet	4 (9.80%)	8 (24.20%)	0.093
Perineum	0	0	

Table II. Location of warts in treatment and placebo group

Age (years)	Treatment group	Placebo
<20	11 (26.82%)	10 (30.30%)
20-40	26 (63.41%)	21 (63.63%)
>40	4 (9.75%)	2 (6.06%)

Table III. Comparison of different age intervals in treatment and placebo group
p-value=0.825 (non-significant)

Study	Age Range (years)	Mean ±S.D
Group A	13-44	32.15±8.10
Group B	13-38	30.28±7.15

Table IV. Comparison of age (years) in treatment and placebo group

p-value=0.328 (non-significant)

Duration (years)	Group A	Group B
≤2	30 (73.17%)	24 (72.72%)
>2	11 (26.82%)	9 (27.27%)

Table V. Duration of warts in treatment and placebo group

p-value=0.966 (non-significant)

Response	Group A	Group B
Complete response	25 (60.97%)	0
Partial response	6 (14.63%)	2 (6.45%)
No response	10 (24.39%)	29 (93.54%)

Table VI. Response rate after six weeks of treatment among the two study groups

p-value=0.000 (Highly significant)

The mean age of participants in the placebo group was 30.28 ± 7.15 years and in the treatment group was 32.15 ± 8.10 years (Tabl. IV). Patients who responded completely to oral zinc sulphate developed mild to moderate pruritus, erythema and an initial increase in the size of the warts within two to three weeks of starting the treatment. Mild transient epigastric pain was reported by 6% of patients but did not require cessation of treatment. A total of 26 patients (60.97%) showed complete resolution of the warts; 6 (14.6%) patients showed partial response; there was no response to treatment in 10 (24.3%) patients. In the placebo group there was partial response in 2 (6.45%) patients while 29 (93.5%) patients showed no response to placebo (Tabl. VI). The patients who responded completely to oral zinc sulphate were regularly followed up for a period of six months with no evidence of recurrence of the warts**.**

Discussion

Viral warts are an extremely common benign condition caused by infection of epidermal cells with the human papillomavirus (HPV), resulting in cell proliferation. A thickened warty papule on the skin or mucous membrane is the typical clinical presentation. The most common sites involved are the hands, feet and the face. Two large population based studies found prevalence rates of 0.84% and 12.9% respectively [4,5]. Prevalence rates are higher in children and young adults. Studies in school population have shown prevalence rates of 12% in 4-6 years old and 24% in 16-18 years old [6,7].

The current treatment for warts involves the physical destruction of infected cells which sometimes results in scarring. Common therapeutic modalities for viral warts include cryotherapy, keratolytics, topical immunotherapy with contact sensitizer, oral cimetidine, antimitotic agents, carbon dioxide laser, electrosurgery, photodynamic therapy, intralesional injection of antigens and topical immune response modifiers. None of these modalities is universally effective [8].

Zinc is an important element that is found in every cell in the body. More than 300 enzymes in the body need zinc in order to function properly. It is also essential for the proper functioning of the immune system. In zinc deficiency, the function of the macrophages and T cells is impaired with fifty percent reduction in leucocytes and 40-70% reduction in antibody-mediated and cell-mediated immunity [9-11]. The addition of zinc to a culture system results in polyclonal stimulation of lymphocytes [12]. Zinc has been previously used as an immunomodulator in a number of dermatological diseases such as erythema nodosum leprosum and dissecting cellulitis of scalp [13]. Al-Gurari FT et al. used oral zinc sulphate at a dosage of 10mg/kg for a total period of two months in the treatment of viral warts with a cure rate of 87% [14].

The present study was done to find out the efficacy of oral zinc sulphate at lower doses and for a shorter duration in order to minimize side effects and to improve compliance respectively. Of the patients who completed the six weeks therapeutic trial of oral zinc sulphate, 60.9% showed a complete response and 14.6% a partial response in comparison to partial response of 1.61% in the placebo group [p-value=0.000 (Highly significant)]. Resolution of warts occurred without any scarring but was associated with transient hypo as well as hyper pigmentation.

In a study by Stefani et al. adverse effects reported by the patients treated with zinc sulfate were nausea, vomiting and diarrhoea. These adverse effects were attenuated by dividing the total dose into three daily doses and taking the medication together with meals [15]. Only mild epigastric pain (6%) was observed in our patients which did not require interruption of treatment.

This could possibly be due to a lower dose of zinc sulphate used in our study.

This study confirms the role of oral zinc sulphate as a systemic treatment modality for viral warts with the advantage of being non-invasive, non scarring, and having the potential of preventing recurrences.

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DERMATOSCOPÍA: CONTRIBUCIÓN COMO MÉTODO PARA DEFINIR MÁRGENES QUIRÚRGICOS DE CARCINOMAS BASOCELULARES DE CARA, CUELLO Y TRONCO

DERMATOSCOPY: CONTRIBUTION AS A METHOD TO DEFINE SURGICAL MARGINS IN BASAL CELL CARCINOMAS OF THE FACE, NECK AND TRUNK

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Resumen
La escisión quirúrgica incompleta del Carcinoma Basocelular (CBC) es posible por lo que métodos preoperatorios de marcación de márgenes tumorales es importante.
Guías para el manejo de los CBC han sido establecidas, sin embargo la determinación de una medida más adecuada de los márgenes es deseable, tal y como está establecido para los melanomas.
La Dermatoscopía es un procedimiento simple, barato, no invasivo que fue inicialmente utilizado para la evaluación de lesiones pigmentarias. Debido a que la misma técnica ha sido usada exitosamente en la evaluación de otras lesiones, como el CBC, hemos utilizado esta técnica para determinar los márgenes preoperatorios en este tipo de tumores.
El objetivo de este estudio fue comparar la determinación preoperatoria de los márgenes apropiados en la resección de los CBC usando dermatoscopía versus evaluación clínica, lo cual nos permitiría mejorar los resultados quirúrgicos.

Abstract
The incomplete excision of basal cell carcinoma (BCC) is possible that's why presurgical marking methods of tumor margins are important.
Guides for the CBC handling have been established, however determining a better measure of the margins is desirable, as it is established for melanomas.
Dermoscopy is a simple, inexpensive, noninvasive method, which was initially used for the evaluation of pigmented lesions. Because the same technique has been used successfully in the evaluation of other injuries, as the CBC, we used this technique to determine preoperative margins in these tumors.
The aim of this study was to compare the preoperative determination of appropriate margins of BCC using dermatoscopy versus clinical assessment, which would allow us to improve surgical outcomes.

Palabras clave: Carcinoma Basocelular (CBC); márgenes quirúrgicos; dermatoscopía
Key words: basal cell carcinoma (BCC); surgical margins; dermatoscopy

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Introduction

El carcinoma basocelular (CBC) es el tumor epitelial maligno más frecuente en la piel, correspondiendo al 75% de los cánceres cutáneos no melanoma [1,2]. Se presenta especialmente en la raza blanca, observándose un continuo incremento de la incidencia del mismo en las últimas décadas, involucrando a pacientes cada vez más jóvenes [3].

La tasa de curación depende del tamaño de la lesión, del sub-tipo histológico, la localización anatómica y la conducta terapéutica [4,5].

Para elegir el tratamiento más apropiado, debe considerarse el tamaño del tumor, su ubicación, el tiempo de evolución del mismo y el tipo histológico que presenta.

Otros factores importantes a considerar, son la edad del paciente, patologías concomitantes y la calidad de la piel peri tumoral, así como también, la experiencia del médico tratante [1,6].
La extirpación quirúrgica del tumor es la terapia de primera elección, con altas tasas de efectividad, aunque en ocasiones es difícil determinar el límite real de la lesión debido a la extensión subclínica del tumor [7,8].
La dermatoscopía es una técnica no invasiva, de fácil aplicación, que inicialmente fue utilizada para lesiones pigmentarias de la piel y actualmente es utilizada para mejorar el diagnóstico clínico de CBC [9,10].

Objetivos

• Evaluar la utilidad de la dermatoscopía en la obtención de márgenes libres de tumor durante la marcación pre quirúrgica de lesiones con diagnóstico de CBC.
• Comparar la determinación de márgenes quirúrgicos por dermatoscopía con la determinación de los mismos, hecha por observación puramente clínica.

Material y Método

Fueron incluidos pacientes con diagnóstico clínico presuntivo de CBC localizados en cara, cuello y tronco, que consultaron al servicio de Dermatología del Hospital de Clínicas, FCM-UNA, entre los meses de marzo de 2011 a enero de 2012, de ambos sexos, y con edades comprendidas entre 18 a 90 años, y que dieron su consentimiento escrito para participar del estudio.
Todas las lesiones fueron examinadas clínicamente y por dermatoscopía.
Los participantes fueron divididos en dos grupos:
• **El grupo 1** consistía en aquellos pacientes con CBC extirpados quirúrgicamente y con diagnóstico confirmado por histopatología, cuyos márgenes fueron marcados pre quirúrgicamente por dermatoscopía, utilizando para ello un dermatoscopio portátil con polarización transversal fija (DERMLITE II MULTIESPECTRAL™), con lente de 10 aumentos y 32 LED.
• **El grupo 2** incluía a pacientes con CBC extirpados quirúrgicamente y con diagnóstico confirmado por histopatología, cuyos márgenes fueron marcados pre quirúrgicamente mediante una evaluación clínica.
En cada caso se realizó la marcación con lápiz demográfico delimitando el tumor del tejido sano, considerando tejido sano a la piel sin patrones dermatoscópicos compatibles con CBC o piel con textura normal al evaluar clínicamente.
La incisión quirúrgica se realizó en el borde externo de cada marcación. El margen profundo se delimitó en todos los casos en el tejido celular subcutáneo. Todas las muestras fueron enviadas para estudio histopatológico.
Los especímenes fueron analizados histológicamente. Los mismos fueron fijados en formol neutro tamponado al 10% y procesados de manera rutinaria en procesador automático de tejidos, previa disección macroscópica siguiendo las recomendaciones del Colegio Americano de Patología (CAP). Las secciones fueron teñidas con hematoxilina y eosina.
Se realizó el informe de los márgenes, si se hallaban comprometidos o libres de lesión tumoral en regiones laterales y profundas.
Se realizó luego una comparación de los resultados histopatológicos de los márgenes entre ambos grupos utilizando la prueba estadística del chi cuadrado.

Resultados

El estudio incluyó 81 lesiones en 64 pacientes, 33 eran mujeres y 31 pacientes eran hombres, entre 18 a 90 años (promedio 58.7 años) todos con confirmación histopatológica de CBC.
El grupo 1: 49 lesiones en 37 pacientes: mujeres 20, hombres 17; con edades comprendidas entre 18 y 84 años (promedio 59.10 años). Los patrones histopatológicos de los CBC fueron: 43 nodulares, 5 multicéntricos superficiales, 1 infiltrante.
El grupo 2: 32 lesiones en 27 pacientes: mujeres 13, hombres 14; con edades comprendidas entre 30 y 90 años (promedio 58.2 años). Los patrones histopatológicos de los CBC fueron: 28 nodulares, 2 multicéntricos superficiales, 1 esclerodermiforme y 1 infiltrante.
Las lesiones estaban localizadas en las siguientes áreas anatómicas: nariz 17, surco nasogeniano 7, frente 3, mejilla 16, tronco 12, región malar 14, cervical 4, región temporal 5, región preauricular 2, tal y como se muestra en la Figura 1.

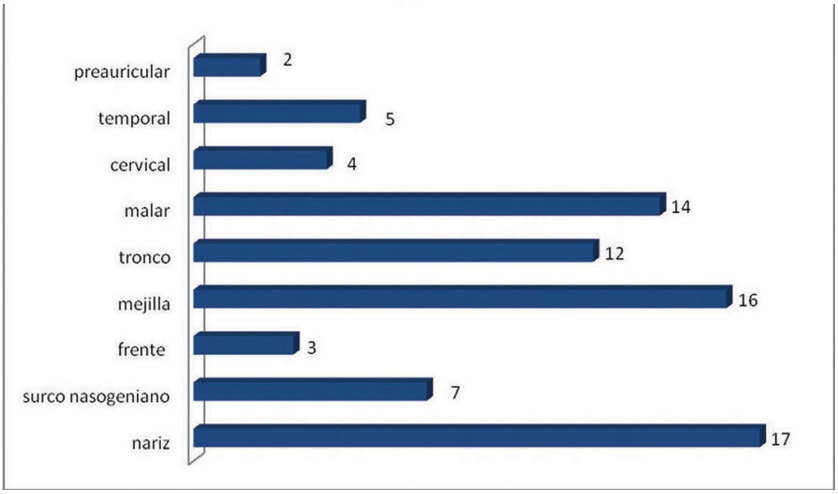

Figura I. Distribution according to location of the lesions. n: 81
Figure I. Distribución según localización de lesiones. n: 81

De las 81 lesiones, 7 dieron resultados histopatológicos de márgenes comprometidos.
Los patrones histopatológicos encontrados se muestran en la Figura 2.
• En el grupo 1, de 49 lesiones extirpadas, 1 de ellas presentó márgenes laterales comprometidos, correspondiendo a un CBC multicéntrico superficial localizado en tronco.
• En el grupo 2, de 32 lesiones extirpadas, 6 de ellas presentaron márgenes comprometidos, siendo el patrón histopatológico nodular el predominante en 5 lesiones y el patrón esclerodermiforme en 1 lesión.
Comparando ambos grupos se encontró una diferencia estadísticamente significativa (p< 0,01) en los resultados (Tabl. I).

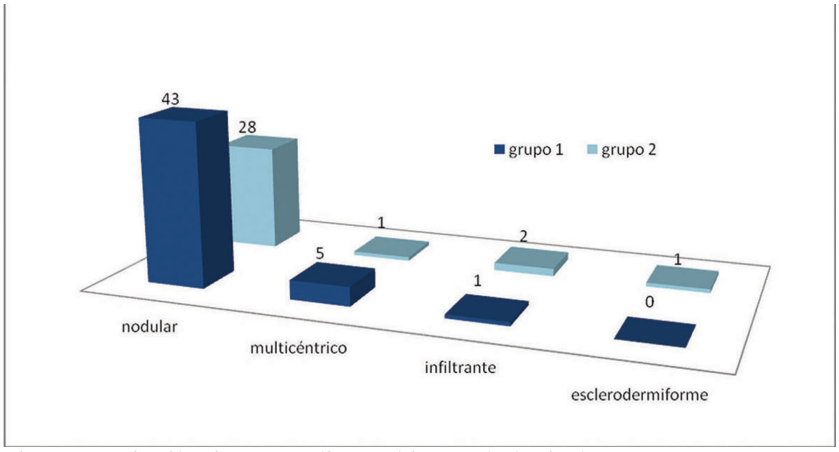

Figura II. Distribution according to histopathological pattern. n: 81
Figure II. Distribución según patrón histopatológico. n: 81

Patrón histopatológico	Grupo 1: Evaluación por dermatoscopio		Grupo 2: Evaluación clinica	
	Lesiones	Margen positivo	Lesiones	Margen positivo
Nodular	43	0	28	5
Multicéntrico superficial	5	1	2	0
Esclerodermiforme	43	0	1	1
Infiltrate	43	0	1	0

Tabla I. Comparación de los márgenes de resección quirúrgicos del CBC por dermatoscopía y clínica
Table I. Comparison of surgical resection marginsof BCC by dermoscopy and clinical assessment

Discusión

El CBC es un tumor maligno de piel de crecimiento lento, localmente invasivo. Incompletamente escisionado, especialmente cuando está localizado en la cara, es más fácil su recurrencia. Por esta razón, la determinación adecuada de los márgenes de CBC es crucial en la evaluación preoperatoria del paciente [9,11].
Para el tratamiento de los CBC existen varias alternativas terapéuticas como criocirugía, terapia fotodinámica y cirugía convencional, siendo esta última la más utilizada [10,12,13].
La importancia de obtener márgenes libres de tumor es evitar las recidivas. Se reportan tasas de 4 a 7% de márgenes comprometidos tras cirugía convencional en unidades de cirugía británicas y 6% en dos estudios de Australia [10,12].
Aunque con la cirugía de Mohs se observan tasas de recidivas menores, ésta no es utilizada en todos los centros, ya sea por costo o por no disponer de la infraestructura, como en el nuestro.
En estudios retrospectivos previos, CBC con escisión incompleta van de un rango de 4% a 16.6% con la cirugía tradicional. Debido a que en muchos centros dermatológicos usan la cirugía tradicional debido a ser más simple, barata y más corta con respecto a la cirugía de Mohs, el consenso principal sigue siendo como obtener márgenes pre quirúrgicos adecuados del tumor [9,14,15].
Es necesario encontrar técnicas que permitan realizar marcaciones seguras de los márgenes. Se han realizado dos trabajos con excelentes resultados demostrando la utilidad de la dermatoscopía en la marcación de márgenes pre quirúrgicos de CBC [4,16,17].
En una serie estudiada sobre CBC, se encontró que el 38% de las mujeres y el 25% de los hombres menores de 35 años, con diagnóstico de CBC, tenían un tipo histológico de comportamiento agresivo, en oposición a los mayores de 60 años con tipos histológicos más circunscritos, concluyendo entonces, que los individuos más jóvenes, son propensos a desarrollar CBC con patrones de crecimiento más agresivos [18].
Diferentes métodos han sido propuestos, pero la dermatoscopía es, en nuestra opinión con los resultados obtenidos en nuestro estudio, el método más simple, más reproducible, seguro, barato y útil para obtener menores tasas de márgenes comprometidos [19,20].

Conclusiones

1. La dermatoscopia es un método de fácil aplicación que demostró ser más efectivo en relación a la observación clínica aislada en la asignación de los márgenes quirúrgicos en cirugías convencionales de CBC.
2. Este hecho es relevante y estadísticamente significativo, y con la utilización de este método se evitarían numerosas recidivas tumorales, sobre todo en paciente jóvenes, donde muchos estudios demuestran que suelen tener tipos histológicos de comportamiento agresivo, en oposición a los mayores de 60 años con tipos histológicos más circunscritos.

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A STUDY ON THE SURGICAL TREATMENT OF INGROWING TOE NAIL WITH NAIL EXCISION WITH CHEMICAL MATRICECTOMY VERSUS NAIL EXCISION ALONE

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Abstract
An in growing toenail develops when the proper fit of the nail plate in the lateral nail groove is altered. We selected 30 patients of ingrowing toe nail for the study. The patients were divided into two groups of 15 patients each. In group I patients, nail avulsion with chemical matrictectomy with 88%phenol was done. In group II only nail avulsion was done. In group I patients the surgical success rate was 98% and in group II, the surgical success rate was 86.6%. No patient complained about the cosmetic appearance of toe nail after the operation.

Key words: ingrowing; toe nail; matricectomy; excision; phenol

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Introduction

Ingrowing toenail is a common problem affecting mainly adolescents and young adults, with a male predominance of 3:1 [1,2]. The disorder generally occurs in big toes. It is painful, often chronic and affects work and social activities. Most patients initially complain of pain later drainage, infection and difficulty in walking occur [3].

Several factors contribute to the occurrence and worsening of ingrowing toenails:

incorrect cutting of nails; hyperhidrosis; poor foot hygiene; excess external pressure, including poor stance and gait, ill-fitting footwear and excess trauma; excess internal pressure caused by over curvature of the nail plate; arthritis;subungual neoplasm a; skeletal abnormalities and inflammatory processes; associated systemic diseases, including diabetes; obesity; and nail changes in the elderly [4,5]. Congenital misalignment is another cause, especially in infracts.

Aims

The aim of our study was to compare the treatment of ingrowing toe nail with nail excision with chemical matricectomy versus nail excision alone.

Material and Methods

We selected 30 patients of ingrowing toe nail for the study. The patients were divided into two groups of 15 patients each. In group I patients, nail avulsion with chemical matrictectomy with 88% phenol was done. In group II only nail avulsion was done. Prior approval of the hospital ethical committee was taken and informed consent was taken from all the patients before starting the study. The routine investigations including complete haemogram anf fasting blood sugar were done in all the patients. Each patient was reviewed weekly until full wound healing was achieved and the postoperative healing period ranged from two to four weeks. The patients were f ollowed for 18 months to see for any recurrences and complications. Patients with vascular disease were excluded. If infection was present before the operation, it was treated initially by topical and oral antibiotics and daily warm soaks with dilute povidine iodine (Betadine) solution. Surgical treatment was instituted as soon as the nail and skin fold became dry.

The toe was firstly cleaned with povidine iodine solution. Anesthesia was obtained with a standard digital block employing 2% xylocaine without epinephrine. The toe was exsanquinated by rubber operating glove tourniquet (the cut end of a rubber finger being rolled back towards the big toe base). A dry field is important for the optimum cauterizing effect of phenolization. A 2-3 mm lateral nail segment was cut free along the length of the lateral fold and removed with a straight hemostat, taking care to ensure nail removal lower than the basal lateral matrix.

Hypertrophied granulation tissue was curetted. The phenol was applied with partially stripped cotton applicators, saturated with 88% liquefied phenol (distilled water was used as solvent), by vigorously massaging it into the matrix area. Care was taken to prevent spillage of phenol onto the surrounding skin. The cotton applicator was changed twice during a total application time of 3 min. After completion of this procedure, the area was lavaged with 70% isopropyl alcohol to neutralize the residual phenol. The tourniquet was removed and the wound was dressed with an antibiotic ointment, followed by longitudinal and circumferential gauze wrapping. The dressing was then secured with adhesive tape. After the operation pain killer was given for pain control. The patient was allowed to walk immediately after the operation and directed to elevate the affected foot whenever possible. Most patients returned to normal ambulation and activity as early as one day after the operation. It was not necessary to admit the patient to the hospital. The dressing was removed after 48 h in the clinic. Following this, antiseptic soaks with dilute povidine iodine solution for 15 min once a day, followed by the application of an antibiotic ointment were started and continued usually for a period of approximately 2-4 weeks, until the drainage ceased. Patients were reviewed in the clinic weekly until full wound healing was achieved. All the patients were followed for a period of 18 months. Recurrence was defined as evidence of ingrowth of the nail edge or spicule formation. A total of 42 phenol ablations were performed on 30 patients with stage II and III disease. Each patient was reviewed weekly until full wound healing was achieved and afterwards, to assess the long- term ecacy of the treatment, they were followed up for a mean period of 18 months. The healing period after the operation ranged from 2 to 4 weeks.

Results (Tabl. 1-3)

The data was tabulated and results were analysed.

Sr No	Groups	Postoperative Complications		
		Postoperative necrosis	Nail spicules	Superficial chemical burns
1	I	1 (6.6%)	2 (13.3%)	1 (6,6%)
2	II	1 (6.6%)	1 (6.6%)	-

Table I. Postoperative complications

Sr No	Groups	Recurrence	
1	Group I	1	6.6%
2	Group II	3	20%

Table II. Recurrence in both the groups

Sr No	Groups	Success
1	Group I	98%
2	Group II	86.6%

Table III. Success rate after treatment

Discussion

In our study the mean age of the patient was 28 yrs. Males outnumbered females and male: female ratio was 2:1. A total of 42 nail ablations were done in 30 patients. The healing period ranged from 2-4 weeks. In group I, recurrence was seen in one patient, where as in Group II patients, recurrences were seen in 3 patients. These patients were treated again using phenol matricectomy. In group I patients the surgical success rate was 98% and in group II, the surgical success rate was 86.6%. No patient complained about the cosmetic appearance of toe nail after the operation. Regarding the post operative complications, post operative necrosis was seen in 6.6% patients, in both the groups, nail spicules were seen in 13.3% patients in group I and 6.6% patients in group II. Superficial chemical burns were seen only in one patient in phenol ablation group (Group I).

There are various stages of ingrowing toe nail. In stage 1, there is erythema, slight edema and pain, particularly with pressure. In stage 2 (Fig. 1), there is an increase in the severity of symptoms, the wound becomes locally infected and starts to drain. In stage 3, all of signs and symptoms are amplified and there is associated formation of granulation tissue and lateral wall hypertrophy. There are many options for the treatment of ingrowing toenail, ranging from simple conservative approaches to relatively extensive surgical procedures requiring considerable surgical experience [6-8]. Conservative approaches include soaking the foot in warm water; use of topical or oral antibiotics; silver nitrate cauterization of the granulation t issue proper nail-trimming technique; elevation of the corner of the nail with a small wisp of gauze or a plastic gutter; improvement of foot hygiene; and clipping a notch into the centre and requires patience from both doctor and patient. Because is time-consuming, demands a high level of patient cooperation third of thick nails [9-12]. This form of management is time-consuming, demands a high level of patient cooperation and requires patience from both doctor and patient. Because of the intensive support necessary, it is not a cheap method of treatment. However, the treatment of stage I disease is conservative management. Stage 2 disease can be managed conservatively but recurrences are frequently seen. Stage 2 and 3 ingrowing toenails are best treated surgically [13-16]. A chemo surgical technique for permanent matricectomy is ideal for the ingrowing toe nail (Fig. 2). Long-term follow-up is needed because symptoms may recur 1–2 years after the operation.

Segmental matrix cauterization with liquefied phenol has been shown to be highly successful in permanently destroying the lateral matrix [17,18]. Phenol (C_6H_5OH) is a colorless crystal derived from coal tar. Liquefied phenol (carbolic acid) has antibacterial, anesthetic and in its concentrated form, escharotic properties. For matricectomies, liquefied phenol is used at a saturated concentration of 88%.

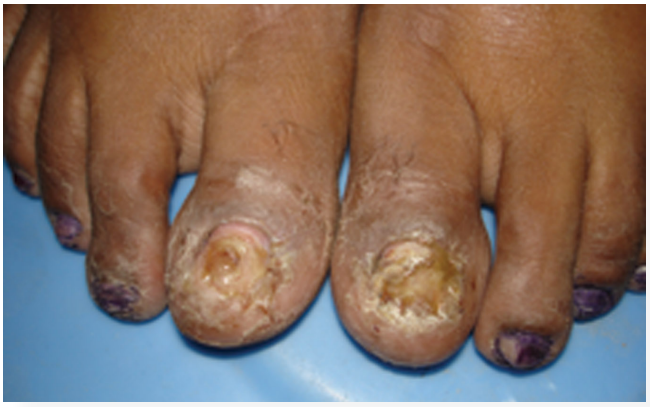

Figure 1. Stage II ingrowing toe nail

The acid mediates its injury via denaturation o f the matrix as well as any other soft tissue proteins with which it comes into contact [19].

We believe that the results of the studies with long- term follow-up periods are more important for evaluating the success of this procedure as recurrence may occur even 1 or 2 years later. Surgical techniques are an important factor in the success of this method. To avoid recurrence after phenol cauterization sufficient width of nail must be removed (a full quarter). Care must be taken not to leave nail spicules in the sulcus or under the eponychium. Phenol must be applied using sterile cotton-tipped applicators by vigorously massaging it in to the matrix area for a sufficient time (application for < 3 min results in high recurrence rates) [20,21] and absolute hemostasis must be obtained as blood partly neutralizes the cauterizing effect of phenol. Newer methods of segmental nail bed ablation, including electrodessication, sodium hydroxide treatment, negative galvanic current therapy and carbon dioxide laser treatment need further evaluation. In all the patients, the procedure was done on the hallux. The heling period ranged from 2-4 weeks.

Conclusions

The technique is easy to perform and is associated with little morbidity and has a success rate of 98%. Today, phenol cauterization is the treatment of choice for most podiatrists and physicians. We conclude that phenol cauterization is an excellent surgical method for the treatment of ingrowing toe nail because of its simplicity, low morbidity and high success rate. We conclude that phenol cauterization for the treatment of ingrowing toe nail is excellent because of its simplicity, low morbidity and high success rate. It can easily be done as an out patient procedure. Phenol cauterization is the treatment of choice in our institution.Long term follow up is needed because symptoms may recur 1-2 years after the operation.

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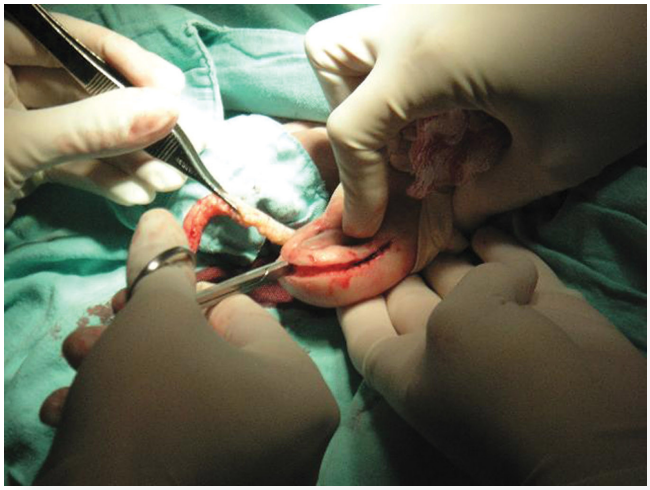

Figure 2. Intraoperative picture of in growing toe nail removal

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THE SPARING PHENOMENON. A CASE SERIES OF THE INVERSE KOEBNER AND RELATED PHENOMENA

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Abstract
Introduction: The sparing of the involvement of a cutaneous disease in a site that has been previously subjected to a skin disease, congenital nevus or physical insult has been reported in literature by various names, including the inverse Koebner phenomenon.
Objectives: To review cases that we have seen and to document the reported cases and unify them with a single term, the "Sparing phenomenon".
Materials and Methods: We report four new examples of this phenomenon and performed a PubMed literature search on related search terms and summarized the reported cases.
Results: We report four new cases of this phenomenon. An additional 16 reported cases of the sparing phenomenon were identified. Herpes zoster was the most reported inflammatory disease site followed by; skin irradiation was the commonly documented physical insult. Drug reactions and psoriasis were the most common diseases that spare these sites. The time gap between first and second insult was highly variable.
Conclusions: We proposed the term "Sparing phenomenon" to describe the skin disease sparing on an area which was previously subjected to skin disease or physical insult. By introducing this new term to the dermatology glossary, it would be easy to collect and analysis to understand the immuno-pathophsiology of this skin reaction described in various names.

Key words: phenomenon; koebner phenomenon; inverse koebner phenomenon

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Introduction

In 1876 the German physician Heinrich Koebner described a characteristic phenomenon in a psoriasis patient who had been bitten by a horse and developed new psoriatic lesion at the site of trauma [1]. Subsequently this skin reaction, which has been documented in various other skin diseases, was named as the "Koebner phenomenon", "Isomorphic response" or "Isomorphic phenomenon".

In contrast to this well-known observation in which skin disease is produced in the site of trauma, infrequently disease may be spared in the site of trauma. Cochran and colleagues in 1981 first described a macular papular drug reaction which spared the sites of previous X-irradiation in a patient with had been treated for Wilm's tumor [2]. Bernhard et al later introduced the term "Koebner non reaction" or "Isomorphic nonresponse" to refer the absence of a drug reaction the at site of the previous x-irradiation [3].

A variety of other related observations have also been reported. The Renbok Phenomenon or "Inverse Koebner Phenomenon" was described as normal hair growth in psoriatic patches noted in patient with co-occurrence of psoriasis and alopecia areata [4-7].

In 1995 Wolf et al introduced "Isotopic nonresponse" to describe the absence of an eruption at the site of another, unrelated, and already healed skin disease in their article of "Isotopic response" [8].

We propose to unify these disparate observations and terms under the rubric, "The Sparing phenomenon". In brief, the sparing phenomenon refers to absence of manifesting a particular skin disease on an area previously affected by another skin disease and physical or chemical insult (e.g., U.V or X-Irradiation).

Methods

We present 4 cases that fit the criteria of Sparing phenomenon seen in our clinics from 2003 to 2006. A comprehensive PubMed literature review was performed. Search terms included "Koebner nonreaction", "Inverse Koebnerization", "Isomorphic nonreaction", and „Renbock phenomenon".

The reference sections of articles obtained were also searched for relevant articles.

Results

Case Series:

The demographics and presentation of four are included in Table I which summarizes the clinical presentation, the diseases involved, the time interval between two diseases and the affected site of our patient's diseases. Three cases related to previous herpes zoster site and one case on an area previously affected by contact dermatitis were spared by cutaneous t- cell lymphoma (CTCL), Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS-TEN) and rubber slipper dermatitis (Fig. 1, 2).

Literature Review and Summary:

All the cases reported under the specific name such as "Koebner non-reaction", "Inverse Koebner phenomenon", "Isomorphic non response" and "Renbok phenomenon" are presented in Table II. Failure of a drug eruption to occur in a site that had undergone irradiation was the first documented sparing reaction in the literature [2]. Since then, non-existence of various forms of drug reactions in an areas previously subjected to an insult has been reported. Ampicillin and clotrimaxazole-trimethopim were the most noted culprits [2,3,9].

An area subjected to herpes zoster was the often resistant site for the many diseases including leprosy and CTCL [10-13]. Psoriasis sparing an area of alopecia areata and previously irradiated site was found in three occasions and non occurrence of drug reaction and CTCL in an area exposed to ultra violet light (swimming suit sparing) were documented in two instances [3-5,14,15]. There were two occasions granulomatous skin diseases sparing previous scar tissues [16,17].

There did not seem to be any association between first and second disease, the time gap between two insults were few weeks to 20 years. The most commonly involved area was face and scalp followed by chest and abdomen. Interestingly the left side of the body presented with the "Sparing phenomenon" more often right, unless previous injury was irradiation.

Patient number	Age & Sex	First disease	Interval between first and second disease	Second disease	Site involved (Sparingsite)
1	84 Female	Herpes zoster	4 months	Cutaneous t cell lymphoma	Left lower abdomen
2	57 Male	Contactdermatitis	3 months	Phyto-Photodermatitis	Feet
3	62Male	Herpes zoster	3 months	Cutaneous t cell lymphoma	Left upper arm
4	53 Female	Herpes zoster	2 months	SJS-TEN	Left face

Table I. "Sparing phenomenon" cases seen at our hospitals

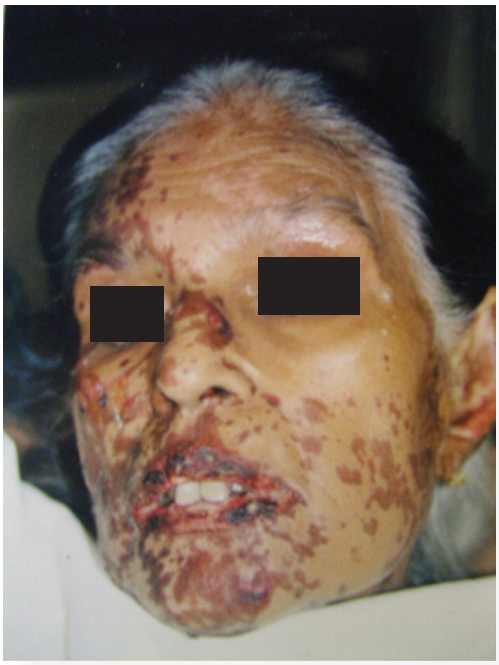

Figure 1. SJS/TEN sparing previous Herpes Zoster area

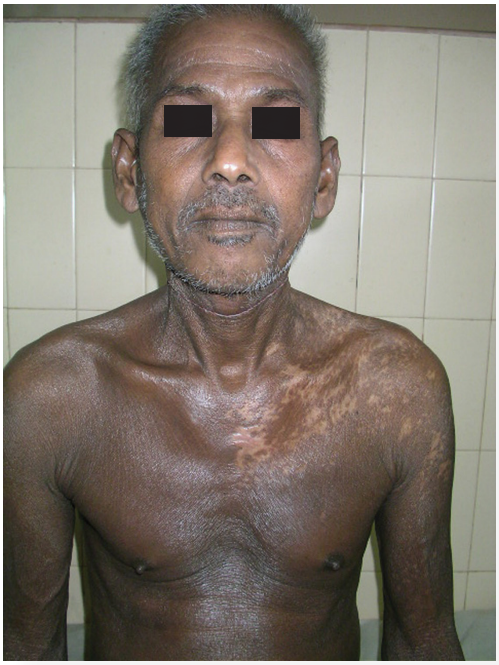

Figure 2. CTCL sparing previous Herpes Zoster area

Case No.	Age and Sex	Previousdisease/ Congenital nevus/ Physical insult	Interval	Second disease	Site involved (Sparing site)
1.Cochran et al 1981	12 Female	Radiation for Wilm's tumor	6 years	Drug reaction	Right side abdomen/ back
2.Bernhard et al 1982	26 Female	Radiation for liver secondary of Adenocarcinoma of unknown origin	Few days	Drug reaction	Right side abdomen
3.Bernhard et al 1982	-Female	Ultraviolet light exposure	Few days	Drug reaction	Uncovered area of bathing suit
4.Pavitran 1987	Middle age Female	Tuberculoid leprosy	-	Drug reaction	Face
5.Katayama et al 1990	63 Male	Herpes zoster	4 weeks	Contact dermatitis	Left side abdomen
6.Nasca et al 1994	53 Female	Radiation for Adenocarcinoma of right lung	4 weeks	Steroid acne	Right scapula
7.Huilgol et al 1995	74 Female	Vaccination scar	-	Generalized Granuloma annulare (+Multiple myeloma/Leukaemia)	Left upper arm
8.Ozkaya--Bayazit et al 1999	72 male	Burn scar	-	Annular elastocytic giant cell granuloma	Left forearm
9.Grilli et al 2002	72 Female	Ultraviolet light exposure	-	Mycosis fungoides	Uncovered areas of summing suit
10.Rosina et al 2003	18 Female	Alopecia areata	-	Psoriasis	Scalp
11,12 Jain R et al 1993	Two patients	Herpes zoster	-	Borderline leprosy	-
13.Twersky et al 2004	58 Male	Herpes zoster	3 weeks	Cutaneous t cell lymphoma	Left side abdomen
14.Nikkels et al 2004	32 Female	Herpes zoster	Few days	Contact dermatitis	Left side abdomen
15.Martin et al 2006	53 Female	Radiation for intraductal carcinoma of breast	-	Psoriasis	Right breast
16.Cardio et al 2007	39 Female	Alopecia areata (Ophiasis)	20 years	Psoriasis	Scalp

Table II. Reported cases related to "Sparing Phenomenon"

Discussion

Two out of four of our hospital's cases of sparing phenomenon that to our knowledge have not been described in the previous literature such as S.J.S -T.E.N sparing the area initially subjected to herpes zoster and strap marks of rubber slipper dermatitis are unaffected by phyto-photodermatitis. Three patients who spared the previous herpes zoster affected area also showed left side predilection.

The term Renbok phenomenon or "Inverse Koebner phenomenon" (Happle et al in 1991) applies to normal hair growth in psoriatic patches noted in patient with both psoriasis and alopecia areata. In 1995 Wolf et al introduced "Isotopic nonresponse" to describe the absence of an eruption at the site of another, unrelated, and already healed skin disease in their article of "Isotopic response".

Because of very little evidence available in the literature as well as similarities between most reported cases of this unique entity we decided to broaden the definition of Sparing Phenomenon, rather than narrowing primary insult only to a skin disease.

When we have a better understanding about the Immuno-Patho-Physiology of this skin reaction, it would be easy to classify homogenous cases together for academic purposes in future.

Possible hypotheses for pathophysiology of this phenomenon are:

1. The structural changes (cellular, vascular, neural) caused by first insult prevent the occurrence of second disease at the same site.
2. Changes of the microenvironment (immune and cytokines pathways) in the affected site caused by first injury leads to resistant to subsequent disease at the same site.
3. Combination of both reasons.

The exact pathophysiology of the skin disease sparing the previous skin insult has not been identified clearly, but several possible mechanisms which were described in the literature can be classified under the following headings.

Cellular Alterations:

Langerhans cells play an important major role in allergic contact dermatitis, drug reactions and epidermotrophism in CTCL. Irradiation has been reported to induce loss of Langerhans cell and other immunological changes in the subjected skin [18]. Reduction of Langerhans cell number and it's activity in herpes zoster lesion and their peripheral area has recently been documented by Katayama et al and Nikkles et al. [10,12,13]. This abnormality in Langerhans cell number could influenced drug reaction, allergic contact dermatitis and CTCL didn't occur in the area affected by irradiation and herpes zoster.

Vascular Component Alterations:

The effect of ionizing radiation on cutaneous blood vessles that resulted in a reduced activity of blood vessles wall, a diminished vascular bed and reduced carriage of constitute agents to the affected site, and there by none existing of drug rash over the radiation portal was explained by Cochran and Bernhart et al. [2].

Cytokines Alterations:

Radiation treatment induced cytokines imbalance prevent the over expression of Type 1 pro-inflammatory cytokines which are commonly considered to be responsible for initiation, maintenance and recurrences of psoriasis were explained by Martin et al. [14]. Psoriasis lesion induced microenvironment which is rich in TNF-alfa is not a favorable environment for inflammation seen in alopecia areata was postulated by Hoflman, Happle and several others [7].

Role of Intercellular Adhesion Molecule 1(ICAM-1):

Interaction of the ligand/receptor pair Lymphocyte Function Antigen 1 (LFA-1)1 and ICAM-1 initiate and control the cell-cell interactions of leucocytes with parenchymal cells in all stages of immune reaction.

It has been shown that ultraviolet radiation leads to suppression of ICAM-1 on the surface of cultured human keratinocytes at 24 hours [19]. Thus prolonged repeated continuous ultraviolet radiation might have ability to suppress the ICAM-1 for long period of time. Keratinocytes of patients with lepromatous leprosy lesions were found to lacking in the ICAM-1 expression and the down regulation of ICAM-1 on herpes zoster virus infected keratinocytes are well documented entities in recent literature [13,20,21].

Hence the reduction or inhibition of ICAM-1 induction on keratinocytes by ultraviolet radiation, lepromatous leprosy or herpes zoster virus probably disables the keratinocytes to function as accessory antigen presenting cells and inhibits its role in LFA-1/ICAM-1 Mediated T cell response, and there by prevent the appearance of drug reaction and CTCL on previous skin insult.

Conclusion

By defining new term, "Sparing phenomenon" for already existing entity in different names, we believe that it is easy to locate and collect similar cases under a one key ward, to better understanding the Immuno-patho-physiology of this unique skin reaction as well as use of this mechanism as a therapeutic intervention for most serious skin disease like CTCL and SJS-TEN.

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EVALUATION OF THE EFFECT OF INJECTION OF DUTASTERIDE AS MESOTHERAPEUTIC TOOL IN TREATMENT OF ANDROGENETIC ALOPECIA IN MALES

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Abstract
Introduction: Androgenetic alopecia (AGA) is hereditary and androgen dependent, progressive thinning of the scalp hair that follows a defined pattern.
Aim ot the work: is to evaluate the efficacy and safety of mesotherapy using dutasteride in treatment of androgenetic alopecia in males.
Materials and Methods: Ninety male patients were randomly assigned into three groups; group A containing 30 patients who received pure dutasteride, group B of another 30 patients who received dutasteride containing solution and group C of the remaining 30 patients who received saline. Each group was given nine mesotherapy sessions. Assessment was done using trichogram, independent observer assessment of photographs and patients self assessment together with evaluation of possible systemic absorption using semenogram and serum dihydrotestosterone (DHT).
Result: Statistical analysis of the thrichogram results, the effect on semenogram and the serum level of dihydrotestosterone.showed that dutastride containing solution was the best.
Conclusion: Mesotherapy using dutasteride is a good option for treatment of male pattern hair loss; resulting in reduction or cessation of hair loss and promotion of new hair growth.

Key words: methotherapy; dutastride; male; androgenetic alopecia; trichogram

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Introduction

Pattern hair loss (PHL), or androgenetic alopecia (AGA) or common baldness, is the most common cause of hair loss in men [1-3]. It is distinctive due to the pattern of progression of the scalp hair loss.

Dutasteride shares important characteristics with finasteride. While finasteride inhibits type II 5-α reductase, dutasteride inhibits both type I and II isoenzymes [4-6]. However, there is evidence that dutasteride is three times as potent as finasteride at inhibiting type II 5-α reductase and more than 100 times as potent at inhibiting type I enzyme. This suggests enhanced efficacy over the existing finasteride, so scalp and serum levels of DHT are more affected i.e. dutasteride decreases serum DHT by more than 90% [7], while finasteride decreases serum DHT by 70% [8,9].

The half-life of dutasteride is 4 weeks, compared with 6 to 8 hours for finasteride. This suggests that the effects on sexual function are longer lasting (several months) and more difficult to reverse [5]. Men being treated with dutasteride should not donate blood until they have been off of the medication for at least 6 months [5,10].

● Side effects:

1) Sexual side effects including impotence (occurring in 69/817 on finasteride 5mg, vs. 55/813 on dutasteride), decreased libido (in 46/817 on finasteride vs. 39/813 on dutasteride), ejaculation disorder (in 12/817 on finasteride vs. 10/813 on dutasteride). There were no statistically significant differences between dutasteride-and finasteride-treated patients but there were statistically significant differences between dutasteride and placebo group initially [11]. These adverse events are characterized as either mild or moderate in severity and often resolve with continuation of the medication [12].

2) Effects on semen:

In a double-blind, placebo controlled trial of men given dutasteride 0.5 mg daily or placebo; there were significant decrease from baseline in sperm count. Semen volume was decreased by a corresponding amount. There was also significant reduction in sperm motility. However, no significant changes were observed in sperm morphology [13].

Aim of the work:

The aim of the work is to evaluate the efficacy and safety of mesotherapy using dutasteride in treatment of androgenetic alopecia in males.

Patients:

• This study was carried out on 90 male patients complaining of pattern hair loss. They were recruited from the outpatient clinic of Dermatology, Andrology and Venereology Department, Alexandria Main University hospital.

Inclusion criteria:

• Age: 18-55 years.
• Free from clinically significant condition (Diabetes, history of stroke, history of any thromboembolic phenomenon or cancer).
• Not seeking pregnancy.
• Baseline semen analysis within normal range.
• Baseline serum DHT level within normal range

Exclusion criteria:

• Patients using the following medications: inhibitors of CYP3A4 (verapamil) or drugs with antiandrogen effect (finasteride) or hair growth promotors (minoxidil) in the last six months .
• Patients suffering from ejaculatory or erectile dysfunction.

Methods

Informed consent was taken from every patient and the study was approved by Alexandria university research ethics committee.

• Patients were randomly assigned into three groups:
• Group A: 30 patients who received mesotherapy injections of pure dutasteride. (Dutasteride 0.005% and polysorbate 80 in sodium chloride, Dallas, Texas).
• Group B: 30 patients who received mesotherapy injections of dutasteride containing solution. (Dutasteride 5mg, dexapanthenol 500 mg, biotin 20 mg, pyridoxine 200 mg per vial of 10 ml i.e. 0.05% dutasteride, purchased from Mesodermal. USA).
• Group C: 30 patients who received mesotherapy injections of 0.9% saline.(control).

All patients were subjected to the following:

• 1-Full history taking
• 2-Clinical examination
• 3-Routine laboratory Investigations (CBC, FBS, LFT, RFT...)
• 4-Semen analysis before starting therapy and one week after last session
• 5-Serum DHT before starting therapy and one week after last session
• 6-Trichogram before starting therapy and one week after last session
• 7-Photographs of the scalp

Schedule:

• Once per week for four weeks.(week 0,1,2,3)
• Once every two weeks for one month.(week 5,7)
• Once per month for three months. (week 11,15,19)

Results

This study was carried out on 90 male patients complaining of pattern hair loss. Patients' age ranged from 18-55 years.

Duration of AGA ranged from 6 months up to 5 years. Family history was positive in 85% of cases.

Comparison between the effects of dutasteride, dutasteride containing solution and saline on trichogram:

The results were more evident and good in group B:

By Wilcoxon Signed Rank test, there is statistically significant increase between anagen hair percent before treatment and after treatment (Z=-2.803, P=0.005*) but there is no statistically significant difference between catagen hair percent before treatment and after treatment. Also, there is statistically significant decrease between telogen hair percent before treatment and after treatment (Z=-2.803, P=0.005*). Regarding dystrophic hair percent, there is no statistically significant difference between before treatment and after treatment (Z=-0.561, P=0.575). There is statistically significant increase between A/T ratio before treatment [median=1.5, range (1-4)] and after treatment (Z=-2.805, P=0.005*). Finally, there is statistically significant increase between mean hair shaft diameter before treatment and after treatment (Z=-2.803, P=0.005*).

Comparison between the effects of dutasteride, dutasteride containing solution and saline on semenogram (one week after last session):

By Kruskal Wallis test, there is no statistically significant difference in semen volume, sperm concentration, sperm motility, sperm morphology between group A group Band group C ($X^2_{KRUSKAL\ WALLIS}$=0.366, P=0.833).

Serum dihydrotestosterone (DHT) (normal range: from 250 up to 990 pg/ml).

Comparison between the effects of dutasteride, dutasteride containing solution and saline on DHT (one week after last session):

There was unexpected variation in results of serum DHT in the form of increase in serum DHT in group A while a decline in serum DHT in group B and group C could be explained by the wide normal range for serum DHT and the diurnal variations.

Patient self assessment (Tabl I).

By Monte Carlo significance test, there is no statistically significant difference in patient self assessment in the three groups (Monte Carlo P=0.089).

Independent observer assessment (Tabl II) (Fig. 1, 2)

By Monte Carlo significance test, there is statistically significant difference between the three groups. It is revealed that in group A, the majority (70%) perceived as no change (score=0), 20% as mild improvement (score=1), 10% as moderate improvement (score=2), while group B the majority were perceived as improved mildly or moderately (40% had score=1, 40% had score=2) and 20% perceived as no change (score=0) but neither groups were perceived to have been worse (score=-1). Finally, in group C 30% was perceived as worsened, 40% as no change and 30% as mild improvement. (P=.026*). These results had a similar trend to the results of trichogram being some improvement in groups A and B, more in B, as compared to control group.

	Dutasterise (group A)		Dutasteride containing solution (group B)		Saline (group C)		Sig.
	No.	%	No.	%	No.	%	
Not satisfied	12	40	3	10	18	60	0.089
Satisfied	18	60	27	90	12	40	

Table I. Patient self assessment

* Significant level < 0.05

	Dutasterise (group A)		Dutasteride containing solution (group B)		Saline (group C)		Sig.
	No.	%	No.	%	No.	%	
-1	0	0	0	0	9	30	0.026*
0	21	70	6	20	12	40	
1	6	20	12	40	9	30	
2	3	10	12	40	0	0	

Table II. Independent observer assessment

* Significant level < 0.05

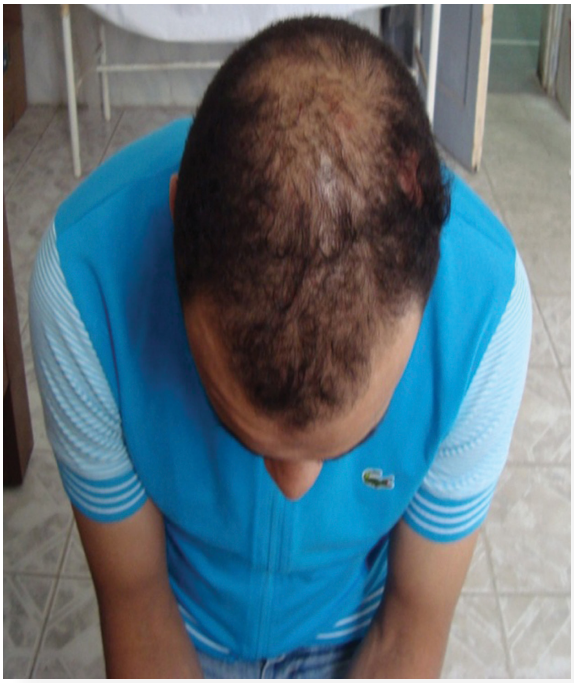

Figure 1. Group A. Before starting treatment (week 0).

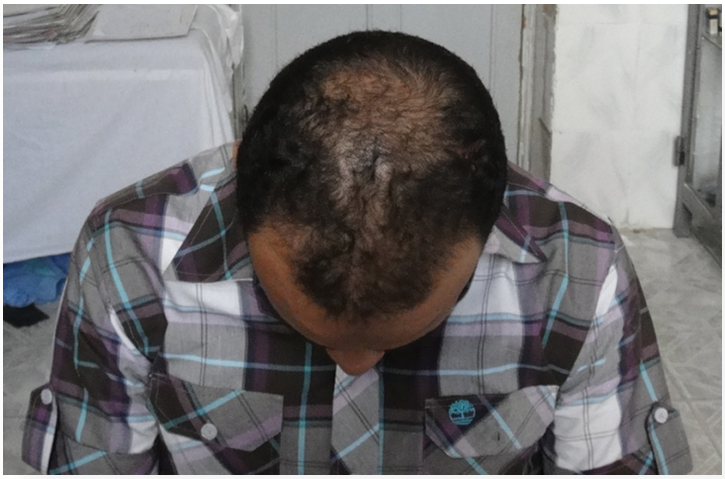

Figure 2. After receiving nine sessions (week 20)

Discussion

Androgenetic alopecia (AGA) or pattern hair loss (PHL) is the most common type of hair loss in men [1-3].

Options for management in men include doing nothing and accepting the cosmetic outcome, pharmacotherapy, hair transplantation, and cosmetic aids. Hair loss is progressive and does not improve or reverse without treatment [14]. Systemic 5α-reductase inhibitors e.g. finasteride and dutasteride arrest progression of androgenetic alopecia in over 90% of men and partially reverse it in over 65% [3].

Few studies have been conducted on dutasteride for the treatment of MPHL (male pattern hair loss) [12]. Hesitancy about the widespread use of dutasteride in the treatment of MPHL results from its potential side effects on erectile, ejaculatory functions (several months) and fertility together with its long half life (4 weeks) [5]. The possibility of using dutasteride locally would minimize these systemic side effects [15].

The control group was included to establish the hypothesized role of trauma and the psychic element of therapy.

Demographic data of the present study revealed that patients were around the same age (median for gp A=29.5 years, gp B=30 years, gp C= 28.5 years), duration of alopecia (median for gp A=1.5 year, gp B=4 years, gp C=4 years) and grade of alopecia, also, there was no significant difference regarding family history. There was no correlation between age, duration or grade of alopecia and the degree of improvement of hair loss. However, it was noted that positive family history was associated with better improvement of alopecia (anagen hair percent and mean hair shaft diameter), though correlation was not statistically significant.

In Abdallah M et al. [15], which is to the best of our knowledge, the only study conducted evaluating mesotherapy injection of dutasteride in treatment of MPHL, there was no significant difference between the two studied groups with respect to age, stage and duration of baldness. Meanwhile, there was no correlation between age of patients and stage of baldness with the scored improvement but there was a reversed correlation between duration of baldness with the scored improvement.

In the present study, analysis of results of trichogram revealed statistically significant increase in anagen hair percent in group B patients. While in group A; the increase was statistically insignificant. Regarding the control group C; there was statistically insignificant decrease in anagen hair percent.

Meanwhile, there was statistically significant decrease in telogen hair percent in group B patients. While group A; showed statistically insignificant decrease. Group C; there was statistically significant increase in telogen hair percent. Reduction in telogen hair count by treatment is expected in responsive cases due to the resulting prolongation of anagen phase so fewer hairs are in telogen phase rather than direct effect of therapy since its duration is not altered in MPHL [16].

Concerning anagen/telogen (A/T) ratio, there was statistically significant increase in group B. While in group A; the increase was mild and not statistically significant. Regarding group C, there was an expected statistically significant decrease in A/T ratio.

In the present study, group A and B showed statistically significant increase in mean hair shaft diameter. While group C showed mild statistically insignificant increase in mean hair shaft diameter, this goes with the alleged role of trauma of mesotherapy injection in improvement of AGA. This was also noted in the insignificant decrease in anagen hair percent in the group C, which possibly means that trauma slowed down the progression of hair loss.

Theoretically dutasteride would be expected to be more effective than finasteride for treating patients with MPHL [12]. This was detected in a randomized placebo controlled study in which the efficacy and safety of oral dutasteride at different doses (0.05, 0.1, 0.5, 2.5 mg) versus oral finasteride (5mg) in the treatment of MPHL was investigated by Oslen et al. [12].Patients were evaluated at 12 and 24 weeks. At 24 weeks, dutasteride 0.1 or 0.5 mg daily were comparable to finasteride 5mg daily and dutasteride 2.5mg was superior to finasteride in stimulating hair growth and suppressing scalp and serum DHT.

From the present results, it could be presumed that improvement was partly due to modification of hair cycle dynamics and partly due to increasing the diameter of the existing hair.

Based on the results of trichogram coming in favour of dutasteride containing solution, it might be suggested that hair growth promoters in the preparation are having a synergistic role with dutasteride or the difference in concentration of the active ingredient being higher in dutasteride containg solution.

Stough D. [14] compared the efficacy of dutasteride (0.5 mg/day) vs. placebo in the treatment of male pattern hair loss in 17 pairs of identical twin males with androgenetic alopecia over 1 year period and found that dutasteride significantly reduces hair loss progression in men with male pattern hair loss.

Eun HC et al. [18] conducted a study on 153 men who were randomized to receive 0.5 mg of dutasteride or placebo daily for 6 months. Mean change of hair counts from baseline to 6 months after treatment start was an increase of 12.2/cm^2 in dutasteride group and 4.7/cm^2 in placebo group and this difference was statistically significant. The improvement noticed in the placebo group was explained by a seasonal factor.

Previous studies confirmed the efficacy of oral dutasteride in treatment of MPHL [14,18] that was also detected using mesotherapy injection of dutasteride. The debate here is it a comparable efficacy or lower efficacy of mesotherapy vs. oral route that could be accepted if poses less incidence of side effects. One must mention that in our study, inspite of the statistically significant improvement noted in the trichogram of patients in the actively treated groups (A and B), this improvement was not so evident clinically.

Concerning patients self assessment there was no statistically significant difference between the three groups regarding satisfaction due to cessation of hair loss and the noticed improvement (60% in group A, 90% in group B and 40% in group C were satisfied) and, moreover, their satisfaction could not be correlated to trichogram results. Even, the majority of patients including those who were not satisfied asked for more sessions which explain the psychological aspect of therapy. In contrast, Abdallah M et al. [15] revealed the active group was significantly more satisfied with treatment than the placebo group.

Independent observer assessment revealed statistically significant difference favoring the actively treated groups than the control group that was scored as mild-moderate improvement.

In an attempt to evaluate the possibility of systemic absorption and the resulting side effects, changes in semenogram were statistically insignificant but it must be mentioned that there was a decline in semen volume in group A, a decline in sperm concentration in group B, and a decline in sperm motility in group A and B. Meanwhile, sperm morphology showed no statistically significant difference between the three groups.

When looking at these results, one can notice that a degree of systemic absorption took place and did affect spermatogenesis although the results were insignificant but there is a trend of decline in actively treated groups compared to the control group concerning semen volume, sperm concentration and motility.

Although the decline was in the normal range, two cases (27 and 40 years old) in group B showed a decline in sperm concentration from 29 million/ml to 7 million/ml and a corresponding decline in sperm motility from A+B=65% to 28% and a concentration from 30 million/ml to 10 million/ml and motility from 60% to 40%, respectively. By repeating the semenogram 3 months later values recovered to almost the pretreatment baseline.

Such serious data detected in the present study, should be investigated on a larger scale and in a dose-dependent manner but until establishment of these data certain precautions should be taken regarding regimen adjustment.

Moreover, dermatologists should be aware of the total dose injected during mesotherapy. In the present study, patients received 1.5-2 ml per session (equivalent to 0.075-0.1 mg for group A and 0.75-1 mg for group B) for 9 sessions i.e. a total of 13.5 -18 ml of mesotharpy injections, given that the concentration of dutasteride in pure solution (gp A) is 0.05 mg/ml and in dutastreide containing solution (gp B) is 0.5 mg/ml, then the cumulative dose of dutatseride for gp A is 0.675-0.9mg and for gp B is 6.75-9mg. Taking in consideration the long half life of dutasteride [5] and the possible effect on spermatogenesis.

When compared with systemic dutasteride therapy, results were similar to a study conducted with Amory JK et al. [13] on 99 healthy men randomly assigned to receive 0.5 mg dutasteride or 5 mg finasteride or placebo once daily for one year and evaluated for semen parameters and serum hormones (DHT and T). The study revealed statistically significant decline from baseline in total sperm count, semen volume, and sperm motility but not sperm morphology in both treatment groups as compared to the placebo that were recovered 24 weeks after drug discontinuation. Also, 5 AR inhibitors significantly suppress serum DHT and transiently increase serum Testosterone. That study also declared the need for further investigations to establish the exact site and mechanism of action underlying the effect of 5AR inhibition on spermatogenesis.

Oslen et al. [12] found that scalp and serum dihydrotestosterone levels significantly decreased, and testosterone levels significantly increased, in a dose-dependent fashion with oral dutasteride tharpy, which returned to baseline levels 12 weeks after termination of therapy for 0.05 mg and 0.1 mg groups.

The question elaborated whether the extent of systemic absorption following mesotherpay is equal to or less than following oral administration of dutasteride given that the scalp is highly vascular.

In our study, results of serum DHT were contradictory and not reliable since there were statistically significant increase in group A but statistically insignificant decline in gp B and C. This could be attributed to the wide normal range of DHT (250-990pg/ml) and its diurnal variation, therefore it is better to be assessed together with serum T and scalp DHT. However, it is unknown to what extent DHT contributes to spermatogenesis. Men with 5α reductase type 2 deficiency have markedly impaired spergmatogenesis but they also have undescended testes which could contribute to the defect in sperm production. [17].

In addition, none of our patients complained of decreased libido, erectile or ejaculatory dysfunction as well as in the previously mentioned mesotherapy study [15]. When compared with oral dutaseride used in a study carried by Andriole GL and Kirby R [11] there was a modestly elevated incidence of impotence, decreased libido, ejaculation disorders, and gynaecomastia in the group who received dutasteride 0.5mg/day and that was statistically significant as compared to placebo. But Eun HE et al. [18] revealed in a recent study that no significant difference was observed between the two studied groups (group received 0.5 mg/d dutasteride and group received placebo) in terms of sexual function. A question to be raised in the context of such findings whether sexual function can be affected by oral dutasteride or systemic absorption of dutasteride during mesotherapy.

Conclusion

1. Mesotherapy using dutasteride is a good option for treatment of MPHL resulting in reduction or cessation of hair loss and promotion of new hair growth.
2. The proposed mechanism of action of dutasteride is partly due to modification of hair cycle dynamics and partly through increasing hair shaft diameter of the existing hairs.
3. The role of trauma of injection in the outcome of mesotherapy is mild.
4. The psychological impact of mesotherapy on the patients undertaking it is considerable and remarkably guides their satisfaction.
5. Systemic absorption of dutasteride following mesotherapy with its deleterious effect on spermatogenesis is possible especially with unlimited injections.
6. Effect on sexual function by dutasteride mesotherapy is questionable.
7. Mesotherapy using dutasteride is not recommended in patients seeking pregnancy, patients with borderline or abnormal semenogram and patients with ejaculatory or erectile dysfunctuion.
8. Further research to establish the exact changes in hair quality and quantity by dutasteride as mesotherapy on larger number of patients.

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TOWARD AN APPROACH FOR CUTANEOUS LEISHMANIA TREATMENT

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Abstract
Introduction: Most drugs being used for cutaneous leishmania treatment are still non well effective, extremely expensive, risky with side effects, more invasive and relapses still occur. The purpose of the study is to achieve more understanding of cutaneous leishmania disease and through that to try an other form of treating substance that can provide better results with less damages to the tissues.
Methods: Seven patients infected with cutaneous leishmania were chosen for DAB-1 application. Clinical as well as microscopic study and follow-up with documenting photos for the lesions, indicating the starting point for the cases before treatment initiation, and the disease development after DAB-1 application was accomplished.
Results: Before treatment, the lesions size was between 1.8-7 cm. Cases were inflamed and ulcerated. After 8 days of treatment, inflammation shrank. After 16 days, the lesions and the ulcers decreased into almost half their size. 24 days post treatment, inflammation began disappearing and epithelial islands continued to grow inside the ulcers filling a considerable part of them. By the end of day 32, ulcers were covered with a continuous layer of epithelium, and heal is achieved after two to three months of treatment.
Conclusion: The study proved that DAB-1 is capable of healing leishmania in 6-8 weeks after application and is compared favorably to the other traditionally used drugs. DAB-1 could be a breakthrough in cutaneous leishmania treatment.

Key words: cutaneous Leishmaniasis; Leishmaniasis; epithelium regeneration

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Introduction

Many studies have indicated that the drug of choice for treating cutaneous leishmania is Sodium antimony gluconate (Pentostam) [1]. It is applied intramuscularly in case of multiple lesions. In a single lesion, it is usually injected into the ulcer margin [2]. The healing process of the lesion usually takes between 14 to 16 weeks and in some cases even more. The heal is usually completed with a scar formation. If present in a delicate location like in the face, the lesion can cause a bad defect and deformation for the patient. Although it is the drug of choice, Pentostam induces side effects [3]. Even with its application, Pentostam cannot induce a complete heal with a perfect epithelization. The final result in the lesion in-position is a permanent scar formation. Follow-up studies in southwestern Europe, using pentavalent antimonials, show a positive response in 83% of cases. However, 52% of patients relapse within a period of one month to three years [4].
Other drugs being used for cutaneous leishmania treatment are paromomycin, Amphotericin B, Fluconazole and Pentamidine, but relapses still occur with a risk of side effect and the drugs remain extremely expensive.
DAB-1 on the other hand, is a topical ointment, which is applied topically to the ulcer lesion. It is produced from natural substances and obviously, has no side effects.
The purpose of this study is to measure the DAB-1 effect on cutaneous leishmania by tracking both the clinical and the cytomorphologic effect, and checking the healing process over a period of two to three months.

Material and Methods

Seven patients infected with cutaneous leishmania and presented with clear lesions were chosen for DAB-1 application. Before applying the ointment, couple of microscopic slides were prepared from each lesion stained with Wright stain and tested for all the suspected pathological features including the parasite form found in the intra or extra cellular space. Clinical as well as microscopic photos for the lesions beginning with the starting point for the cases before treatment initiation were taken for documentation.
Each lesion was cleaned with normal saline and dried with gauze. The ointment is added to a sterile gauze and applied directly over the lesion. The ointment dressing was changed once every day for 24 consecutive days. After that and for the next 24 days, the ointment dressing was changed once every three days. Every three days couple of photos for each lesion were taken to mark the clinical signs of the healing process.

At 8, 16, 24, 32, 45, 60 days interval, other couple microscopic smears were prepared from each lesion, stained with Wright stain and tested to identify the cytomophologic development of the cure process. Documentary microscopic photos were taken for the cytomorphologic features for more detailed study and analysis.

Results (Tabl. I-X)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Lesion size	7 cm	3 cm	5 cm	3 cm	1.7 cm	4 cm	1.8 cm
Inflamed	+++	++	+++	+/-	+/-	++	-
Ulcerated	+++	-	+++	++	-	++	-

Table I. The clinical features present for each lesion before the ointment application

Note: (+++) Highly inflamed, or ulcer> 2cm in diameter. (++) Moderately inflamed or ulcer 1-2 cm in diameter. (+/-) indicates mild inflammation. (-) No inflammation or nodular type with no ulcer

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Lesion size	6 cm	2 cm	4 cm	2 cm	1.3 cm	3 cm	1.5 cm
Inflamed	++	+	++	+/-	+/-	+	-
Ulcerated	+++	-	++	++	-	++	-

Table II. The clinical features development for each lesion after 8 days of the ointment application

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Lesion size	4 cm	2 cm	1.5 cm	2 cm	1 cm	2 cm	1 cm
Inflamed	+	+	+	-	-	+	-
Ulcerated	++	-	++	+	-	++	-

Table III. The clinical features development for each lesion after 16 days of the ointment application

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Lesion size	3 cm	1 cm	1 cm	1 cm	0.8 cm	1 cm	0.5 cm
Inflamed	+	-	+	-	-	+	-
Ulcerated	+	-	+	-	-	+	-

Table IV. The clinical features development for each lesion after 24 days of the ointment application

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Lesion size	3 cm	1 cm	1 cm	1 cm	0.6 cm	1 cm	0 cm
Inflamed	-	-	-	-	-	-	-
Ulcerated	-	-	-	-	-	-	-

Table V. The clinical features development for each lesion after 32 days of the ointment application

Cytomorphologic figures appearance	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Phagocytes with intracellular amastigotes	-	++	++	-	++	+	-
Extracellular amastigotes	-	++	+++	-	+	++	-
Promastigotes	+++	+	+	++	++	++	++
Lymphocytes	++	++	+++	++	+	++	+
Neutrophils	++	-	+	+	-	++	-

Table VI. The cytomorphologic features present in the slides for each lesion before the ointment application

Note: (+++) > 5 cells or leishmania configurations seen per HPF. (++) 3-5 cells or leishmania configurations seen per HPF. (+) 1-3 cells or configurations in average seen per HPF. (-) No cells or leishmania elements seen

Cytomorphologic figures appearance	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Phagocytes with intracellular amastigotes	-	-	-	-	+	-	-
Extracellular amastigotes	-	-	-	-	+	-	-
Promastigotes	+++	++	+++	+	+++	++	+
Lymphocytes	+	++	+	+	+	+	+
Neutrophils	++	++	+	++	+	++	+

Table VII. The cytomorphologic features present in the slides for each lesion after 8 days of the ointment application

Cytomorphologic figures appearance	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Phagocytes with intracellular amastigotes	-	-	-	-	-	-	-
Extracellular amastigotes	-	-	-	-	-	-	-
Promastigotes	+	+	+	+	++	+	-
Lymphocytes	+	-	+	+	+	+	-
Neutrophils	+++	++	++	+	++	+	-

Table VIII. The cytomorphologic features present in the slides for each lesion after 16 days of the ointment application

Cytomorphologic figures appearance	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Phagocytes with intracellular amastigotes	-	-	-	-	-	-	-
Extracellular amastigotes	-	-	-	-	-	-	-
Promastigotes	+	+	+	-	+	+	-
Lymphocytes	+	+	+	-	+	+	-
Neutrophils	+	+	-	-	+	+	-

Table IX. The cytomorphologic features present in the slides for each lesion after 24 days of the ointment application

Cytomorphologic figures appearance	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Phagocytes with intracellular amastigotes	-	-	-	-	-	-	-
Extracellular amastigotes	-	-	-	-	-	-	-
Promastigotes	+	+	-	-	-	+	-
Lymphocytes	+	-	+	-	-	-	-
Neutrophils	+	+	-	-	-	+	-

Table X. The cytomorphologic features present in the slides for each lesion after 32 days of the ointment application

Tables I-V show the clinical features present for each lesion before and after DAB-1 application on time bases.

It is clear from table 1 that the size of the lesions is between 1.8 and 7cm when cases were referred. All the cases except one were clinically inflamed. Four of the cases were ulcerated and the other three were not ulcerated (Fig. 1a, 1b).

After 8 days of treatment with DAB-1, the first sign of healing process to show in table II is the decrease in the size of the lesion characterized by the inflammatory reaction in a range between 16-33%. The inflammation also showed a clear reduction in its virulence while a decrease in the ulcer size appeared in only one case with the ulcer decreased about 0.4 cm in its size (Fig. 2a).

After 16 days of treatment and according to Table III each lesion was reduced in size to about half.

The inflammation virulence was further decreased in almost every case and the inflammation disappeared from two additional cases. All ulcers were reduced in size to less than 2 cm in diameter.

Isolated islands of epithelial cells started to show up inside the ulcers (Fig. 3a).

By the end of day 24 of treatment, as seen in Table IV all the cases were reduced to less than half their original size. The ulcers and the inflammation totally disappeared from 4 of the cases. Mild inflammation and small ulcers with less than 1 cm in diameter were seen in the three left cases. The epithelial islands continued to grow inside the ulcers filling a considerable part of them (Fig. 4a).

By the end of day 32 of treatment, looking back to Table V, a relief in the inflammatory reaction was noticed and the ulcers disappeared from all the studied cases. Ulcers were covered with a continuous layer of epithelium. The size of the lesions continued to be the same as was the case in day 24 but with the disappearance of the clinical disease signs (Fig. 5a). On day 45, the lesion area continued in process toward a normal looking skin (Fig. 6). And on day 60, the lesion looked almost close to normal with a remote inflammation (Fig. 7). After 75 days of treatment initiation, the skin started to appear normal (Fig. 8), and after three months completion, the skin in the area turned into normal looking (Fig. 9).

Tables VI-X show the cytomorphologic features present for each lesion before and after DAB-1 application. In Table VI we notice the cytomorphologic features before DAB-1 application. In four of the cases, the intracellular and extracellular amastigotes were present together with the infected macrophages in the smear. Promastigote- like figures and lymphocytes appeared in all the seven studied cases at different concentration, indicating the chronic nature of the disease. Neutrophils were present in 4/7 cases (Fig. 1c).

After 8 days of treatment as appears in Table VII, a disappearance of the amastigotes and their infected macrophages from the smears appeared in 6/7 cases, while the promastigote like forms continued to appear in all the cases. Under the microscope, a decrease in lymphocytes count and elevation in the neutrophils count appeared in each case. The presence of such increase number of neutrophils is a sign of the disease conversion from a chronic to an acute inflammatory reaction (Fig. 2b, 2c).

By day 16 as shown in Table VIII, there was a total disappearance of the infected macrophages together with the amastigotes from all the cases. Neutrophils continued to appear with a little less count in all cases but one, where a complete disappearance of all the disease microscopic cytomorphology was noticed. Promastigote like forms appeared in 6/7 of the cases but in less concentration. Lymphocytes were present in less count. Larger area of immigrating epithelium was noticed (Fig. 3b, 3c).

In day 24 (Tabl. VIII): A less concentration of all the microscopic disease figures including promastigote like forms, Lymphocytes and neutrophils was noticed with a total disappearance of all the microscopic signs in two of the cases. More epithelial cells were present (Fig. 4b, 4c).

In day 32 very few promastigote like forms were still present in three of the cases and few lymphocytes and neutrophils were seen in the smear. Overall, other smears appeared almost like normal blood smears with few migrating e pithelium (Fig. 5b, 5c).

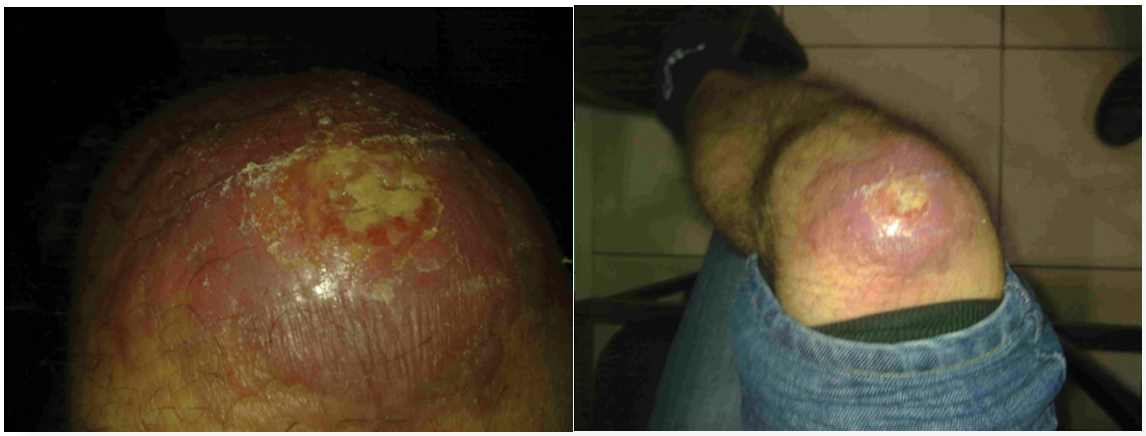

Figure 1a. A closer shot. 1b. A distant -shot. The infected lesion before DAB-1 application

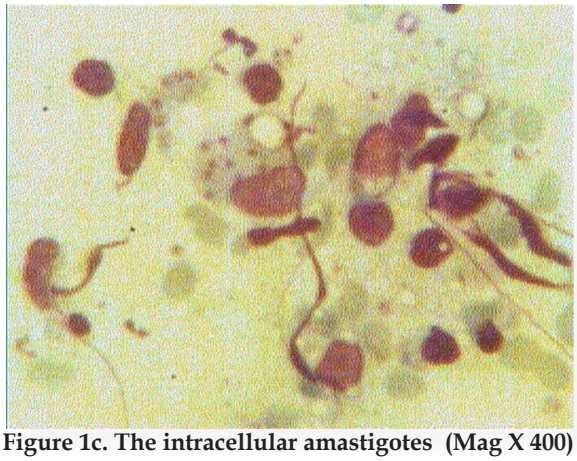

Figure 1c. The intracellular amastigotes (Mag X 400)

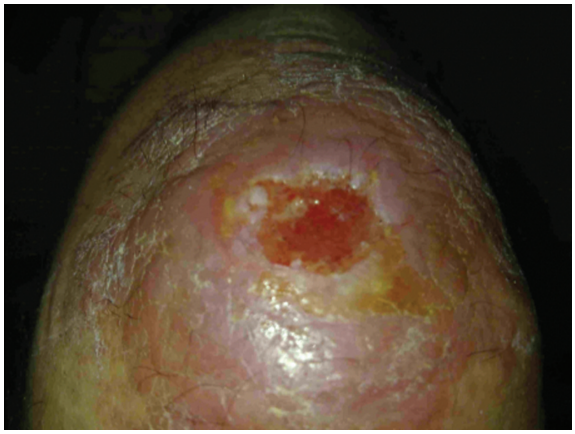

Figure 2a. A closer shot. The infected lesion 8 days after DAB-1 application

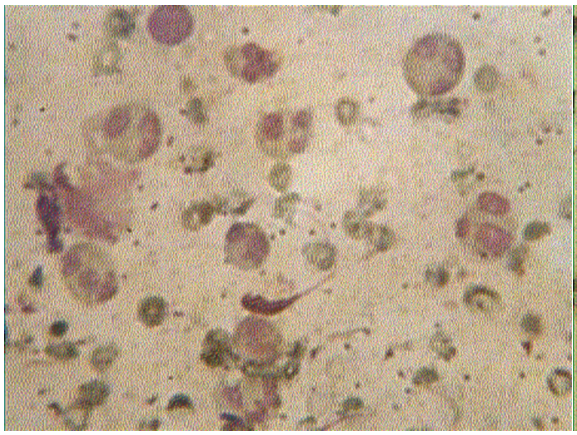

Figure 2b. Note the promastigote and the neutrophils. (Mag. X 400)

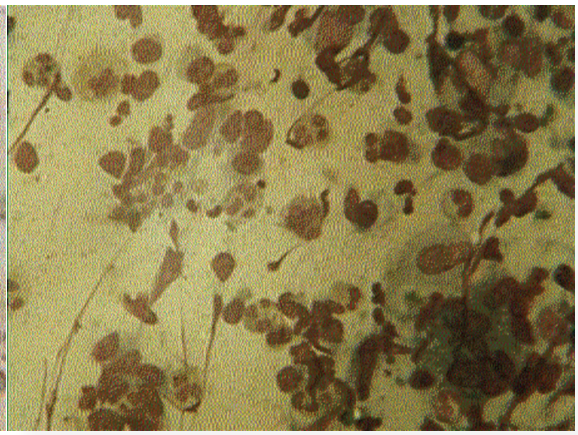

Figure 2c. Note the promastigotes with the cellular elements. Including neutrophils and lymphocytes (Mag. X 200)

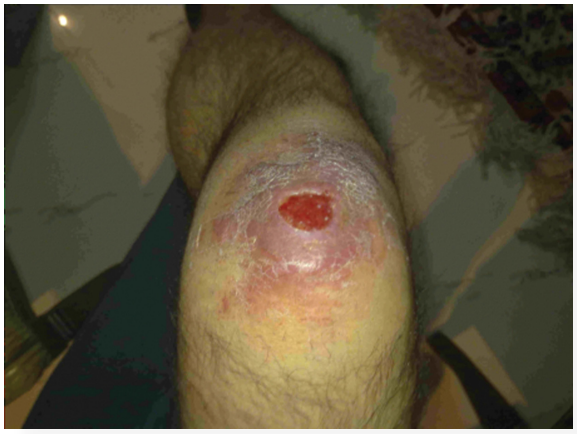

Figure 3a. A distant -shot. The innfected lesion 16 days after DAB-1 application

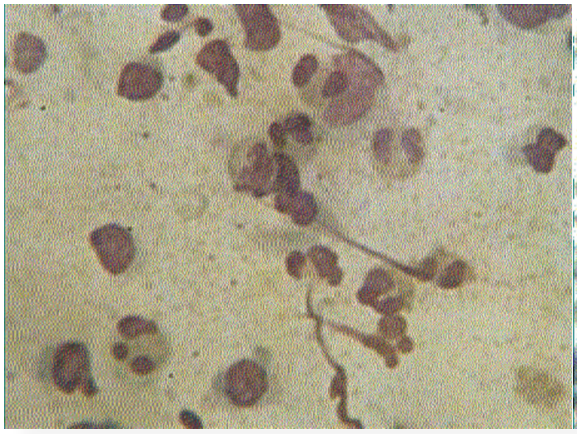

Figure 3b. Note the elevated neutrophils number (Mag. X 400)

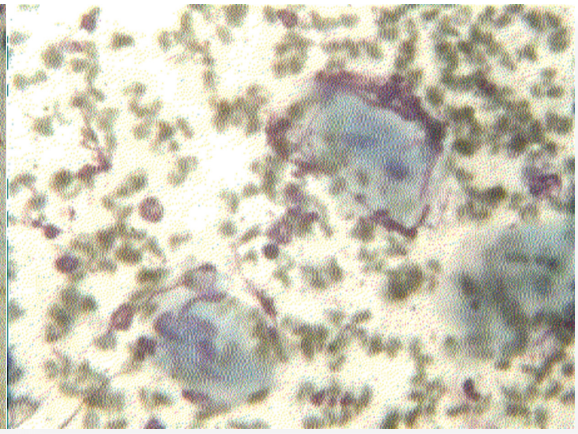

Figure 3c. Note the epithelial cells invading the tissue. (Mag. X 100)

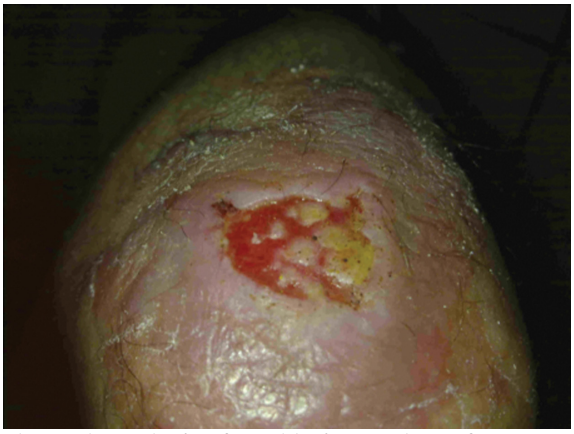

Figure 4a. A closer shot. The innfected lesion 24 days after DAB-1 application

Figure 4b. Note the promastigote appearance. (Mag. X 400)

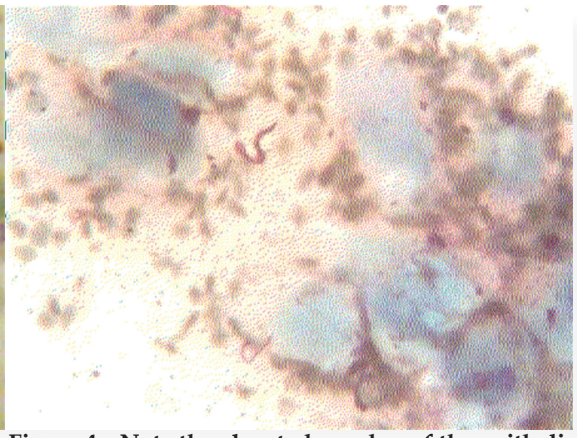

Figure 4c. Note the elevated number of the epithelial cells. (Mag. X 100)

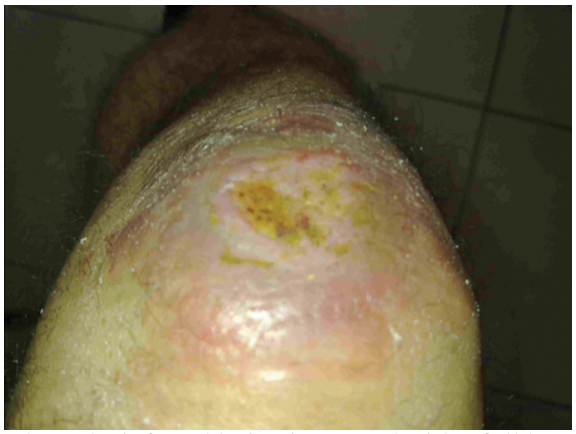

Figure 5a. A closer shot. The infected lesion is covered with a full layer of epithelium. The innfected lesion 32 days after DAB-1 application

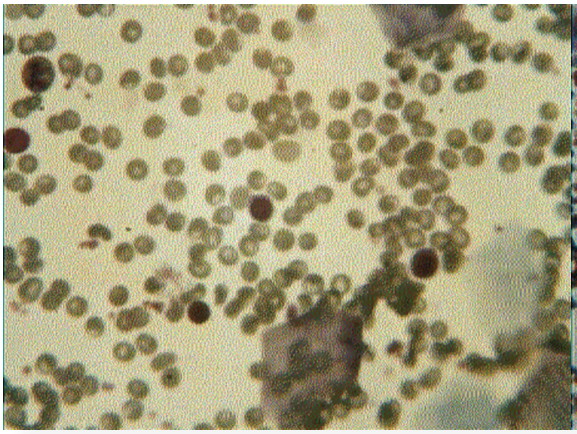

Figure 5b. Note the normal looking blood smear. (Mag. X 200)

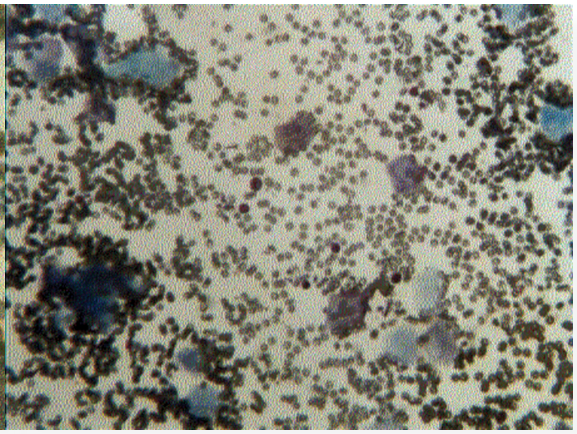

Figure 5c. See the epithelial cells within normal smear. (Mag. X 100)

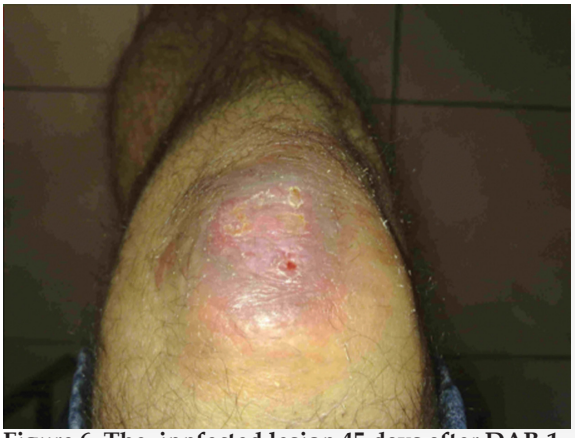

Figure 6. The innfected lesion 45 days after DAB-1 application

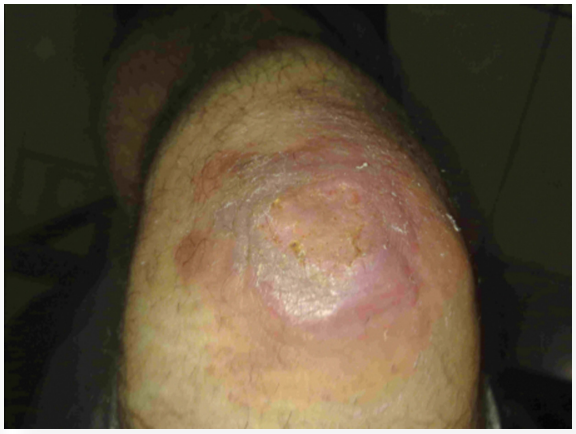

Figure 7. The innfected lesion 60 days after DAB-1 application

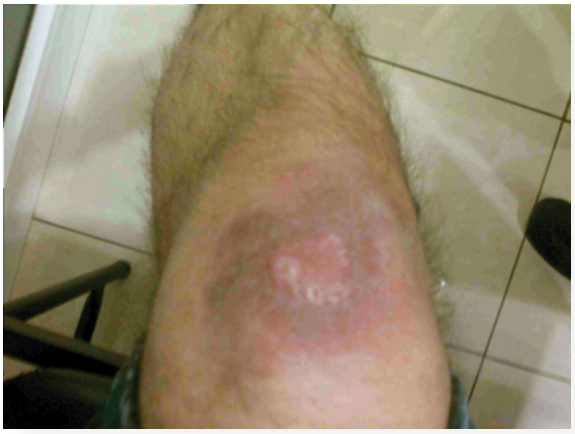

Figure 8. The innfected lesion 75 days after DAB-1 application

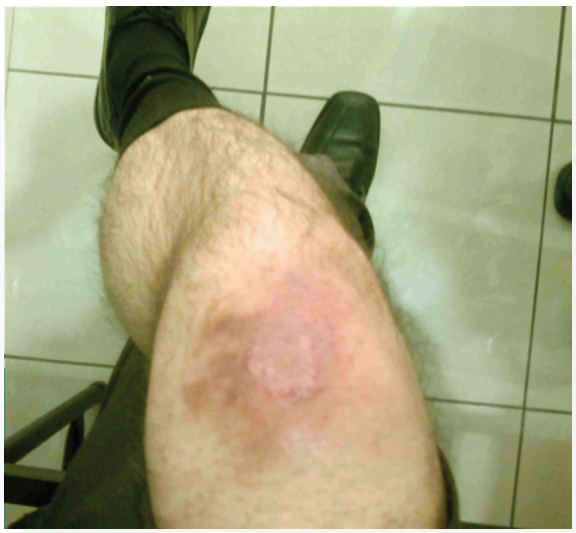

Figure 9. The innfected lesion 90 days after DAB-1 application

Discussion

One of the important things to be illustrated in this study is the total disappearance of the amastigotes form both in the intra and the extracellular reign together with their engulfing phagocytes. It is interesting to see the lesion still clinically hyper active and inflamed with the disappearance of such important disease figures. Other studies have observed this same phenomenon [5]. One answer for that dilemma is that the amastigote form is not necessarily the only influential factor during the whole process of the disease course, or the amastigote might have been active at one stage and then disappeared from the lesion. That contradicts the previous basic understanding of the disease process. It is clear from all previous data and literature presented, that the amastigote form is the main acting player and causing organism in cutaneous leishmania disease process.

According to Hepburn NC who summarizes the general previous understanding of the aspects of the disease: (In all forms of leishmaniasis the presence of amastigotes within the cells of the mononuclear phagocytic system remains the hall mark of the disease, though they sometimes may be difficult to detect) [6]. Indeed, the true fact is that the amastigotes at certain time of the disease are impossible to detect. The disappearance of such giant cells infected with the amastigote form while the disease process both clinically and cytomorphologically is still in action, indicates that such phagocytes, giant cells, macrophages and monocytes, at specific point of the disease process become resistant to be infected with the amastigotes. Literature tells (the amastigote forms multiply by binary fission, within the macrophage until the host cell is packed with the parasites and ruptures, liberating the amastigotes into circulation-then the free amastigotes invade fresh cells, thus repeating the cycle) [7]. In contrary with the previous concept, those amastigotes released into the extracellular fluid at a specific stage, become unable any more, to invade the adoptive phagocytes or replicate within those macrophages.

This inability, is explained by an immune interaction between the host immune system and the leishmania parasite determinants [8] which causes a development of resistance in the phagocytes against the parasites. This is in the disease course, where we notice the disappearance of the phagocytes with the intracellular amastigotes from the smear.

Tables VII -X confirm the disappearance of the amastigotes from the smear at that point.

As noticed in this study, DAB-1 ointment worked favorably on hastening the disappearance of the amastigotes from the lesion when compared to the disease in its natural process.

According to the traditional definition: (Leishmania are intracellular parasites that infect the mononuclear phagocytes.

Leishmania are obligatory intracellular parasites) [7]. This definition means that extracellular amastigotes cannot survive the harsh extracellular environment. Literature did not explain the way the expelled amastigotes disappear after being released from the infected macrophage. As we see clinically, the disease in that stage is deeply active and still not yet healing (Tabl. VII-IX). It is clear then that, the extra cellular amastigotes must have been able to find a way to survive in the extra cellular fluid [9] and to grow from such an inactive form (the amastigote form) which is an ova like form into the active form which is the flagellate a (promastigote like form) [10]. The promastigote form then that replaces the amastigote is the one that is developed and becomes the active form penetrating the subcutaneous tissues and causing the real signs and symptoms of the disease at that stage.

Coming to the pathology of the disease, according to Hepburn: (Over the following months, there is a gradual decrease in the number of amastigotes and macrophages, leaving a granulomatous infiltrate consisting of lymphocytes, epithelioid cells and multinucleate giant cells. At this stage it may be difficult or even impossible to detect organisms "pointing to the amastigote form" in H&E, or Giemsa, stained sections) [6]. As shown in Tables II, III, IV, VI-IX, the lesion at that stage is still clinically deeply inflamed with large ulcer and exudates. In fact, Those clinical and pathological signs still represent an active form of the disease process. Here we notice clearly, the appearance of many cytomorphologic forms that have been developed through the process of amastigote transformation. Those forms are Promastigote and fiber forming promastigote like forms, candle flame forms, the spherical and polygon forms [11]. All those forms are active forms of the parasite inside the tissue, and at that point, they are the ones causing the pathological inflammatory signs (Fig. 1c, 2b, 2c, 3b, 3c, 4b). After the amastigotes are released from the infected macrophages to the extracellular space, the fetus erupting from the amastigote will develop in a series of steps starting from a candle flame shape into a mature promastigote like form [12]. Those active forms of the parasite will never turn back or transform in side the host vertebrate into the amastigote form again. By that the amastigote forms disappear from the smear and what is left is destroyed by the function of neutrophils [13] (Tabl. VII-IX). Once the parasite is in its active form in the body, which is the promastigote form, and without drugs interference, the immune system represented by the lymphocytes will further react to control the flagellate type of the parasite by introducing T type lymphocytes with a protruding tail that is capable to form a base for a nest- like; that will trap those flagellate type of parasites and terminate the disease with a permanent scar formation [11]. That comes in agreement with the statement written by Hepburn: (There is, however, considerable variation: some lesions do not ulcerate, others develop sporotrichoid nodular lymphangitis. Most lesions heal over months or years, leaving an atrophic scar) [6].

In most cases of treatment using the different types of drugs and injections like Sodium antimony gluconate (Pentostam) or Pentamidine, the disease will heal leaving a permanent scar behind it. Relapses still occur and the drugs remain extremely expensive. That is not the case with DAB-1 product. As seen from the follow-up smears, DAB-1 has a stimulatory effect on the epithelium. This study shows that from day 16 of DAB-1 application (Fig. 3a, 3b, 3c), the epithelial cells become active and regenerate moving from the edges forward into the ulcer center, forming isolated islands. In day 24, the islands gather and start covering the whole ulcer and by day 32, one whole layer of epithelium covers the full ulcer (Fig. 4a, 4b, 4c). DAB-1 and according to the cytomorphologic figures seems to be active in killing the parasite. It is obvious that the parasite count was decreasing from the time of DAB-1 application. Not only that, but DAB-1 seems to have a chemotactic effect on neutrophils.

As we notice from Tables VII-VIII, the neutrophils increased in number in the lesion after 8 days of DAB-1 application and continued to increase by time. The fiber forming promastigotes with their fibers are left to the action of those neutrophils to degenerate and get red of. By the end of the disease process, the connective tissues with the upper layer of the epithelium will rejuvenate forming a normal cutaneous tissue with no scar left (Fig. 4c, 5a, 5b, 5c). Follow up of one case up to 2 years after treatment with DAB-1, declares no relapses observed .

Conclusions

DAB-1 is capable of healing leishmania in 6-8 weeks after application and is compared favorably to any other used drugs where the healing process may take between 14 to 16 weeks and in some cases even more.

DAB-1 has the power to stimulate the epithelium regeneration, migration and multiplication. it is more effective than the other applied drugs in generating normal tissues for cosmetic reasons.

DAB-1 has a strong anti-parasite effect on leishmania. This can be confirmed by the parasite disappearance from the smears within time.

DAB-1 seems to have a stimulatory effect on neutrophils function, as they act on the sporotrichoid nodular fibers produced by the parasite reducing the effect of the scar formation.

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TOWARD AN APPROACH FOR CUTANEOUS LEISHMANIA TREATMENT

by Mohammed Wael Daboul

comment:

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Cutaneous leishmaniasis is a major health problem in some parts of the world including Middle East countries. Afghanistan, Iran, Iraq, Syria, Kuwait, Lebanon, Jordon, Saudi Arabia, Sudan, Libya are known an endemic area for leishmaniasis. The disease is caused by L.tropica and transmitted by the sandfly, Phlebotomus species. Migration and displacement of people lead to increasing numbers of new cases annually. In most cases, lesions are located on the limbs and face. In case of outbreaks, lesions may be larger and multiple (1-3)

Treatment may be divided in two groups in cutaneous leishmaniasis depends on the extension of lesions; topical application in local lesions and oral or parenteral administration in extensive lesions. Most cutaneous sores will slowly resolve spontaneously providing lifelong immunity. Surgical excision and cryotherapy may be applied for small lesions. For larger lesions, intralesional injection of pentavalent antimony is suggested. Alternative treatments include topical paromomycin ointment and oral allopurinol plus probenecid and oral miltefosine. If these treatments fail, the next option is parenteral antimony, oral fluconazole, Amphterin B, pentamidine. Many of these have serious adverse effects (2-5).

A new therapeutical approach is carried out by Daboul M W in a limited number of cases with cutaneous leishmaniasis by local application. The author used a topical ointment named DAB-1 in seven cases. The chemical compound and ingredients of DAB-1 are not given by the author and it is mentioned that this ointment is a natural substance. Some knowledge would be given in the text; is it hand made formula? Is it marketed in Syria? In this study, it is noted that this topical agent healed inflamed and ulcerated lesions and cleared phagocytic and extracellular amastigotes from the lesions. It seems this topical agent might be useful in cutaneous leishmaniasis. Although there are many unexplained and unknown things in the paper about the DAB-1, this compound might be useful as an alternative topical therapy to the conventional topical therapies. It needs more future studies!

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A STUDY ON DERMATOSES OF PREGNANCY

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Abstract
Certain dermatoses are specifically seen in pregnancy or postpartum period. It is therefore important for the clinicians to recognize and treat these cutaneous disorders to minimize maternal and fetal morbidity. The commonest pregnancy related dermatoses was polymorphic eruption of pregnancy seen in 22% patients, prurigo of pregnancy was seen in 7% patients, pemphigoid gestationis was seen in 3% patients, pruritic folliculitis of pregnancy was seen in 2% patients and intrahepatic cholestasis was seen in 1% of patients. It was seen that the skin disorders were commonest in the third trimester (60%), followed by 31% patients in second trimester and 9% patients in first trimester.

Key words: pregnancy; dermatoses; prurigo; pruritis; urticaria; polymorphic eruption

Cite this article:
Neerja Puri, Asha Puri: A study on dermatoses of pregnancy. Our Dermatol Online. 2013; 4(1): 56-60

Introduction

Pregnancy is a time of immense hormonal, immunologic, and vascular changes [1]. Whether physiologic or pathologic, these changes affect virtually every organ of the pregnant woman, including the skin [2]. Indeed, certain dermatoses are seen almost exclusively during pregnancy or the postpartum period. Hence, awareness and recognition of these conditions and familiarity with their treatment and outcomes are important [3]. These conditions can be divided into three main categories: physiologic changes associated with pregnancy; preexisting dermatoses affected by pregnancy; and dermatoses specific to pregnancy. This paper concentrates on the dermatoses specific to pregnancy, common dermatological disorders asspociated with pregnancy and sexually transmitted diseases of pregnancy. Although the dermatoses of pregnancy are believed to be a direct result of gestation or the products of conception, they are classified as pathologic processes [4]. The main diseases under this heading include pruritic urticarial papules and plaques of pregnancy, pemphigoid gestationis, intrahepatic cholestasis of pregnancy, pruritic folliculitis of pregnancy, and prurigo of pregnancy [5].

Material and Methods

The study was conducted in the dermatology out-patient department with referral cases coming from obstetrics and gynecology OPD. Ethical committee clearance was obtained. Written informed consent was taken from all the patients before thev study. Detailed history including demographic data, chief complaints related to skin, presence of itching, skin lesions, onset in relation to duration of pregnancy, jaundice, vaginal discharge, past or family history of similar lesions, exacerbating factors, associated medical or skin disorders etc. was elicited and recorded. Complete cutaneous examination was done in all cases to study all the physiological changes of skin and its appendages. If any specific dermatosis of pregnancy was present, the morphology of skin lesions, distribution and the sites involved were studied. Relevant systemic examination was carried out. If any preexisting skin disease was present, any evidence of exacerbation or remission was recorded. Appropriate investigations were done to confirm diagnosis if required. Bedside laboratory procedures like Tzanck smear, KOH mount and Gram's stain were carried out. To confirm diagnosis skin biopsy and DIF were done in a few cases. In all cases with history of pruritus related to specific disorders of pregnancy, liver function tests were done. Screening with VDRL and ELISA for HIV was done in all the cases. Examination of the ‚contact' was done in all cases of sexually transmitted disease. Results were tabulated and analyzed.

Results

The commonest pregnancy related dermatoses was polymorphic eruption of pregnancy seen in 22% patients, prurigo of pregnancy was seen in 7% patients, pemphigoid gestationis was seen in 3% patients, pruritic folliculitis of pregnancy was seen in 2% patients and intrahepatic cholestasis was seen in 1% of patients (Tabl. I).

Sr No	Specific pregnancy dermatoses	Number	Percentage (%)
1	Polymorphic Eruption Pregnancy	22	22
2	Pemphigoid gestationis	3	3
3	Prurigo of pregnancy	7	7
4	Pruritic folliculitis of pregnancy	2	2
5	Intrahepatic cholestasis of pregnancy	1	1

Table I. Specific dermatoses of pregnancy

The commonest associated dermatological disorder in pregnancy was striae distensae (62%) ,16% patients had scabies and 15% patients had superficial fungal infections. Melasma was seen in 14% patients, candidiasis in 12% patients, gingivitis in 6% patients, acne in 5% patients and urticaria was seen in 4% patients (Tabl. II).

Sr No	Dermatological disorder	Number	Percentage (%)
1	Scabies	16	16
2	Superficial fungal infections	15	15
3	Candidiasis	12	12
4	Striae distensae	62	62
5	Urticaria	4	4
6	Melasma	14	14
7	Gingivitis	6	6
8	Acne	5	5

Table II. Asociated dermatological disorders in pregnancy

From the above table, it is clear that the commonest sexually transmited disease in pregnancy was discharge per vaginum seen in 28% patients, genital warts were seen in 65 patients, molluscum contagiosum was seen in 5% patients and syphilis was seen in 4% patients (Tabl. III).

Sr No	Sexually Transmited Disease	Number	Percentage (%)
1	Syphilis	4	4
2	Genital warts	6	6
3	Molluscum contagiosum	5	5
4	Discharge per vaginum	28	28

Table III. Sexually transmitted diseases in pregnancy

Discussion

In our study, it was seen that the commonest age group affected was between 21-30 years of age followed by 30% patients in the age group of 31-40 years of age; 15% patients were between 11-20 years of age and 10% patients were more than 40 years of age. There were 40% primigravida and 60% multigravida in our study. The commonest pregnancy related dermatoses was polymorphic eruption of pregnancy seen in 22% patients, prurigo of pregnancy was seen in 7% patients, pemphigoid gestationis was seen in 3% patients, pruritic folliculitis of pregnancy was seen in 2% patients (Fig. 1) and intrahepatic cholestasis was seen in 1% of patients. It was seen that the skin disorders were commonest in the third trimester (60%), followed by 31% patients in second trimester and 9% patients in first trimester. The commonest associated dermatological disorder in pregnancy was striae distensae (62%), 16% patients had scabies and 15% patients had superficial fungal infections (Fig. 2). Melasma was seen in 14% patients, candidiasis in 12% patients, gingivitis in 6% patients, acne in 5% patients and urticaria was seen in 4% patients. The commonest sexually transmited disease in pregnancy was discharge per vaginum seen in 28% patients, genital warts were seen in 65 patients, molluscum contagiosum (Fig. 3) was seen in 5% patients and syphilis was seen in 4% patients. It was seen that the commonest symptom was pruritis seen in 46% patients and pain was seen in 4% patients. Discharge per vaginum was seen in 28% patients and the discharge was candidal in 20% patients, trichomonal in 6% patients and the cause was bacterial vaginosis seen in 2% patients.

Many of the symptoms and signs are so common that they are not usually considered as being abnormal, but regarded as physiological and can sometimes provide contributory evidence of pregnancy [6].

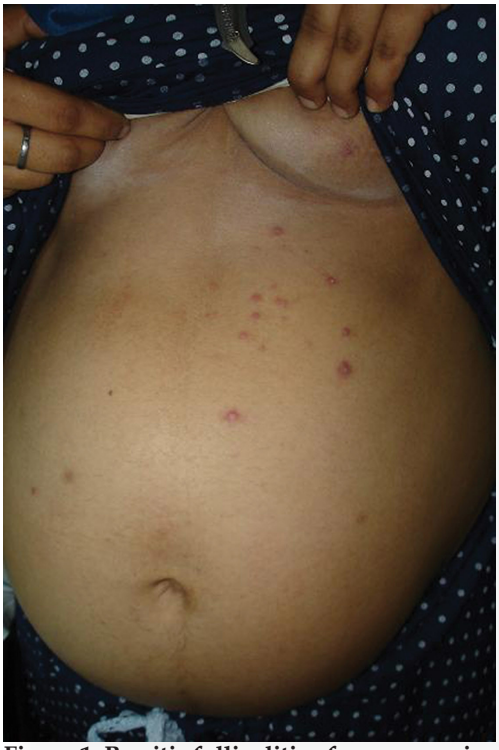

Figure 1. Pruritic folliculitis of pregnancy in a seventh month pregnant patient

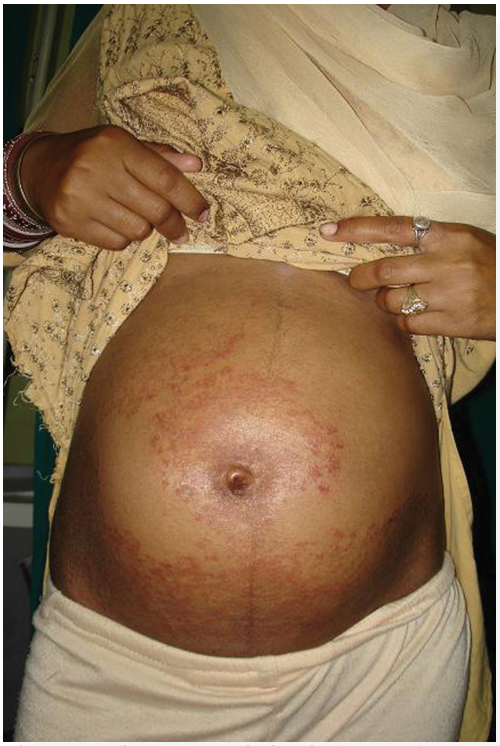

Figure 2. Tinea corporis in sixth month pregnant patient

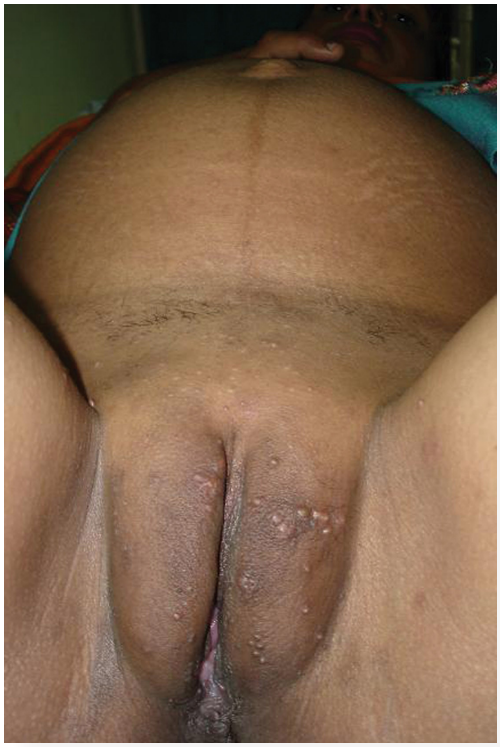

Figure 3. Genital MC in a eighth month pregnant patient

The commonly encountered physiological changes include striae distensae (occurring in up to 90% of pregnant women), hormonal alterations resulting in melasma (occurring in up to 75% of women during pregnancy) and generalized hyperpigmentation [7,8]. Vascular alterations result in edema, palmar erythema, spider nevi, varicosities, cutis marmorata, gingival edema and redness. Similarly the activity of eccrine and sebaceous glands increases, while that of apocrine gland decreases. In addition, pregnancy can modify a number of concomitant dermatoses and there are some pathological skin conditions that are virtually pregnancy specific. The most common physiological changes are pigmentary alterations, stretch marks, vascular spiders and telogen effluvium [9].

Pruritic urticarial papules and plaques of pregnancy (PUPPP) is the most common dermatosis of pregnancy, and is also known as toxemic rash or polymorphic eruption of pregnancy. Pruritic urticarial papules and plaques occur in 1 of 160 to 240 pregnancies, and are more common in white women [10]. Classically, this disease occurs in primigravidas during the third trimester, and the incidence is higher in multiple gestations (ie, 0.5% of single births, 2.9% of twin pregnancies, and 14% of triplets) [11]. Pruritic urticarial papules and plaques most commonly present as intensely pruritic papules within striae distensae. Over the next several days, erythematous, urticarial papules and plaques spread to involve the trunk and extremities [12,13]. The periumbilical region, face, palms, and soles are usually spared. Occasionally vesicles, purpura, targetoid, eczematous, or polycyclic lesions are seen. A relationship to skin distension has been proposed due to the higher prevalence of PUPPP in multiple gestations and in women with increased weight gain during pregnancy, or the condition may represent a cutaneous response to the presence of circulating fetal cells that have invaded maternal skin [14,15].

Pemphigoid gestationis (PG), also known as herpes gestationis (HG), is an autoimmune bullous disease of pregnancy. Despite its name, this disease has no relationship to herpes simplex virus, but was so called because of the herpes-like nature of the blisters [16]. This dermatosis classically develops in the second or third trimester (mean of 21 weeks) [17].

It occurs in 1 in 50,000 pregnancies, and has a strong association with HLA-DR3 and HLA-DR4, which might explain the greater prevalence of this condition in white women compared to black women [18]. Pemphigoid gestationis begins with the sudden onset of intensely itchy, urticarial lesions, which are found on the abdomen in 50% of cases. At this stage, it is very difficult to distinguish this disease from PUPPP. The lesions then progress to a generalized bullous eruption that usually spares the face, mucous membranes, palms and soles [19]. The disease often resolves during the latter part of pregnancy, and flares at delivery or immediately postpartum in more than 60% of cases; 25% of cases appear for the first time after delivery [20]. Biopsy results reveal a subepidermal blister with an eosinophil-predominant infiltrate. The infiltrate is localized to the dermal-epidermal junction and perivascular areas [21]. Direct Immunofluorescence (DIF) is the most sensitive and specific assay for differentiating PG from PUPPP. Performed on perilesional skin, DIF shows a linear band of C3 and/or IgG at the basement membrane. Salt-split skin studies demonstrate antibody binding to the roof of the vesicle [22].

Intrahepatic cholestasis of pregnancy (ICP) is caused by maternal intrahepatic bile secretory dysfunction. A genetic predisposition for this disorder has been described. This disease is characterized by intense generalized pruritus that usually begins in the third trimester. Although constant, the pruritus is classically much worse at night. It may be most severe on the palms and soles. The important feature of intrahepatic cholestasis is the absence of primary lesions, such that excoriations are the only cutaneous finding [23]. Jaundice is present in a minority of patients. Symptoms tend to dissipate within days of delivery, but there is a tendency toward later development of gallbladder disease in these women. There is a potential for recurrence in subsequent pregnancies or with OC use. Fetal risk is also a matter of concern.

Pruritic folliculitis of pregnancy (PFP) classically occurs in the second and third trimester [24]. Women present with generalized red, follicularly based papules. These are distributed on the chest and back in most cases, and resemble the monomorphic acne that may occur in women who are taking oral corticosteroids. The lesions are variably pruritic. Although the pathogenesis is unknown, many consider PFP to be a form of steroid acne. There is no evidence of immunologic or hormonal abnormalities in this condition. Interestingly, there is an overall preponderance of male infants (2:1) delivered to women with this condition [25]. Histologically, the condition is characterized by sterile folliculitis. Features include acute folliculitis with mixed inflammatory cells, upper dermal edema, spongiosis, and a negative Gram stain. Direct immunofluorescence is negative.

Prurigo of pregnancy (PP) is the most poorly characterized gestational dermatosis. It has also been described as Besnier's prurigo of pregnancy and papular dermatitis of Spangler. Prurigo of pregnancy is a diagnosis of exclusion, and a large number of pruritic entities unrelated to pregnancy must be considered. It classically occurs in the second half of pregnancy, affecting about 1 in 300 pregnant women [26]. This condition presents clinically as discrete, bite-like papules on the extremities that resemble scabies or other arthropod bites. The lesions consist of erythematous papules and nodules on the extensor surfaces of extremities and occasionally the abdomen [27]. Prurigo of pregnancy is often seen in women with an atopic background, and is associated with increased serum levels of immunoglobulin E (IgE)-supporting the notion that PP may represent a gestational variant of atopic dermatitis occurring as a result of common pruritus gravidarum [28]. Liver function studies, including serum bile acids, should be performed to rule out cholestasis or hepatitis. At a minimum, the differential diagnosis also should include an allergic reaction and scabies or other infestation. The histopathology of PP is nonspecific, usually demonstrating a chronic, inflammatory cell infiltrate with superficial excoriation. Direct immunofluorescence is negative. Treatment is symptomatic, including topical emollients, topical midpotency corticosteroids, and systemic antihistamines. There is no associated maternal or fetal risk. The eruption typically resolves soon after delivery.

Approximately two million pregnant women are affected by sexually transmitted diseases or STDs during each year in the United States. Pregnancy offers no protection against sexually transmitted diseases leaving pregnant women vulnerable to the same STDs as women who are not pregnant. Sexually transmitted diseases can cause devastating consequences women who are not pregnant; the consequences of sexually transmitted diseases can be significantly more dangerous for pregnant women [29]. The occurrence of genital warts while pregnant can be a foremost basis of apprehension for mothers to be. It puts the unborn child at risk of getting the infection. There is also a chance that genital warts can be passed along to newborn babies through a contaminated birth canal. The main concern is that the unborn baby of a mother infected with genital warts may contract laryngeal papillomatosis, which is a life-threatening condition.

Conclusions

Pregnant women are prone to suffer from a wide range of dermatological problems and sexually transmitted diseases, apart from the specific dermatoses of pregnancy. This study emphasises the need for a scrupulous and meticulous search for dermatological and sexually transmitted diseases instead of a casual cursory examination and dismissing the patients with symptoms attributing them to the normal course of pregnancy. These pruritic dermatoses are unique to the gravid state. A detailed history and awareness of clinical presentation facilitate confirmation of the diagnosis, and will direct the most appropriate laboratory evaluation in an effort to minimize maternal and fetal morbidity. In addition, monitoring of liver function deserves special consideration.

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PIEZOGENIC PEDAL NODULES OF YOUNG CHILDREN AND THEIR PARENTS

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Abstract
Skin of atlets foot is open on constant effect of disadvantageous outword factors, which could be reason of illnesses in this area. Very ofen incidence disease is Piezogenic Foot Nodules (PN) These papules represent herniations of subcutaneous fat through the collagen matrix of the reticular dermis. Suggests that as many as 10% to 20% of the population may be affected with both symptomatic and asymptomatic lesions. Painful piezogenic papules are reported more frequently in women than in man. Among athletes they appear mainly at the marathon runners and valleybol players. Trauma may also initiate the formation of pedal papules. These are soft, skin collored, typically asymptomatic, medial heel papules and nodules, appear on the side of the heel, ussualy the medial aspect, when the subject is standing and disappear when weight is taken off the foot. Papules may be painful when there is herniation of fat into the dermis with a resultant reduction in dermal thickness. They could concern one or both feet. Ussually there are plural changes. There is no satisfactory medical or surgical treatment.
Aim: The aim of work is presentation family occurrence of PN.
Material and methods: Research concerned 50 children (girls and boys) in age about 5,5 years.
Results: Incidence of PN observed at 16 % children and 22.06% in check up group (5 children). In children and parents group 100% changes concerned heels. Pain reportered only 4 parents (5,88%).
Conclusions: Appearance skin changes during fat ill on Piezogenic Nodules is connected with doing more activity. Painful papules can limit participation in sports and may affect occupational activity.

Key words: skin diseases; children; foot

Cite this article:
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Introduction

Skin plays many functions that are important for human organizm. It takes part in its defense mechanisms. When it comes to dermatoses, in certain cases skin is the only organ involved - in others skin changes are one of many symptoms preceding or accompanying various entities and illness syndromes. Sometimes, due to characteristic features, skin changes can be a clue facilitating correct diagnosis. Cutaneous eruptions, both on child's skin and on adult man' s skin, can often be a significant track leading to the origin of a disease.

Changes on the skin can be restricted and therefore characteristic for specific localization, e.g. foot - the most peripheral part of a lower limb in human anatomy. Its structure is characteristic only for human being due to his vertical posture. Foot skin injuries are often observed in groups of physically active people. Therefore, the sportsmen are more affected by them than any other working group. What is more, certain entities are specific only for particular sport disciplines [1-3].

Piezogenic Pedal Nodules (PPN) – cutaneous herniae described in 1968 by Shelley and Rawnsley are not such uncommon entities [4]. Changes are manifested as nodules or papules and localized most often along the sole of the feet. They are flesh-coloured or yellowish. Their size oscillates between 0,5 and 1,5 cm. Other less frequent localizations are: wrists or thenar.

PN occurs very often. We can distinguish two forms:
1) asymptomatic, observed in 10-20% of population [2]
2) painful one, observed mainly among the sportsmen or patients with diagnosed connective tissue diseases [5].

Having painful forms of PPN is also characteristic for the people with the injuries of the foot area. PN appear when a patient is in a vertical position.

They disappear once he or she is in horizontal one. Moreover, patients can very often feel pain during standing or walking [2]. Changes may affect one or both feet. Nevertheless, the appearance on both sides is more frequent [6].
Usually changes are multiple. Singh et all observed a 22-year old men with 22 nodules and pustules on one foot and 17 on the other [7].
The main cause of PN changes is penetrating epiderma propria by subcutaneous fatty tissue on feet edges during the moment of increased weight [6,8]. Cutaneous herniae created in that way are related to resistance or genetic reduction of the number of septi in fatty tissue.
PPN – like changes can occur at any age.
In differential diagnosis lipomas, connective tissue mole/ stigma or neurofibroma are considered.
The most affected group of people consists of sportsmen, esp. athletes.
The aim of this work was to present the appearance of PPN on feet in the family.

Material and Methods

The research involved 50 children, girls and boys of 1-10 years (average: 5,5 years old) and their parents-68 people, men and women aged from 25 to 46 years (average age: 35,5). All of the parents, currently or in the past were members of sport clubs: 15 people played basketball, 29-volleyball, 18-football and 6 were athletes.
The diagnosis was made on the basis of characteristic clinical symptoms. An interview regarding the incidence of connective tissue diseases as well as feet injuries in the past of the family or the interviewee was held.

Results

PN appeared in the group of 8 children (16%) (Fig. 1), (aged 4-10 years old): 25% were boys, 75%-girls. In the group of adults PPN was diagnosed in 15 cases (22,06%) (Fig. 2): 10-female (66,67%), 5-male (33,34%). None of the children complained about pain, whereas in the adult group 4 people (5,88%) suffered from pain.
The interview regarding past feet` injuries was positive among 2 children with PPN. Other 2 children have positive interview related to connective tissue diseases (one of these children's parents suffered from Morphea, the second from RZS).
In the group of children with PPN the following changes were observed:
- 1 child (12,5%) - only one foot affected,
- The rest of children (87,5%) - changes appeared on both feet.

The changes were localized on children's heels.
Among adults proportions were almost identical:
- whole skin changes were linked to heel localization,
- in 80% of cases changes appeared on one foot,
- in 20% of cases on both feet.

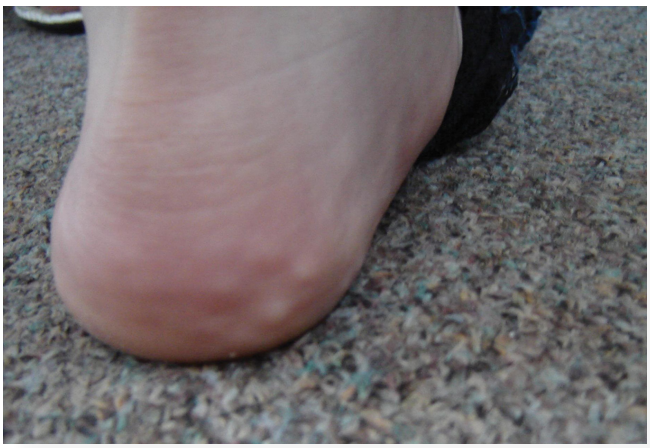
Figure 1. Piezogenic Pedal Nodules in children

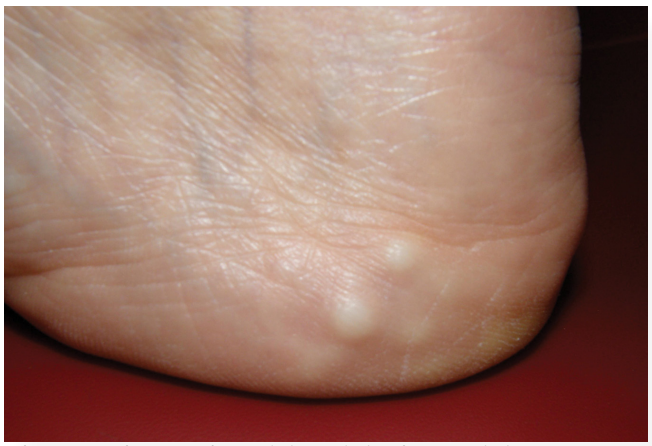
Figure 2. Piezogenic Pedal Nodules in an adult

Discussion

PN are observed in 10-20% of the the society [2]. In the population of our research (126 people) PPN were diagnosed in 23 cases (18,25%).
PN can appear at any age. Greenberg and Krafchik noted incidence of PPN in 5,9% of examined newborns and in 39,45% infants from Canada [9]. Lorralde de Luna et all described 4 PPN cases among newborns from Argentina [10].
There is significant correlation between PPN and physical activity: PPN is often described in the group of people taking up different sport disciplines. This is the factor that can trigger changes among people of genetical predisposition (reduction of the number of septi in fatty tissue or their resistance) [11]. In our group this correlation reached 22,06%. Intensiveness of pain can differ. Laing in his group described pain syptoms in 86% cases of herniae [12]. In the male group analyzed by us pain appeared in 5,88%. Pain accompanies PPN in cases of connective tissue disease or past feet injuries.
Doukas believed that the major causative factor of PPN is either positive feet injury history or genetically inhabited connective tissue diseases [13]. Kahana et all described PPN incidence among more than 34,5% patients with Ehlers-Danlos Syndrome [5]. Family incidence of PPN was also described [14].
In our research familial occurance was expressed in 8 cases, in 4 cases changes correlated with injuries and connective tissue diseases.
Treating in case of asymptomatic changes is not needed. In other cases painfull nodules and papules can be excised surgically [15]. It is recommended to reduce body weight (especially for overweight people) and to avoid long staying in standing positions [2].

Doukas et all suggested non-surgical approach towards treatment. They injected betametazone and bupivacaine in equal parts (1-2ml/injection), in 3 doses, in 1-3-5 –month intervals. The last 3rd injection resulted in pain vanishing. Moreover, they also tried using electroacupuncture [16]. Pantious et all used special orthopedic coverings for heels in cases characterized by intense pain [17].

Conclusions

The appearance of changes in the course of PPN is significantly related to the intensiveness of physical activity. Training is a factor that can trigger changes in people with genetic predisposition.

There is a possibility of the incidence of PPN among family, especially if one of the parents was physically active and trained a lot in the past.

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MERKEL CELL CARCINOMA VERSUS METASTATIC SMALL CELL PRIMARY BRONCHOGENIC CARCINOMA

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Abstract
Introduction: Merkel cell carcinoma (MCC) of the skin is a rare, aggressive, malignant neuroendocrine neoplasm. The tumor classically demonstrates positive immunohistochemistry (IHC) staining for chromogranin A(ChrA), cytokeratin 20 (CK20), neuron specific enolase (NSE) and/or achaete-acute complex-like 1 (MASH1). The newly identified Merkel cell polyomavirus (MCPyV) has been found to be associated with most MCC cases. The primary histologic differential diagnoses of cutaneous MCC is small cell primary bronchogenic carcinoma (SCLC); moreover, both are of neuroendocrine origin. SCLC accounts for approximately 10-15% of all primary lung cancer cases; this histologic subtype is a distinct entity with biological and oncological features distinct from non-small cell lung cancer (NSCLC). In contradistinction to MCC, SCLC is classically IHC positive for cytokeratin 7 (CK7) and transcription factor (TTF-1). Similar to SCLC, MCC cell lines may be classified into two different biochemical subgroups designated as Classic and Variant.
In our review and case report, we aim to emphasize the importance of a multidisciplinary approach to the approach to this difficult differential diagnosis. We also aim to comment about features of the cells of origin of MCC and SCLC; to summarize the microscopic features of both tumors; and to review their respective epidemiologic, clinical, prognostic and treatment features. We want to emphasize the initial workup study of the differential diagnosis patient, including evaluating clinical lymph nodes, a clinical history of any respiratory abnormality, and chest radiogram. If a diagnosis of primary cutaneous MCC is confirmed, classic treatment includes excision of the primary tumor with wide margins, excision of a sentinel lymph node, and computed tomography, positron emission tomography and/or Fluorine-18-fluorodeoxyglucose positron emission tomography scan studies.

Key words: Merkel cell carcinoma; thyroid transcription factor; somatostatin; IMP3; small cell lung carcinoma (SCLC)

Abbreviations and acronyms: Merkel cell carcinoma (MCC), thyroid transcription factor 1 (TTF-1), immunohistochemistry (IHC), neuron specific enolase (NSE), small cell lung carcinoma (SCLC), chromogranin A(CgA), insulin-like growth factor II mRNA binding protein 3 (IMP3), neurofilament protein (NF), cytokeratin 7 (CK7), cytokeratin 20 (CK20), surveillance, epidemiology, and end results (SEER), non-small cell lung cancer (NSCLC), computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), Merkel cell polyoma virus (MCPyV).

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Introduction

Merkel cell carcinoma (MCC) of the skin is an aggressive but rare malignant neuroendocrine tumor. This tumor has a high rate of recurrence and metastasis the main histopathological differential diagnosis is cell lung carcinoma (SCLC). Most MCC are usually positive to cytokeratin 20 (CK20) stain as well as may show some neuroendocrine differentiation, expressing either neuron specific enolase (NSE), chromogranin A, or both [1-2]. MCC small-cell lung carcinoma (SCLC), and both are of neuroendocrine origin. Comparable to SCLC, MCC cell lines are classified into two different biochemical subgroups designated as ‚Classic' and ‚Variant' [3]. MCC mostly affects elderly people and occurs predominantly on the sun-exposed areas of the skin, suggesting ultraviolet exposure (UV) exposure in its etiology and need to be differentiating with melanoma [5-7].

Merkel cells

Merkel cells are neuroendocrine in origin, expressing markers such as neuron-specific enolase (NSE) and bombesin. These cells are located in the basement membrane zone (BMZ) at the dermal epidermal junction, where they function as mechanoreceptors [8-11]. Ken Hashimoto, M.D., emeritus professor at Wayne State University in Detroit, Michigan, USA made great contributions to our understanding of Merkel cells. Dr Hashimoto showed that the Merkel cells could readily be identified via electron microscopy because of their characteristic round, dense cytoplasmic granules, their association with Schwann cells, and their smooth periphery surrounded by a basal lamina [8-11]. Dr Hashimoto further showed that Merkel cells were distributed in the nail matrix, nail bed and the skin of the fingers, including hairless portions. In primitive mesenchyme, the Merkel cells were surrounded by a sheath of Schwann cells or cells similar to Schwann cells. Non-myelinated terminals of axons (neurites) within such Schwann or Schwann-like cells were often in contact with the Merkel cells [11]. Dr Hashimoto also described dense cytoplasmic granules surrounded by a unit membrane, titled Merkel cell granules; these granules were found in variable numbers, and tended to concentrate toward one side of the cell cytoplasm. In selected sections, well developed areas of the Golgi apparatus were noted [8-11]. From the periphery of the Merkel cell, spine-like processes projected into surrounding Schwann cells. Very fine filaments (2-4 nm) originating from the plasma membrane formed a bundle and filled each spine. The proximal end of the bundle fanned out into the peripheral cytoplasm at the root of the spine. Schwann cell-Merkel cell junctions often produced desmosome-like plasma membrane thickenings on both cells [8-11]. The Merkel cells tended to cluster in certain areas of the epidermis, usually in the skin basement membrane zone. Clear cells were also noted among the grouped Merkel cells, which did not contain typical Merkel cell granules [8-11]. The identity of these cells was not certain. The epidermal Merkel cells were connected to the adjacent keratinocytes via desmosome-like mesenchymal Merkel cells; they projected little spines into the surrounding keratinocytes. These spines contained bundles of fine filaments, comparable to those seen in traditional mesenchymal Merkel cells. When two Merkel cells came into contact, desmosome-like densities were developed on the plasma membrane of every apposed cell. The distribution of the Merkel cell granules was polarized in the direction of adjacent basal lamina, and the Golgi apparatus was typically found near the nucleus in the opposite side cytoplasm of the cell [8-11]. Neurites, if found, were present outside the basal lamina and adjacent to the accumulated granules [8-11]. The neurites could surround the basal and lateral borders of the Merkel cell, but in these preparations no specialized junctional structures were detected between the Merkel cell and the neurites. Most Merkel cells were not in direct contact with the basal lamina to any significant extent; in contrast, they were contacted either by neurites or processes of basal cells [8-11]. In exceptional instances, a large area of the basal surface of the Merkel cell was exposed to the basal lamina. In such an area, half desmosome-like structures were present both in the basal plasma membrane of the Merkel cell and the basal lamina itself. Anchoring fibrils were attached to the dense areas of the basal lamina. In the skin of the finger, eccrine glands were descending from the epidermis. Within the mass of epithelial cells forming the eccrine gland anlagen, Merkel cells were frequently observed [8-11].

Organelles of Merkel cells

Merkel cell granules are apparently packaged in Golgi body-derived small vesicles [8-11]. Between the unit membrane and the dense core substance of each granule, an electron-lucid halo could be appreciated. Moreover, granules with a similar halo were often seen in the Golgi body area and probably represented immature granules. As the dense core substance filled the vesicles, they moved toward one side of the cell, frequently the opposing side relative to the Golgi body [8-11]. In many mature granules, additional spaces delimited by unit membrane were also completely filled with the dense substance. The electron density of each granule varied, and the size of each granule also varied (80-200 nm); however, the granule density and size did not correlate. Multivesiculated bodies, and large dense bodies with delimiting unit membranes (compatible with lysosomes) were also found, numbering a few in each cell [8-11]. Some lysosomal dense bodies contained half-digested melanosomes, which in turn appeared comparable to large melanosomal complexes of keratinocytes. Melanosomes were also seen in isolation within some epidermal Merkel cells. Interestingly, some epidermal Merkel cell cytoplasmic vacuoles also contained what appeared to be Merkel cell granules. Such vacuoles were thus interpreted as autophagosomes [8-11]. In some cells, bundles of tonofilaments separated Merkel cell granules into groups. Free ribosomes were less numerous in Merkel cells than in keratinocytes. In some Merkel cells, glycogen particles were seen [8-11]. The Merkel cell nucleus was slightly indented, but not significantly compared to other types of cells. Within the Merkel cells, a nucleolus was often absent. Finally, filament-filled, short peripheral spines on the Merkel cells were noted, and likely represent a unique structure for Merkel cells. No similar organelle has been found in keratinocytes, melanocytes or Langerhans cells; dendrites of these cells lack a filamentous core structure, and are long and slender. The functional significance of the Merkel cell spines is not clear; they may 1) assist cellular locomotion via flagella-like movement, 2) assist in cellular stability by engaging with neighboring keratinocytes, or 3) represent a defensive, pressure sensitive extension of the cell when Merkel cells are mechanically constricted between surrounding keratinocytes [8-11].

Possible neuroectodermic origin of Merkel cells

Dr. Hashimoto's studies also suggest that the Merkel cells originate from the neuroectoderm, next migrate into the skin with the growth of peripheral nerves, and finally settle into the basal keratinocytic layer of the epidermis [9-11]. The 1) large number of mesenchymal Merkel cells observed, as well as 2) the rarity of dermal Merkel cells in adult human skin seem to support this concept [12]. The Merkel cell migration hypothesis was previously proposed by Breathnach & Robins; moreover, Breathnach, Lyne and Hollis reported that in very young sheep embryo skin, no Merkel cells were found in the epidermis. In more mature embryo skins (57-144 days gestation) Merkel cells were identified in the epidermis [13,14].

Both melanocyte and chromaffin cells originate from the neural crest; the melanocyte finally settles in the epidermis. However, it is not clear whether all mesenchymal Merkel cells eventually migrate to the epidermis; some may remain intact in the postnatal dermis, and some Merkel cell granules may be autophagocytosed in the dermis and/or epidermis [9-11]. The absence of Merkel cells in adult eccrine glands and hair follicles suggests that such autodigestion of granules may actually occur at a certain stage of fetal skin development, as the same mechanism has been suggested for the disappearance of melanocytes from selected areas of the human hair outer root sheath [8-11]. Dr Hashimoto suggested that the epidermal entry of Merkel cells could occur in a consistent sequence. First, the Merkel cell would be stripped of its Schwann sheath, in its superior portion at the mesenchymal-epidermal tissue junction. Next, the Merkel cell would penetrate the epidermal basal lamina, and make contact with basal layer keratinocytes. Desmosomes would then be formed between the Merkel cells and keratinocytes. The interrupted basal lamina would then establish continuity with the basal lamina of the Schwann cell that accompanied the Merkel cell to the point of epidermal entry. As the epidermal basal keratinocytes migrate upward within the epidermis, Merkel cells connected to them would be pulled up into the epidermal basal layer [8-11]. Neurites would, in turn, follow each Merkel cell. The counterbalanced kinetic forces between such upward traction and opposing forces provided by both 1) desmosomal junctions between the Merkel cells and adjoined basal layer keratinocytes and 2) half-desmosomes with the basal lamina would determine the final anatomic position of each Merkel cell [8-11]. Notably, when nerve endings of a sensory nerve attempt to enter the epidermis as free nerve endings, they also shed their Schwann sheath, and the epithelial basal lamina fuses with that of the Schwann cell [15]. It has also been noted that if the Merkel cell granules were equivalent to synaptic vesicles of cholinergic pre-synapses, one would expect to see a discharge of some of the granules into the extracellular space; however, this phenomenon has not been documented. Moreover, no specialized junctions such as synaptic complexes have been found between Merkel cells and adjacent neurites. The 1) absence of plasma membrane fusion of the Merkel cell granule and 2) absence of specialized junctions between Merkel cells and intra-epidermal sensory nerve endings has been confirmed in adult skin and mucous membrane Merkel cells [9,14]. On the other hand, the concentration of the granules in the cytoplasm in apposition to adjacent neurites takes place as soon as the Merkel cell enters the epidermis, suggesting that these granules are indeed a source of stimuli for the neurites themselves [9].

Epidemiology of MCC

MCC is a rare cutaneous neoplasm. Studies revealed an increase in incidence from 0.15 to 0.44 cases for every 100.000 inhabitants between 1986 and 2001. Around 50% of the patients eventually develop metastatic disease, predilecting the liver, bones and brain[16-17]. The etiology of MCC is still unknown. In a recent large Danish study, it was also reported that the incidence of MCC is rising [18]. The authors reviewed the medical records of 51 patients diagnosed with MCC from 1995 until 2006 in eastern Denmark. The nationwide incidence of MCC was also determined from the Danish Cancer Registry for the period 1986-2003 [18]. The authors found that 14/51 of the MCC patients developed recurrence, and 37/51 (73%) died during the study period. The mean clinical follow-up period was 13 months (range 1-122) [18]. Moreover, a group of 153 total 1986-2003 MCC patients were identified in the Danish Cancer Registry, and the incidence rate had increased 5.4 fold over this 18 year period. The prevalence was highest in people over age 65; the authors suggested treatment with curative intent should include excision of the primary tumor with wide margins, excision of a sentinel lymph node (SLN), computed tomography (CT) or positron emission tomography (PET) of the thorax and abdomen, and adjuvant radiotherapy to the surgical bed. The authors also recommended that in the case of advanced disease, systemic palliative chemotherapy should remain an option [18].

Etiology of MCC

The skin of the head and neck is a common site for MCC, classically presenting in fair complected, elderly patients [3]. Radical surgical excision with pathological verification of complete removal of the tumor is the recommended treatment. Early MCC can be cured by surgery with or without postoperative radiation therapy, whereas advanced MCC is currently considered to be incurable. In 2008, a new polyoma virus sequence was detected in the genome of MCC tumors [18,19]. Merkel cell polyoma virus (MCPyV) appears to be the first example of a human oncogenic polyoma virus. Specific mutations in the viral genome and its clonal integration to the tumour genome represent strong evidence against MCPyV being a passenger virus that secondarily infects MCC tumors. MCPyV genomes are clonally integrated into tumor tissue in approximately 85% of all MCC cases [18]. All integrated viral genomes recovered from MCC tissue or MCC cell lines harbor signature mutations in the early gene transcript encoding for the large T-Antigen (LT-Ag). These mutations selectively abrogate the ability of LT-Ag to support viral replication while still maintaining its Rb-binding activity, suggesting a continuous requirement for LT-Ag mediated cell cycle deregulation during MCC pathogenesis [19]. The growing incidence and recognition of MCC in elderly and/or immunosuppressed individuals suggests that these two factors (advanced age and immunosuppression) represent likely links to the etiology of MCC [20,21].

Clinical features, demographics and survival rates of MCC

MCC characteristically develops rapidly and asymptomatically over months. Most MCCs are located on sun-exposed areas. The clinician needs to be aware of the asymptomatic, nontender, rapidly expanding nature of these tumors, especially in patients 1) over fifty years of age with 2) a lesion in sun-exposed area and 3) any past history of immunosuppressive therapy. About 50% of MCCs present on the head and neck; 40% present on the extremities and the remainder on the trunk and genitalia. MCC rarely arises on sun-protected areas such as the oral and genital mucosae; in these cases, the tumor is characterized by a particularly poor prognosis. It usually presents as solitary, firm, flesh-colored to red nodule with a smooth, shiny surface, and occasionally with telangiectasias.

MCC is an aggressive neoplasm. Its 5-year disease-specific survival rate approximates 60% [22]. Although MCC is still regarded as a rare tumor entity, its incidence is significantly increasing. In this regard, the American Cancer Society estimated almost 1500 new cases in the United States in 2008 [23]. The newly identified MCPyV has been found associated with most MCC cases. Nevertheless, the precise molecular pathogenesis of MCC and its link to MCPyV is not yet fully understood. In a large study, one group of authors performed a surveillance study utilizing data from the U.S. National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) Program from 1973 to 2006. The authors analyzed the demographics and survival characteristics of MCC [23]. The authors reported that SEER had documented 3870 new cases of MCC during this period. The incidence was higher in men (2380 cases, 61.5%) than in women (1490 cases, 38.5%). Most patients were Caucasian (94.9%) between 60 and 85 years of age. MCC was rare in African Americans. The most common clinical site of presentation was the head and neck [23]. The salivary glands, nasal cavity, lip, lymph nodes, vulva, vagina and esophagus were the most common extracutaneous sites. The 10-year relative survival rate was higher in women than men (64.8% vs. 50.5%, $p < 0.001$). Patients 50-69 years had the highest 10-year relative survival rate(59.6%). Stage of disease was the best predictor of survival [23]. The authors reported that MCC arises predominantly in the skin of head and neck, in Caucasian men over 70 years of age. Age did not predict survival; however, gender, anatomic site and tumor size revealed clear differences [23].

Histopathology of MCC

MCC usually appears as a dermal tumor nodule, that frequently also invades the subcutaneous adipose tissue. Under hematoxylin and eosin(H&E) examination, the tumor cells are small, round cells with basophilic nuclei and minimal cytoplasm (Fig. 1). Mitoses are frequent, and apoptotic tumor cells are frequently present. The papillary dermis and adnexa are often spared. Three histologic subtypes of MCC have been recognized: 1) the small cell variant, histologically indistinguishable from bronchogenic small cell carcinoma, 2) the intermediate variant, featuring vesicular, basophilic nuclei with prominent nucleoli and high mitotic activity, and 3) the trabecular variant, featuring cords of tumor cells. Overall, uniform, poorly cohesive cells containing cytoplasmic argyrophilic granules and round to oval nuclei with indented cell membranes are common histologic features of MCC. In the latest data, the trabecular form is considered the best differentiated with a better prognosis, while the small cell form is considered relatively undifferentiated with a worse prognosis. However, comprehensive data are not available and mixed and transitional histologic forms are frequently encountered; thus, no definitive histologic-prognostic association exists. A tumor size ≤ 2 cm, female gender, primary tumor localized in the upper limb, and pathologically proven negative lymph nodes are factors highly significant for a favorable prognosis and have been incorporated into the new staging system for MCC [25-27].

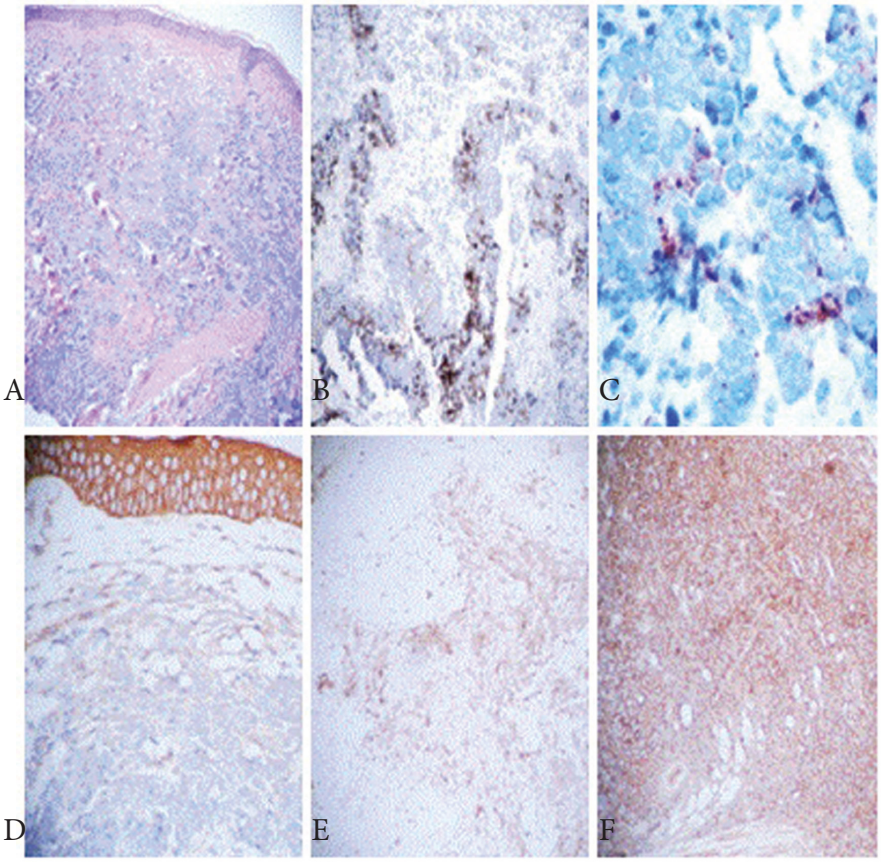

Figure 1. a. H&E staining reveals cords and sheets of dark blue tumor cells, infiltrating the dermis. **b.** Focal areas of the tumor demonstrated positive IHC staining for Ber-EP4 (red arrow, brown staining). **c.** Only focal areas of the tumor were paranuclear dot IHC positive for CK20 (red arrow, brown staining). **d.** IHC IMP3 positive staining in the epidermis above the tumor, and in focal areas of the tumor (red arrows, brown staining). **e.** Focal tumoral IHC positive staining for somatostatin (red arrow, brown staining). **f.** Diffusely positive IHC staining on the tumor cells for Chromogranin A (red arrow, brown staining).

Differential diagnosis of MCC

The histologic differential diagnosis of MCC includes SCLC, basal cell carcinoma, amelanotic malignant melanoma, malignant lymphoma, carcinoid tumor and atypical fibroxanthoma [24, 29].

Efficacy in identifying microscopically positive SLNs and radiologic imaging

Sentinel lymph node biopsy (SLN) enables the identification of occult nodal metastases; it is believed that up to 20% of primary MCCs have metastases to proximal lymph node chains [29,30]. A recent study in patients with MCC demonstrated significant positive (8/16) and false negative (8/16) results in SLN. Thus, the authors concluded that given the high rate of SLN positivity, SLN should play a role in the management of MCC. Given the risk of false negative SLN, close observation of regional nodal basins is warranted in patients who have presented a negative SLN. Additional studies are required to investigate the impact of SLN on survival. The role of lymphoscintigraphy in MCC also warrants further studies [30]. Another large study assessed the use of SLN in conjunctival and eyelid MCC tumor patients, and addressed SLN in therapeutic management as recommended by a multidisciplinary consensus committee [31]. The authors performed a single center, prospective, nonrandomized clinical study between January 2008 and January 2010. Seventeen patients were included: 4 (2 conjunctival and 2 eyelid) melanomas, 4 eyelid MCCs, 8 (2 conjunctival, 2 eyelid, 2 eyelid/conjunctival, and 2 corneal/conjunctival) squamous cell carcinomas, and 1 eyelid meibomian gland carcinoma. Preoperative lymphoscintigraphy was performed one day before surgery to label lymph node(s) [31]. A surgical biopsy was then performed along with an extemporaneous pathological examination; these procedures were followed by a secondary complete lymph node dissection, performed only in instances of positive histology. The authors found that in all cases, one or more SLN were identified (3-13). Two biopsies (1 MCC and 1 squamous cell carcinoma) revealed neoplastic invasion of the SLN, and led to complete cervical node dissection. Adjunct regional treatment was indicated for 1 melanoma, 4 MCCs, and 2 squamous cell carcinomas. One false negative result was noted in the group of squamous cell carcinomas after 6 months, and it was treated. No relapse or death events were observed for the remaning 16 patients. The mean overall follow-up period was 18.2 months [30]. The authors concluded that as in previous studies, SLN biopsy for eyelid and conjunctival tumors is both safe and effective in identifying microscopically positive SLNs. The SLN procedure may also revive interest in the study of cervicofacial lymphatic drainage. The investigation was to be expanded and extended to other medical teams [31]. The study was of special interest in MCC since the majority of MCC cases present in the head or neck. In another study of 240 patients with primary MCC evaluated between 1981 and 2008, 99 had diagnostic imaging at initial presentation with biopsy proven primary cutaneous MCC, and had histopathologic nodal evaluation within 4 weeks of the initial scan [32]. The authors showed that computed tomography (n= 69) demonstrated a sensitivity of 47%, a specificity of 97%, a positive predictive value of 94%, and a negative predictive value of 68% in detecting nodal basin involvement. Fluorine-18-fluorodeoxyglucose positron emission tomography scanning (n= 33) demonstrated a sensitivity of 83%, a specificity of 95%, a positive predictive value of 91%, and a negative predictive value of 91% in detecting nodal basin involvement. [32].

Immunohistochemical (IHC) staining on MCCs

The "small round blue cell" histologic pattern of MCC must be differentiated from several other tumors, such as small cell bronchogenic carcinoma, carcinoid tumor, malignant lymphoma, and small cell malignant melanoma. Therefore, immunohistochemical (IHC) stains are required to confirm the diagnosis. MCCs are positive for selected epithelial and neuroendocrine markers, but are negative for hematolymphoid and melanocytic markers [33-47]. Table I shows characteristic IHC staining patterns for these entities. Positive staining for anti-Cytokeratin 20 (CK20) and neuron specific enolase (NSE) are quite specific for MCC. CK20 staining usually shows a paranuclear dot-like pattern, present in 97% of all MCCs stained with this antibody. This highly sensitive staining feature is very important in histopathologic analysis, to distinguish MCCs from other small round blue cell tumors. Thyroid transcription factor-1 (TTF-1) is usually expressed in small-cell bronchogenic carcinoma, but is consistently absent in MCC. TTF-1 belongs to a family of homeodomain transcription factors, and is selectively expressed in thyroid, lung and diencephalon derived tumors. TTF-1 has been further identified as a transcriptional regulator of thyroid-specific genes. Leukocyte common antigen/CD45 (LCA) is negative in MCC, but classically positive in malignant lymphoma [32-47]. SCLC is usually Cytokeratin 7(CK7) positive, but this marker is negative in MCC. Neurofilament protein (NFP) is usually positive in MCC, and consistently negative in SCLC. The differentiation between MCC and malignant melanoma is based on the negativity of the latter for CK 20 and its positivity for S-100 and HMB-45; MCC is classically negative for these markers[32-47]. Further, the tumor cells of MCC display additional antigens in varying frequency and intensity; these include Chromogranin A (CgA), synaptophysin, tenascin-C and CD56/NCAM. Finally, achaete-scute complex-like 1 (MASH1) is important in the development of the brain and the neuroendocrine system including pulmonary neuroendocrine cells. A recent study using a cDNA array identified MASH1 as one of the best gene markers to differentiate SCLC from MCC [46].

Treatment of MCCs

A wide local removal of the tumor is required, as well as removal of any positive and/or suspected lymph nodes in proximity to the MCC. MCC is a radiosensitive tumor. Radiotherapy has an important role in its treatment; chemotherapy may also be utilized in the treatment of MCC [48]. Even following aggressive surgical and radiation treatment MCC has a high rate of locoregional recurrence, including in early stage disease [50]. Recently, guidelines for the diagnosis and treatment of MCC were reported by the Cutaneous Oncology Group of the French Society of Dermatology [50]

Tumor	CK20	CK7	NSE	NF	TTF-1	S100	MASH1	LCA/ CD45	Mart-1/ Melan A	CgA
MCC	+	−	+	+	−	−	+	-	-	+
SCLC	−	+	+	-	+	−	−	-	-	+
Melanoma	−	−	−	-	−	+	−	-	+	-
Lymphoma				-	-		-	+	-	-

Table I. Comparison of immunohistochemistry staining in MCC with that of histologic differential diagnoses

Metastasis of MCCs

In addition to classic sites such as lymph nodes, liver, bone and brain, MCC can also metastasize to sites such the leptomeninges, intraspinal areas (epidural and intradural), pancreas, small bowel mesentery, gingiva, kidneys and other sites [51-55].

Case Report

A 76 year old female presented for a routine dermatologic examination; an asymptomatic, erythematous papule was observed on the left back. The patient's medications included potassium chloride, fexofenadine, Janumet® for diabetes mellitus, meloxicam for osteoarthritis, Cozaar,® miodipine, metoprolol for high blood pressure and Crestor® for high cholesterol. The patient's past medical history included arthritis, skin cancer, type 2 diabetes and elevated blood pressure. Her surgical history included a hysterectomy in 1980, removal of an ovarian cyst in 1984, knee surgery in 1993 and rotator cuff surgery in 2003. The patient's mother had a clinical history of melanoma. A skin biopsy of the erythematous papule was obtained; hematoxylin and eosin (H&E) staining and immunohistochemistry staining was performed.

Methods

Our H & E staining and IHC studies were performed as previously reported [56-60]. For IHC, we utilized the following antibodies: monoclonal mouse anti-human TTF-1, insulin-like growth factor II mRNA binding protein 3 (IMP3), ribosomal protein S6-pS240/phosphorylation site specific, serotonin, survivin, synaptophysin, bromodeoxyuridine, tissue inhibitor of metalloproteinases 1 (TIMP-1), CK20, NSE, neurofilament protein, cyclo-oxygenase enzyme 2 (COX-2), Cyclin D1, CD56/NCAM, Chromogranin A (CgA), calretinin, epithelial membrane antigen (EMA/CD227), Ber-EP4, pancytokeratin (clone AE1/AE3), proliferating cell nuclear antigen (PCNA), MIC2 and Ewing's sarcoma marker (CD99). We also utilized a polyclonal rabbit anti-human antibody to somatostatin. All antibodies were obtained from Dako (Carpinteria, California, USA). Our study was IRB exempt because we utilized archival samples without specific patient identifiers.

Results

Microscopic examination of the H&E sections demonstrated a malignant neoplasm comprised of small round blue cells infiltrating through the dermal collagen and subcutaneous adipose tissues. Specifically, no epidermal involvement was observed. The tumor was present as trabecular cords, and nests; areas of crush artifact and zonal necrosis were noted. However, no Azzopardi phenomenon was appreciated within the tumor. Individual tumor cells displayed round, regular nuclei with fine, dispersed chromatin, indistinct chromocenters and minimal amphophilic cytoplasm. Frequent tumor cell mitotic figures were seen, and numerous apoptotic cells are also observed within the tumor. The neoplastic process extended to the deep specimen borders in the sections examined. On IHC analysis, the tumor cells also displayed focally positive, membranous and cytoplasmic staining with the CgA special stain. Minimal „paranuclear dot" cytoplasmic staining was noted on review of the CK20 special stain. The following stains were completely or predominantly negative on the tumor cells: ribosomal S6-pS240, COX-2, Cyclin D1, neurofilament, calretinin, synaptophysin, CD99, TIMP1, serotonin and NSE. The following stains were positive in punctate, focal tumoral areas: CD56/NCAM, EMA/CD227, survivin, bromodeoxyuridine, Ber-EP4, PCNA, TTF-1, IMP3, Cytokeratin AE1/AE3 and.somatostatin.

Discussion

Our case demonstrates selected IHC positive staining favoring a diagnosis of metastatic primary bronchogenic small cell carcinoma, including positivity to TTF-1 and IMP3; in addition, we noted minimal tumoral staining to somatostatin, CK20, NF and NSE. Multiple authors have demonstrated that differential IHC staining may assist in distinguishing MCC and SCLC. Previously documented differential IHC staining in this context includes CK7, CK20, NSE, CgA, synaptophysin, NF, TTF-1, CD56/NCAM, S-100 protein, vimentin, c-erb B-2 oncoprotein, and CD117/c-kit antigen [32-47]. Thus, our findings demonstrate the complexity of this differential diagnosis workup. The tumoral clinical presentation and H&E findings favored a diagnosis of primary MCC; however, our IHC staining favored a diagnosis of metastatic SCLC, and unfortunately our patient was lost to followup. Interestingly, we found limited tumoral IHC positivity to IMP3(insulin-like growth factor II mRNA binding protein 3), a 580 amino acid oncofetal RNA binding protein containing four K homology domains. IMP3 is normally expressed in early embryonic tissues, and may also be expressed in a proportion of non-small cell lung carcinomas and pancreatic adenocarcinomas. Further, K homology domain-containing proteins may be overexpressed in high-grade neuroendocrine lung carcinomas and extrapulmonary small cell carcinomas [62-63].

Conclusions

Merkel cell carcinoma is a rare neuroendocrine tumor of the skin. Epidemiological factors strongly associated with this tumor include patient age over 65 years, fair complected skin, chronic sun exposure and immune suppression. The primary differential diagnosis of MCC is metastatic primary bronchogenic small cell carcinoma. Many challenges remain regarding the diagnosis and treatment of MCC. In order to provide clinical practice guidelines for the diagnosis and treatment of MCC, there is a need for further prospective multicenter evaluation its staging and treatment, including updating classifications for TNM staging [64]. Despite aggressive surgical and radiation treatment, MCC has a high rate of locoregional recurrence, even in early stage disease. Thus, SNL biopsy is useful for the staging and management of MCC patients. Finally, further research is needed to identify better clinical prognostic markers for this disorder.

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MYXOID DERMATOFIBROSARCOMA PROTUBERANS OF THE VULVA WITH MYOID NODULES: CLINICOPATHOLOGIC AND IMMUNOHISTOCHEMICAL STUDY OF A CASE

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Abstract
Dermatofibrosarcoma protuberans is a slow growing dermal spindle cell tumor seldom seen in the vulva and its myxoid variant, a rare type of dermatofibrosarcoma protuberans is characterised by extensive myxoid degeneration. We present the case of a 62 year old woman with an enlarging vulval swelling. Mass was excised surgically. Histopathologically the tumor consisted of uniform spindle-shaped cells showing strong positivity with CD34. In addition to the typical storiform pattern and lace like infiltration, prominent myxoid stromal changes were seen. Herein we report an interesting case of myxoid dermatofibrosarcoma protuberans, uncommonly reported in the dermatopathology literature.

Key words: dermatofibrosarcoma protuberans; myoid nodules; myxoid variant; vulva

Cite this article:
Geetha Vasudevan, Bikash Singhania, Archana Shivamurthy: Myxoid Dermatofibrosarcoma Protuberans of the vulva with myoid nodules: Clinicopathologic and Immunohistochemical study of a case. Our Dermatol Online. 2013; 4(1): 72-74

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare, locally aggressive dermal mesenchymal neoplasm that usually occurs on the trunk and extremities [1]. The characteristic histologic feature of DFSP is the proliferation of densely packed monomorphous spindle cells, arranged in a storiform pattern. It is uncommon in vulva and usually unsuspected clinically. To our knowledge, only 29 cases of DFSP of vulva have been reported thus far [2]. Herein we present an additional case of this tumor with myxoid areas and discuss its clinicopathological and immunohistochemical features.

Case Report

A 62 year old woman presented with an enlarging vulval swelling. The lesion had been growing over a period of 6 months. There was no history of weight loss, loss of appetite, vaginal or rectal bleeding, pain, fever, itching, trauma or surgery in the affected area. Five years earlier, the patient had undergone hysterectomy for uterine leiomyoma.

Clinical examination revealed a hard, bosselated, mobile mass measuring 6 x 8 cm, extending medially to labia minora. Mass was excised surgically and subjected to histopathological examination.

The gross specimen consisted of skin covered swelling measuring 10 x 7 x 5 cm. On sectioning the surface showed homogeneous glistening white, vaguely lobulated areas with myxoid areas (Fig. 1).

Microscopy showed hyperkeratotic epidermis,a subepidermal grenz zone and a partially circumscribed cellular spindle cell tumor composed of spindle shaped fibroblast like cells arranged in repetitive short intersecting fascicles (Fig. 2), imparting a storiform configuration with a very occasional mitosis (1/10 hpf) along with extensive foci of myxoid change containing prominent thin walled vasculature focally showing myoid nodules (Fig. 3). Tumor was seen infiltrating the adjoining adipose tissue in a characteristic lace like pattern with involvement of all margins and base.

Immunohistochemically, the tumor cells showed strong positivity for CD34. No staining of tumor cells with S-100 and Smooth muscle actin was seen leading to a diagnosis of myxoid dermatofibrosarcoma protuberans with myoid nodules.

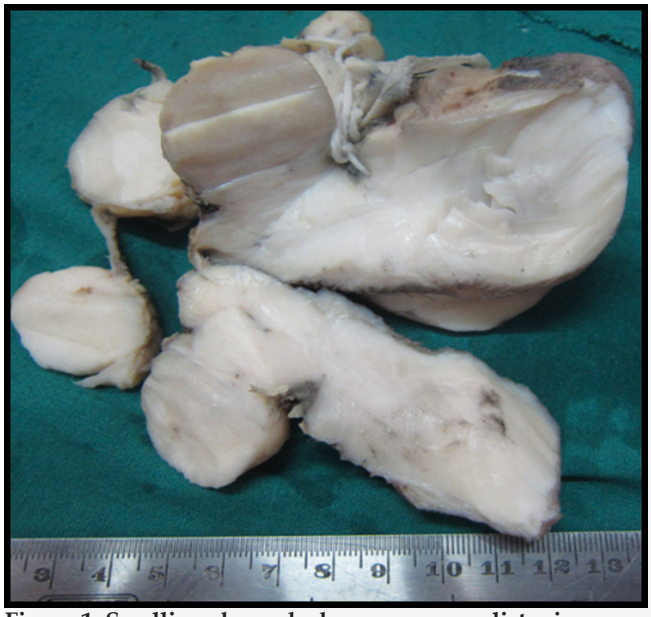

Figure 1. Swelling showed a homogeneous glistening white,vaguely lobulated cut section

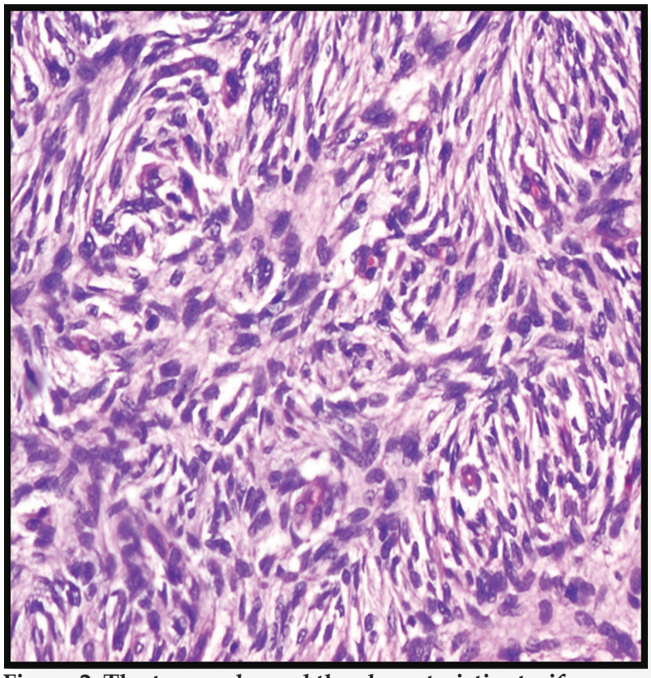

Figure 2. The tumor showed the characteristic storiform pattern (H&E, x 40)

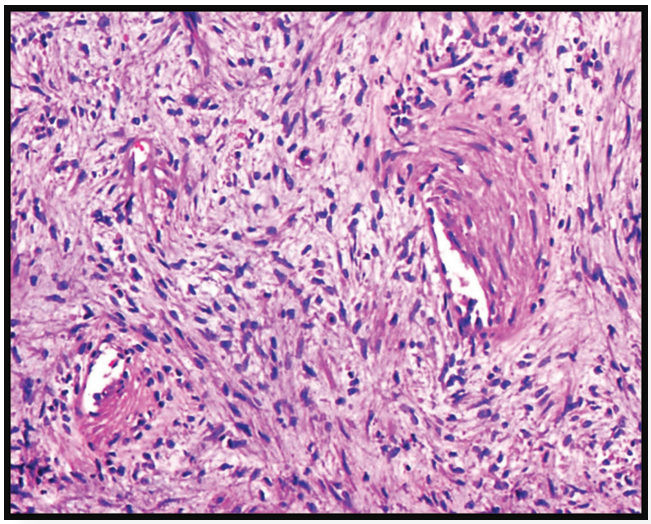

Figure 3. Myoid nodule centred along a blood vessel (H&E, x 40)

Discission

DFSP is a rare, slow growing, but locally aggressive tumor. DFSP of the vulva typically occurs as a firm, well circumscribed nodular mass attached to the overlying skin, but movable over the deeper tissues. Occurrence at sites of previous trauma has been reported, and many patients have a previous, long preoperative history [3].

Our patient neither had previous trauma nor operation history, except hysterectomy for uterine leiomyoma, 5 years ago. Histologically, DFSP consists of relatively uniform spindle cells containing elongated nuclei, without significant cytologic atypia or pleomorphism, and arranged in a predominantly typical storiform pattern. Although the tumor is usually located in the dermis, it invariably shows the infiltrative growth pattern, with trapping of the subcutaneous fat tissue in the characteristic honeycomb appearance.

Myxoid DFSP is a rare variant of this neoplasm, characterized by prominent myxoid stromal changes. The first such case was cited in 1983 by Frierson and Cooper [4]. Since then only a few cases have been reported. The pathogenesis of myxoid change remains uncertain, with majority of the cases presenting as a slowly growing, firm subcutaneous mass. The commonly involved sites were the extremities, followed by the head and neck [5]. In addition to the typical histological features of DFSP, the tumor cells in the myxoid type of DFSP are embedded in an abundant, palely eosinophilic myxoid stroma with prominent thin-walled vessels, the latter are frequently present throughout the tumor [5]. An unusual feature of DFSP is the myoid nodule. Originally construed as evidence of myofibroblastic differentiation [6], these structures seem to be centred in some cases around blood vessels [7,8], as seen in our case and likely represent an unusual non neoplastic vascular response to the tumor. Immunohistochemical findings are consistent with the typical DFSP, with the positive staining for CD34 ranging from 84% to 100%, and negative for other markers, such as S-100, desmin and actin [9].

Prominent myxoid changes can often obscure the typical storiform pattern, causing considerable diagnostic confusion [10]. The differential diagnoses of DFSP are diverse and the entities that may be considered are shown below in a tabular form Table I.

In summary, we present an interesting case of Myxoid DFSP, uncommonly reported in the dermatopathology literature. Possibility of this variant of DFSP should also be considered while evaluating myxoid soft tissue neoplasms.

Entity	Distinguishing features
Benign fibrous histiocytoma	- Short fascicles, haphazard growth pattern. - Presence of secondary element (giant cells, inflammatory cells). - **CD34**: Focal staining in occasional cases.
Myxoid neurofibroma	- Presence of tactoid structures, wavy buckled nuclei. - Lack of highly cellular areas with mitotic figures. - **S-100**: Protein positivity.
Myxoid liposarcoma	- Presence of lipoblasts and atypical, undifferentiated mesenchymal tumor cells. - **CD34:** Usually negative.
Myxofibrosarcoma	- Well-circumscribed tumor, with overall increased cellularity. - **EMA:** Positive staining in many low grade myxofibrosarcoma.
Superficial angiomyxoma	- Lesions tend to be displayed in a lobular growth pattern. - Scattered neutrophils surrounding the vessels.

Table I. The differential diagnoses of Dermatofibrosarcoma protuberans

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CARCINOMA IN CUTANEOUS LICHEN PLANUS

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Abstract
Carcinoma occurring in the cutaneous lesions of Lichen Planus though rarely mentioned in literature does occur and should be kept in mind while treating such lesions. We report a 16 year female who developed a squamous cell carcinoma in a long standing verrucous lichen planus in the lower leg.
This case is being presented to indicate the possibility of malignant transformation of cutaneous lichen planus to carcinoma, especially in the hypertrophic forms and the need to have an early diagnosis so that it can be treated in the initial stages. A high degree of suspicion should be present whenever we come across a non healing lesion in a patient with lichen planus. A few markers, which may give us a clue for increased chances of malignant transformation in these cases is presented.

Key words: hypertrophic lichen planus; squamous cell carcinoma; reverse sural artery flap

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Introduction

Lichen planus is a common papulo-squamous disorder affecting about 1-2% of the population. Lichen planus several forms. It can affect the oral mucosa, skin, nails and genatalia. Cutaneous lichen planus may affect any area but it is often seen on the front of the wrists, lower back, and ankles. Usually the lesions near the ankle are scaly and itchy and form the hypertrophic variant.
New lesions occur when the old lesions are clearing. When the lesions cleared they are often replaced by greyish brown discolouration especially in dark skinned individuals. Usually these lesions heal with the conventional treatment.
Neoplastic transformation in lichen planus has been described, especially in the oral form of the disease where an estimated 0.3-3% of patients may develop squamous cell carcinoma. Malignancy though uncommon with cutaneous lichen planus has been described in chronic hypertrophic lesions of lichen planus on the legs [3-5].

Case Report

We described a 16-year-old female, who presented to our Department in may 2011 with a non healing ulcer on her left ankle which had been present for approximately one year. She had been treated elsewhere but with no signs of healing. She had been diagnosed as having hypertrophic variant of lichen planus 7 years back.
On examination multiple raised pigmented verrucous plaques on dorsum, shins and ankles of both her legs were found. In some lesions there were areas of depigmentation (Fig. 1). A biopsy of one of the hypertrophic plaques showed classic features of a lichen planus.
An ulcero proliferative globular growth measuring 6cms x 6cms x 2cms was present on her left heel (Fig. 1). This was restricted in mobility and soft to firm in consistency, tender and there no bleeding on manipulation. The edges of the wound has plaques which suggested it had arised from a lichen planus lesion (Fig. 2). This was being treated by regular dressings. Earlier topical betamathesone and salicylic acid had been tried with only partial response. Both the legs had post inflammatory changes at sites of earlier lesions. The left inguinal lymph were enlarged with a firm consistency. Results of the histological examination of the ulcer biopsy, removed under local anesthesia on 28.05.2011, referred to a diagnosis of squamous cell carcinoma. FNAC of the inguinal lymph nodes suggested metastatic squamous cell carcinoma. A wide local excision (2cms margin) with a reverse sural artery flap cover was done (Fig. 3).
Results of the histological examination confirmed malignancy (squamous cell carcinoma) (Fig. 4).

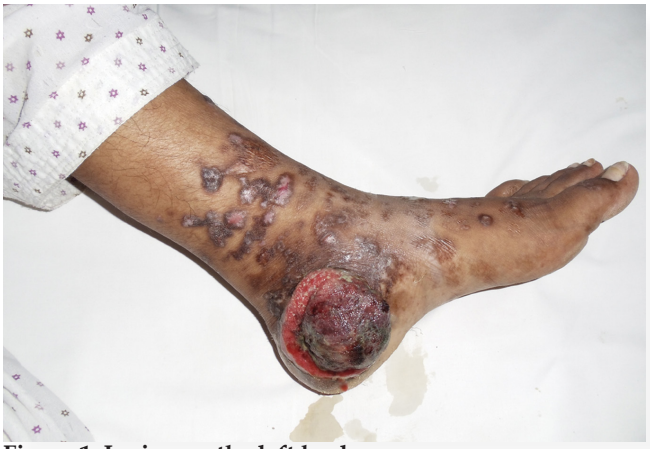

Figure 1. Lesion on the left heel

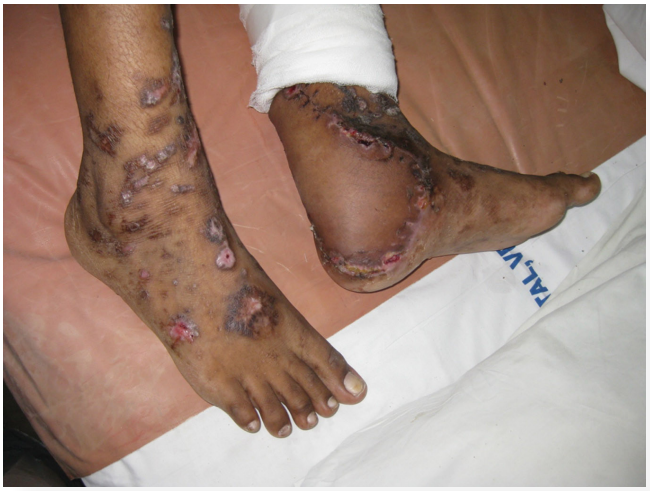

Figure 3. Post operative picture after excision and flap cover

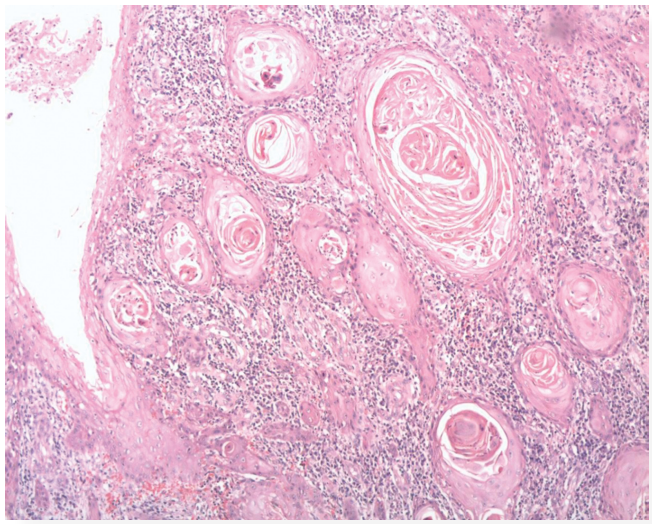

Figure 4. Squamous cell carcinoma

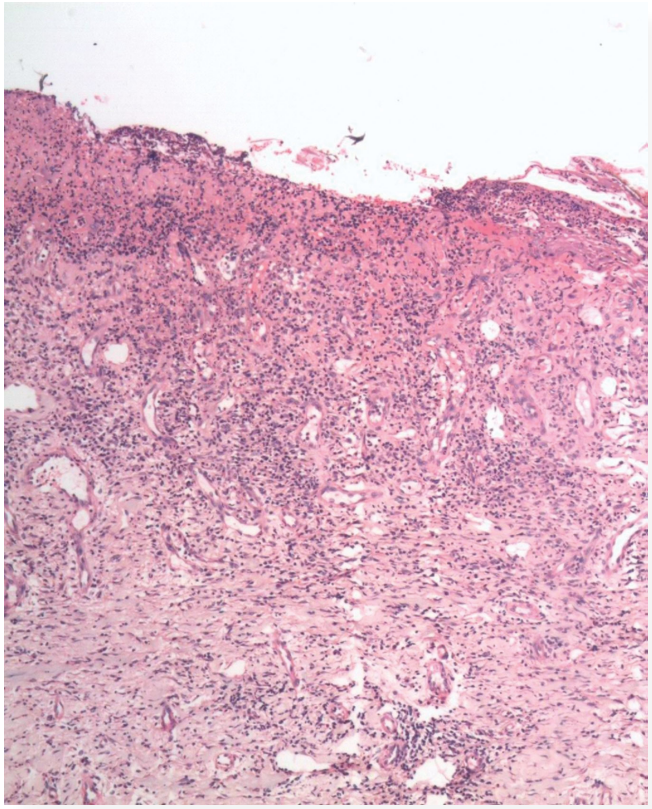

Figure 2. Skin biopsy of plaque over right foot with ulceration, crusting, non specific chronic inflammation

Discussion

Most squamous cell carcinoma (scc) is induced by ultraviolet light, while carcinogenic chemicals and human papilloma viruses are also implicated. While an increased risk of the development of carcinoma in oral LP is generally accepted, it is still unclear if there exists a true association between cutaneous lichen planus and Squamous cell carcinoma.

Squamous cell carcinoma complicating cutaneous Lichen Planus (LP) has an incidence of 0.4% and most of the reported cases are hypertrophic type [4]. It is essential that one identifies lesions which are likely to transform into carcinoma and a diagnosis is made early.

One such marker could be the presence of areas of depigmentation in the lesions. Such lesions have increased probability to turn malignant [5]. Depigmentation was present on our case too.

Another common feature of all cases reported so far in literature is the presence of the lesions in the legs (specially the ankles). Hence such cases must be viewed with increased suspicion [6-9].

Conclusion

Hypertrophic lichen planus on the legs tend to persist and has a propensity for malignant transformation even in young patients. Therefore non healing ulcers overlying such lesions should be viewed with great suspicion and biopsy performed to rule out squamous cell carcinoma.

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LICHEN PLANUS PIGMENTOSUS: TWO ATYPICAL PRESENTATION

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Abstract
Lichen planus pigmentosus (LPP) is a chronic pigmentary disorder with variable pattern of presentation. We here by present two cases of LPP one with parallel band like pigmentation over abdomen sparing the abdominal skin creases and other with parallel band like pattern following the Blaschko's lines over left side of the abdomen. Our cases are unique not only for its presentation but also for the pattern of distribution and LPP should be the differential diagnosis in any pigmentary disorders.

Key words: lichen planus pigmentosus; parallel band; Blaschko's lines

Cite this article:
Falguni Nag, Arghyaprasun Ghosh, Gobinda Chatterjee, Nidhi Choudhary: Lichen planus pigmentosus: two atypical presentation. Our Dermatol Online. 2013; 4(1): 78-79

Introduction

Lichen planus pigmentosus (LPP) is an autoimmune, chronic pigmentary disorder. It was first described by Bhutani et al. [1]. It may be diffuse, reticular, blotchy, and linear. Face, neck, upper part of back, trunk and extremities are common sites of involvement while flexures larea are infrequently involved [2].

Case Report

Case 1

A 17 year old male student, presented with asymptomatic band like pigmentation over abdomen (Fig.1) for last 6 months. Pigmentation first started as small macules over the abdomen sparing the skin creases and the macules gradually enlarged laterally to form a band like appearance parallel to skin fold. The confluent macules were bluish black in colour with an irregular non erythematous border. Face, oral mucosa and other body areas were normal. There was no history of excessive sun exposure, frictional trauma or previous inflammatory condition over the site or any incriminating drug intake prior to onset of lesions.

Routine blood and urine examination was within normal limit. Hepatitis C profile was negative. Histopathological examination of a punch biopsy from the abdominal lesion revealed epidermal atrophy, basal layer degeneration, pigmentary incontinence and few inflammatory cell infiltrates in dermis consistent with lichen planus pigmentosus (Fig. 2).

Case 2

A 35 year old woman presented to us with bluish-black pigmentation over left side of abdomen of three months duration. Lesion initially started as discrete macules which later coalesced with each other to form linear bands like pattern following Blaschko's lines only over the left side of abdomen (Fig. 3). These lesions were asymptomatic and there was no history suggestive of any inflammatory lesion over these sites previously. There were no mucosal lesions. A histopathological examination of abdominal lesion was consistent with a diagnosis of lichen planus pigmentosus (Fig. 4).

Discussion

LPP is an uncommon variant of lichen planus and relatively common pigmentary disorder in Indian and Asian population with distinct clinical and histopathological characteristics [1,2]. As seen in our patient the commonest type of pigmentation is a bluish black one [2]. Other types are slate gray, dark brown and brownish black. Though LPP is most common on sun exposed areas such as face, neck, involvement of the flexural areas such as axillae, submammary areas and groin have also been reported [2,3]. The term LPP-inversus is used for the lesions involving the flexural areas [4]. Lesions initially appear as small macules and gradually become confluent over time to large areas of pigmentation. Lesions may be diffuse, reticular or rarely blotchy and perifollicular [2].

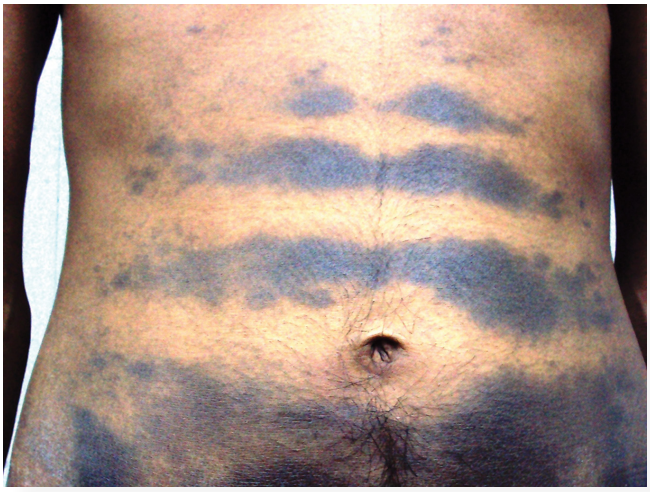

Figure 1. Parallel band of pigmentation

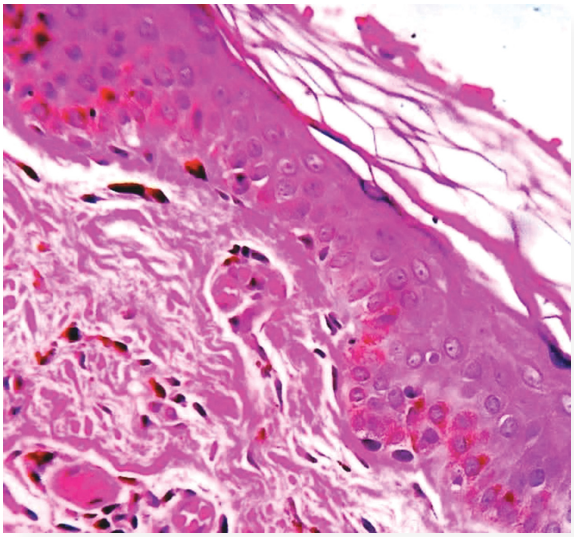

Figure 2. Photomicrograph (x400, H&E stain) showing HPE of LPP

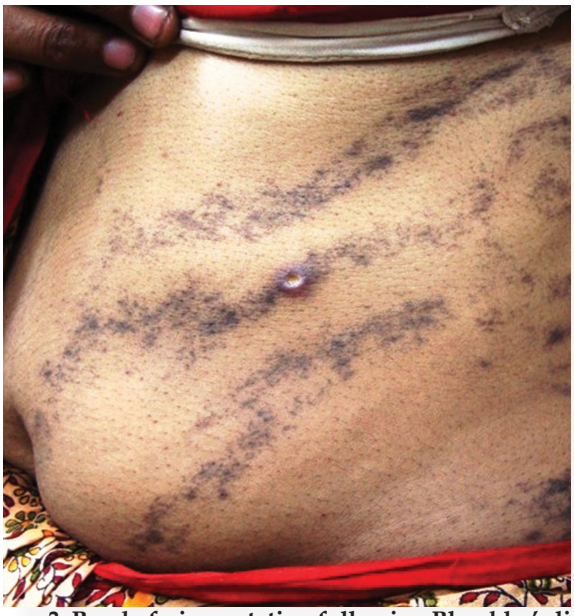

Figure 3. Band of pigmentation following Blaschko's lines

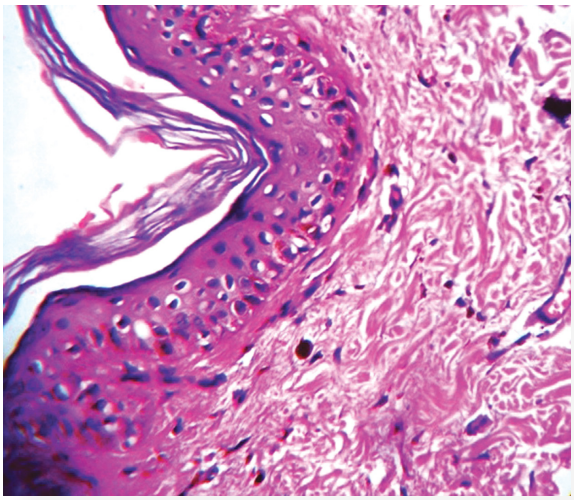

Figure 4. Photomicrograph (x400, H&E stain) showing HPE of LPP

In our first case lesion started similarly as discrete macules and became confluent to form parallel band like pattern over abdomen and speared the skin creases. The commonest differential diagnoses considered was ashy gray dermatosis but an early presentation and the histopathological findings established the diagnoses of LPP. Skin crease sparing may be explained by a relatively less sun exposure over the site for sitting habit. There are few reported cases of linear pattern [5], zosteriform pattern over trunk [6] and involvement of non sun exposed areas such as thigh [7] but to the best of our knowledge there is no reported case of band like distribution of LPP. The commonest differential diagnoses of the linear pigmentation in second case are incontinentia pigmenti, linear and whorled nevoid hypermelanosis but the late onset and histopathological findings ruled out these possibilities. Linearity of the lesions may be related to Blaschko's lines, which suggests the predisposition to develop LPP determined during embryogenesis [5].

Conclusion

Our cases are unique not only in their atypical presentations but also to the pattern of band like presentation. Thus LPP should be a differential diagnosis in every case of pigmentation disorder irrespective their sites and pattern of presentation.

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SARCOIDOSIS PRESENTING ERYTHEMA NODOSUM-LIKE LESIONS: REPORT OF TWO CASES

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Nil
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None

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Abstract
Introduction: Sarcoidosis is a systemic non-infectious granulomatous disorder which exhibits various specific and non-specific cutaneous manifestations. Erythema nodosum-like eruption is a rare specific lesion associated with sarcoidosis, which histologically shows non-caseating epithelioid granuloma. It is suggested that this type is frequently associated with ocular sarcoidosis.
Main observations: We describe two Japanese cases presenting with erythema nodosum-like eruptions on the lower legs, which histologically showed sarcoidal granuloma. The tenderness of erythema nodosum-like eruption is milder than that of non-specific erythema nodosum. Lung involvement was observed in both cases, and ocular involvement was seen in one of them.
Conclusions: Because of the high frequency of extra-cutaneous involvement, we should carry out skin biopsies to reveal specific sarcoidal granulomas appropriately and follow up patients with erythema nodosum-like eruption carefully.

Key words: sarcoidosis; erythema nodusum-like eruption; sarcoidal granuloma

Cite this article:
Taeko Nakamura-Wakatsuki, Toshiyuki Yamamoto: Sarcoidosis presenting erythema nodosum-like lesions: report of two cases. Our Dermatol Online. 2013; 4(1): 80-82

Introduction

Sarcoidosis is a systemic granulomatous disorder of unknown etiology. Approximately, 25% of patients have cutaneous lesions, which exhibit different manifestations depending on different races [1]. Specific manifestations include plaques, papules, maculopapules, subcutaneous nodules, infiltrative scars, and lupus pernio. EN-like eruption usually occurs on the lower limbs, which histologically shows non-caseating epithelioid granuloma located in the dermis to subcutis. On the other hand, erythema nodusum (EN), calcifications, prurigo, erythema multiforme, etc, are non-specific lesions of sarcoidosis, among which EN is occasionally seen. Skin manifestations might be the initial sign to make the diagnosis of sarcoidosis; however, EN-like lesion is not well-known. We report herein rare cases presenting with EN-like eruptions on the lower legs.

Case Report

Case 1:

A 30-year-old man complained of 2-weeks' history of erythema on his lower legs. He had been suffering from diarrhea and high fever. In addition, he had been congested with his eyes 1-month before visiting our department. A physical examination showed numerous erythematous patches with mild tenderness on the anterior aspects of bilateral lower legs (Fig. 1a). The histopathological findings revealed non-caseating granulomas with epithelioid cells throughout the dermis (Fig. 1b). The granulomas were associated with minimal infiltration of lymphocytes and plasma cells. Laboratory examination showed increased serum levels of angiotensin-converting enzyme (ACE) (33.7 IU/L, normal 7 to 25). Chest X-ray and computed tomography (CT) scan revealed bilateral hilar lymphadenopathy. Gallium scintigraphy confirmed the bilateral hilar involvement. Ophthalmological examination revealed granulated uveitis and bronchoscopic lung biopsy showed non-caseating epithelioid granuloma. The skin lesions on his lower legs were diagnosed as a specific granuloma of sarcoidosis. He has been treated with topical corticosteroid ointment and the indurated erythema gradually regressed.

Case 2:

A 65-year-old woman complained cutaneous lesions on the legs. A physical examination showed indurated erythema scattered on the frontal aspects of bilateral legs. Results of laboratory examination revealed slight increase of serum levels of ACE (22.8 IU/L, normal; 8.3 to 21.4) and lysozyme (13 μg/mL; normal 5 to 10.2).

Biopsy specimen revealed non-caseating epithelioid granuloma located in the subcutaneous tissues (Fig. 2).

Chest X-ray revealed bilateral hilar lymphadenopathy. Ocular involvement was not seen.

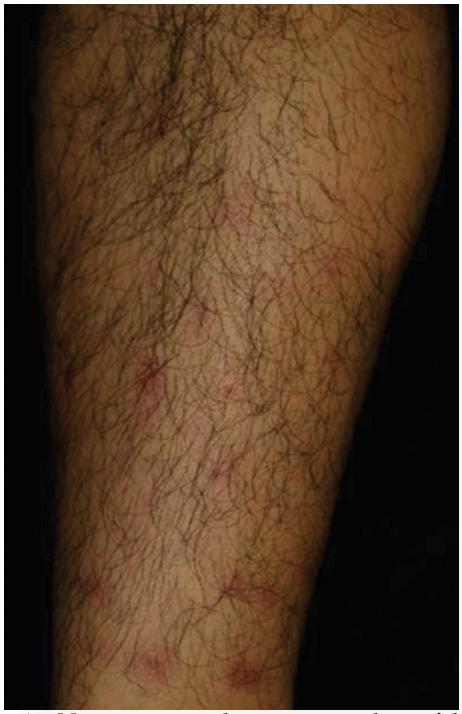

Figure 1a. Numerous erythemaous patches with mild tenderness on the anterior lower leg

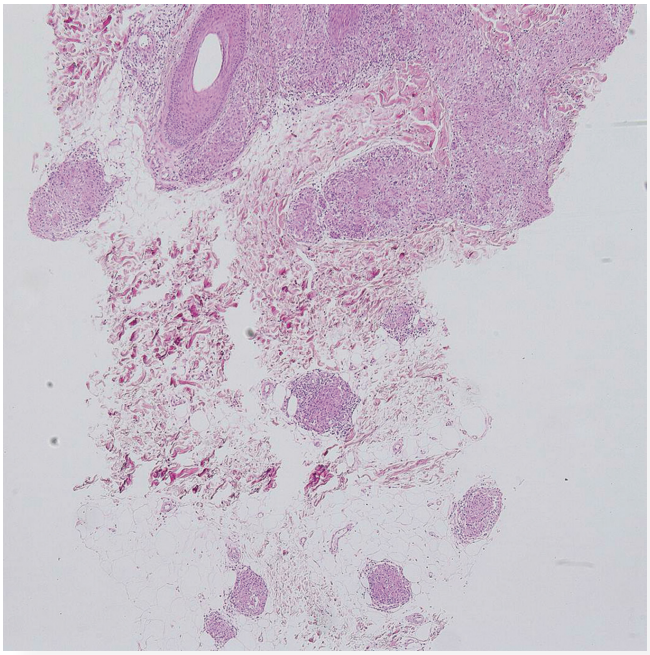

Figure 1b. Histopathological findings reveal circumscribed non-caseating epithelioid granulomas in the mid-dermis to subcutaneous tissues. (H&E stain, ×100)

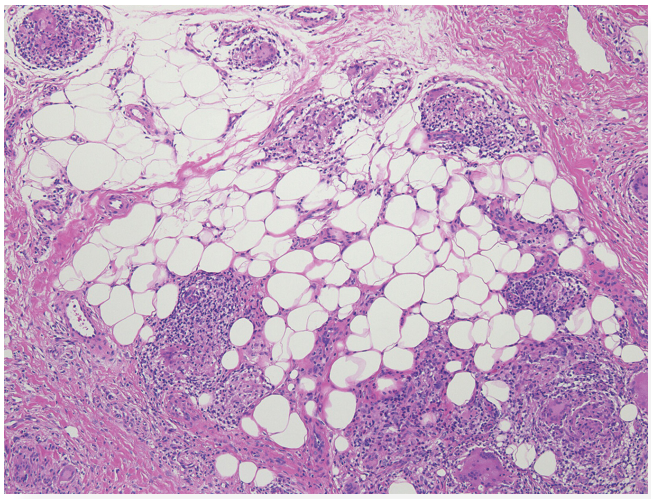

Figure 2. Histological features of Case 2, showing non-caseating epithelioid granuloma in the subcutaneous tissues

Discussion

Skin manifestations in sarcoidosis are seen in about 20-35% of patients [2]. Cutaneous lesions have been classified into specific and non-specific manifestations, based on the presence of non-caseating granulomas in the histologic examination. The most common non-specific lesion is EN which histologically shows septal panniculitis without sarcoidal granuloma. Löfgren's syndrome was first recognized as an acute and benign subtype of sarcoidosis, which usually presents the symptoms of EN, acute polyarthritis and bilateral hilar lymphadenopathy [3]. It is currently considered as a variant of sarcoidosis. A skin biopsy is necessary to make a distinction between specific sarcoidal granuloma and panniculitis of Löfgren's syndrome [4].

By contrast, EN-like eruption is a specific manifestation of sarcoidosis. Apart from EN in Löfgren's syndrome, sarcoidal granuloma is histologically detected. EN-like eruption associated with sarcoidosis has been reported in Japan; however, we can find only a few reports in English literatures [5,6]. EN-like eruption was unusual and the frequency was estimated approximately to be 5% among the cutaneous sarcoidosis in Japan. During these 30 years, we collected 31 cases reported in Japanese and the presented cases herein. 25 out of 31 are females (80.6%) and the mean age is 38 years old. Ophthalmic involvements are particularly seen in 23 (74.2%) of patients with EN-like eruptions, in which skin lesions preceded ocular lesions in 10 patients. Skin biopsies reveal the presence of non-caseating epithelioid granuloma in the mid-dermis to subcutaneous tissues. The clinical symptoms such as tenderness and subcutaneous induration tend to be milder than that of non-specific EN lesion. EN-like eruption tends to regress spontaneously [6].

Conclusion

Because of the high frequency of extra-cutaneous complications, cases presenting EN-like lesions have to be carefully followed up for ocular and lung involvements of sarcoidosis.

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N-TRAPS AND C-ANCAS IN A LUPUS ERYTHEMATOSUS--SCLERODERMA OVERLAP SYNDROME WITH VASCULITIS AND PANNICULITIS

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Abstract
Introduction: Histologic vasculitis must be interpreted with caution, as there is considerable overlap in its clinical, histologic and immunologic presentations.
Case report: A 42 year old woman presented with an plaque on the buttock that was tender to palpation, and had been present for six weeks. Physical examination revealed a large, erythematous plaque with focal areas of atrophy, pigmentation, small crusts, and small blisters. Skin biopsies for routine histology, direct immunofluorescence and immunohistochemical examination were taken.
Methods: Skin biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence, indirect immunofluorescence and immunohistochemistry studies were performed.
Results: Examination of the tissue sections demonstrated an inflammatory process involving capillaries and small blood vessels within the dermis and panniculitic adipose tissue. Focal extravasation of red blood cells into the dermal interstitial tissue was also observed. A mild, focal, lobular panniculitis was also present. Direct immunofluorescence and immunohistochemistry demonstrated deposits of several antibodies on vessels throughout the dermis. In addition, anti-neutrophilic cytoplasmic antibodies and neutrophil extracellular traps were identified.
Conclusions: Few vasculitic processes have pathognomonic histologic findings. Often, the dermatopathologist and clinician must work together, combining clinical, histologic and other laboratory data to determine the nature of the primary disease process. In our case, a diagnosis of vasculitis with autoimmune overlapping auoimmune syndromes represented the consensus diagnostic conclusion.

Key words: intraepidermal nerve fibers; ricin; blistering agents; direct immunofluorescence

Abbreviations and acronyms: Direct immunofluorescence (DIF), anti-neutrophil cytoplasmic antibodies (c-ANCAs), neutrophil extracellular traps (N-traps), basement membrane zone (BMZ).

Cite this article:
Ana Maria Abreu Velez, Vickie M. Brown, Lyndsay Shipp, Bruce R. Smoller, Michael S. Howard: N-traps and C-ancas in a lupus erythematosus-scleroderma overlap syndrome with vasculitis and panniculitis. Our Dermatol Online. 2013; 4(1): 83-86

Introduction

Clinical and histopathologic examination may offer some clues as to the pathogenesis of a vasculitis [1,2]. However, it is frequent to encounter a patient presenting some features of a syndrome, but lacking adequate features to establish a specific diagnosis [2]. A diagnosis of mixed connective tissue disease (MCTD) is considered when a patient presents selected combined features of lupus, scleroderma and myositis [2]. In MCTD, patients may initially present with predominantly lupus-like symptoms. Later, these patients may evolve and present scleroderma-like features. In the diagnosis of MCTD, a specific autoantibody pattern is sought featuring a positive antinuclear antibody (ANA) and positive ribonucleoproteins (RNPs) with a negative Smith (Sm) antibody [2].

Case report

A 42-year-old female presented complaining of a tender, large plaque on the right buttock that has been present for six weeks.

On physical examination, the right buttock and superior lateral thigh revealed a large, edematous, erythematous area with focal hyperpigmentation, inflamed crusts, small bullae and atrophy. The lesion was tender to touch and indurated. The patient described occasional "shooting pains" in the area of the plaque Skin biopsies were taken for hematoxylin and eosin (H&E) analysis. Biopsies for direct immunofluorescence (DIF) and immunohistochemisty (IHC) studies were also obtained. The patient was treated with delayed release Diclofenac sodium for one month, and a tapering course of prednisone. The patient did not improve significantly on this regimen, but colchicine was then given with clinical improvement. Notably, upon clinical improvement her N-traps and c-ANCAs disappeared.

Methods

Hematoxylin and eosin (H&E) stained sections and direct immunofluorescence (DIF) slides were prepared as previously described [2,3]. For DIF, multiple frozen section sets were cut at four microns thickness. DIF was then performed utilizing monoclonal immunoreactants to IgG, IgA, IgM, IgD, IgE, Complement/C1q, Complement/C3, Complement/C4, albumin and fibrinogen (all from Dako, Carpinteria, California, USA).

Immunohistochemistry (IHC) was performed as previously described [2,3]. For the IHC studies, we utilized antibodies to IgG, IgA, IgM, IgD, IgE, Complement/C1q, Complement/C3c, Complement/C3d, fibrinogen, albumin, kappa light chains, lambda light chains, CD45, CD68, myeloproxidase, Complement/C5-9/MAC, HLA-DPDQDR, thrombomodulin, vimentin, ribonucleoprotein (RNP) and vascular endothelial growth factor (VEGF).

Serologic testing: All ANAs, ANCAs and renal tests were within normal limits, but the patient had already completed a tapering course of prednisone. The H&E, DIF and the IHC studies were performed before initiation of immunosuppresive therapy.

Results

Microscopic examination:

Examination of the H&E stained tissue sections demonstrated a mild inflammatory process involving capillaries and small blood vessels within the dermis and subcutaneous panniculus. No fibrinoid changes were identified within blood vessel walls, and minimal leukocytoclastic debris was appreciated. Focal extravasation of red blood cells into the dermal interstitial tissue was observed. No granulomatous inflammation was present (Fig. 1, 2).

DIF studies demonstrated strong staining with FITC conjugated Complement/C3, C1q, IgD, IgG and fibrinogen in blood vessels at all levels of the dermis and panniculus. In addition, FITC conjugated IgA, albumin and IgG antibodies were positive for neutrophil extracellular traps (N-Traps). Anti-neutrophil cytoplasmic antibodies (c-ANCAs), were positive with FITC conjugated IgM and Complement/C3 antibodies. IgE was positive in a shaggy, linear pattern along the basement membrane zone. IHC studies revealed strong positivity with anti-human IgG, IgM, IgG, Complement/C1q, and fibrinogen around the dermal blood vessels. IgA clearly colocalized with the N-Traps when utilizing the myeloperoxidase stain. Significantly, CD68 staining was negative in the N-Trap areas. Complement/C5-9/MAC and HLA-DPDQDR were strongly localized around all vessels throughout the dermis and panniculus (Fig. 1, 2). Ribosomal nucleoprotein (RNP) was positive on the upper layer of the epidermis, within sebaceous glands and in many small vessels of the dermis. Vimentin showed compartmentalization around dermal blood vessels and around dermal appendageal structures.

Discussion

The constellation of clinical, histologic and immunofluorescence features is best characterized as an overlap syndrome with features of lupus erythematosus and scleroderma and including histologic vasculitis and panniculitis [1,4,5]. The histologic findings of small and medium sized vessel vasculitis in association with an early lobular panniculitis support this diagnostic concept; however, some of the observed immunoreactivity did not support our diagnosis, including shaggy deposits of IgE at the BMZ. The clinical etiology of the vasculitis was not certain, given the histologic features present. No histologic granulomatous inflammation was present, although we did consider a differential diagnosis of granulomatosis with polyangiitis (Wegener's syndrome), previously documented as a neutrophilic vasculitis that can feature N-traps and c-ANCAs [5-8]. Our DIF findings of IgA positivity warranted a review of the patient's renal function, which was within normal limits. Previous ANA and ANCA studies were also within normal limits; however, these studies were performed when the patient had received therapeutic systemic steroids for several months. In contradistinction, our DIF studies were performed when the patient had not received recent immunosuppressive therapy, and the c-ANCA and N-trap studies were positive at that time.

Neutrophils constitute a first line of defense against many infectious agents. When attempting to eliminate pathogens, neutrophils release neutrophil extracellular traps (N-traps), chromatin fibers coated with antimicrobial proteins. N-traps trap and destroy pathogens very efficiently, thereby minimizing tissue damage [4,6-8]. Further, N-traps modulate inflammatory responses by activating plasmacytoid dendritic cells. In addition, one study demonstrated that N-traps released by human neutrophils can directly prime T cells by reducing their activation threshold. N-trap-mediated T cell activation thus augments a documented array of neutrophil functions, and demonstrates a novel link between innate and adaptive immune responses [7]. In our case, we further document associated T cells and N-traps in the same autoimmune process.

Regarding our observed shaggy pattern IgE anti–BMZ autoantibodies, we could not find any previous report of a vasculitic process demonstrating this specific pattern. IgE anti-BMZ antibodies may present in bullous pemphigoid in a linear pattern, but would not be expected to demonstrate the overall pattern of IgE in a lupus band [9]. The clinical and pathological significance of our finding remains uncertain. In conclusion, very few vasculitic processes have pathognomonic histologic findings; thus, often the dermatopathologist and clinician must combine clinical, histological, and laboratory data to determine the nature of the primary disease process.

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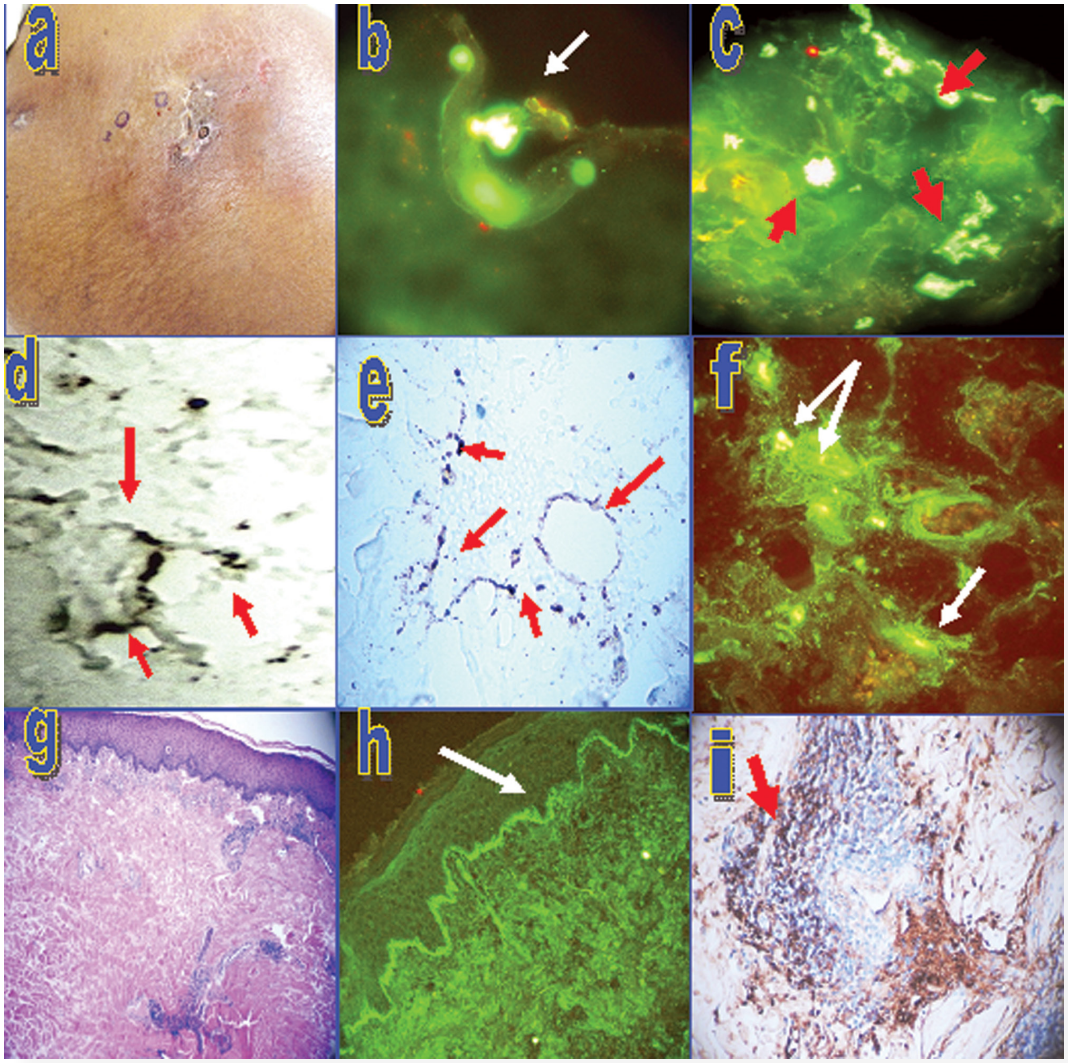

Figure 1. a. Clinical lesions on the buttock featuring large plaques, with focal hyperpigmented, erythematous and atrophic areas. **b**. DIF demonstrating FITC conjugated IgA N-traps being extruded through the corneal layer of the skin (green/white staining; white arrow). **c.** DIF demonstrating N-traps within dermal blood vessels (white staining; red arrows). **d.** IHC demonstrating N-traps, highlighted by positive staining against myeloperoxidase (brown staining; red arrows). **e.** IHC demonstrating N-traps, highlighted by positive staining for IgA (brown staining; red arrows). **f.** DIF demonstrating IgM positivity around dermal sweat glands (white/greenish staining; white arrows). **g.** H&E, demonstrating the inflammatory infiltrate around dermal blood vessels and focal dermal sclerodermoid areas. **h.** DIF demonstrating IgE shaggy deposits at the BMZ (green staining; white arrow). **i.** IHC demonstrating positive staining of fibrinogen around dermal blood vessels.

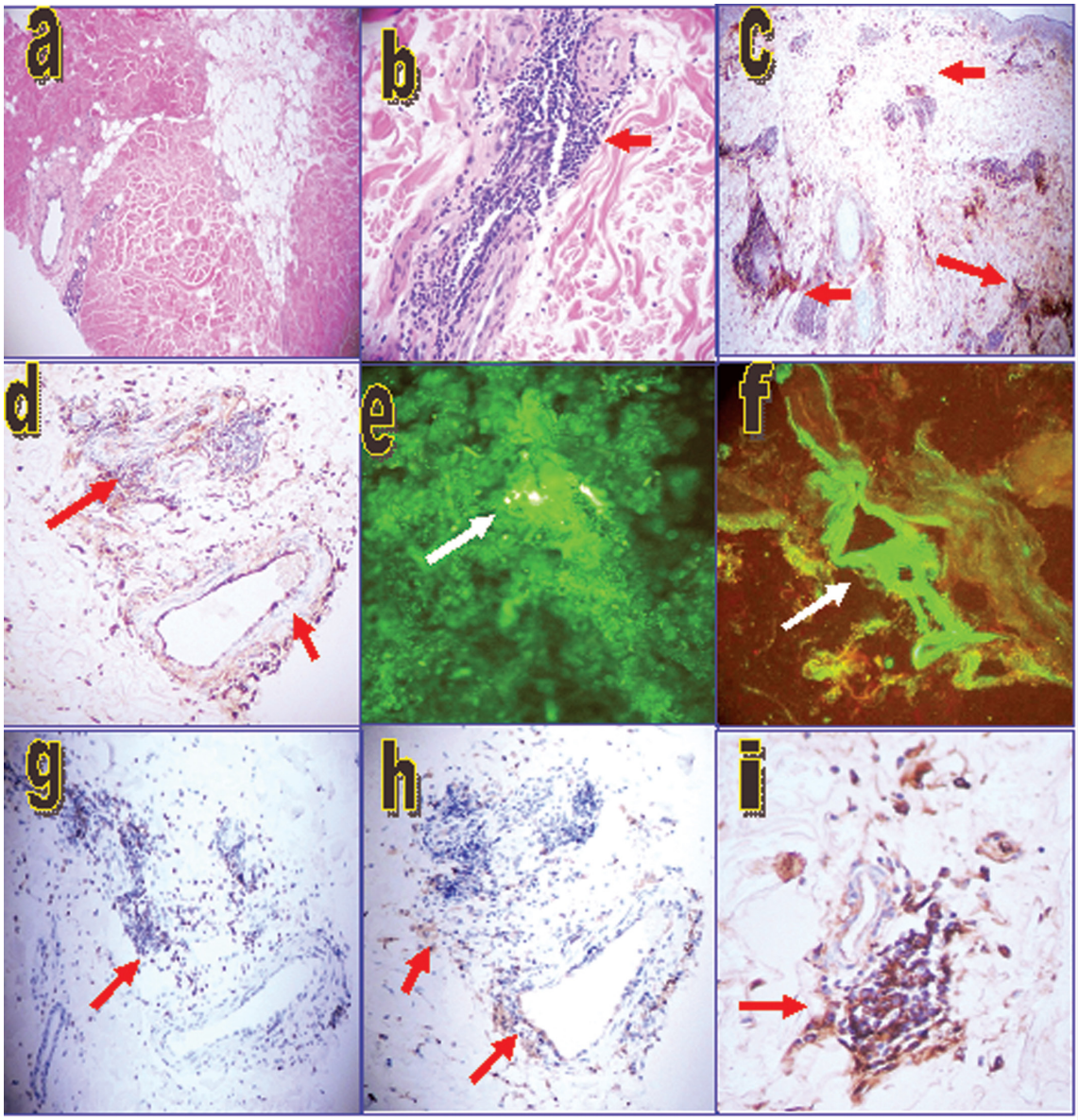

Figure 2. a. Focal H&E sclerodermoid histologic alterations in the dermis (100x). **b.** Demonstrates the H&E inflammatory process involving capillaries and small blood vessels of the dermis (200x). **c.** IHC demonstrating Complement/C3 positive staining around dermal blood vessels (10x), and in. **d.** at higher magnification (400x) (brown staining; red arrows). **e.** and **f.** DIF of FITC conjugated IgA in. **e.** and albumin in **f**, demonstrating positive staining against dermal blood vessels (green/white staining; white arrows). **g.** Positive IHC staining with CD45 of cells around dermal blood vessels (brown staining; red arrow). **h.** Positive IHC staining with HLA-DPDQDR around the dermal blood vessels (brown staining; red arrows). **i.** Positive IHC staining with the Complement/MAC/C5-B9 complex around dermal blood vessels (brown staining; red arrow).

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GENITAL HAILEY - HAILEY DISEASE: A CASE REPORT

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Abstract
Hailey - Hailey disease is a rare autosomal dominant acantholytic disorder, previously not reported from Nepal. We report a case of 30 years old female who presented with pruritic hyperkeratotic papules and plaques on vulva, perianal area and inner left thigh for a period of one year. Biopsy from the lesion showed suprabasal acantholysis with loss of intercellular bridges resulting in a dilapidated brick-wall appearance; characteristic of Hailey - Hailey disease. Treatment of this disease till date is far from satisfactory.

Key words: acantholysis; Hailey - Hailey disease; Nepal

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Deeptara Pathak Thapa, Anil Kumar Jha, Sujata Pudasaini, Chandani Kharel, Shristi Shrestha: Genital Hailey- Hailey disease: A case report. Our Dermatol Online. 2013; 4(1): 87-88

Introduction

Hailey-Hailey disease is a rare autosomal dominant acantholytic disorder. It is characterized clinically by a recurrent eruption of vesicles and bullae at the sites of friction and intertriginous areas. Histopathology is diagnostic of Hailey-Hailey disease. We present a case with an atypical presentation involving vulva, previously not reported from Nepal.

Case Report

A 30 year old female presented in the Department of Dermatology, Nepal Medical College and Teaching Hospital, with pruritic hyperkeratotic plaques on vulva, perianal area and inner left thigh for a period of one year. She initially had itching on the vulvar area. A month later, she noticed hyperkeratotic small raised lesion in vulva, which over three months, coalesced to form bigger lesions and spread to perianal area and inner left thigh. She experienced increase itching during friction and sweating but it did not aggravate during menstruation or stress. She denied history of similar disease in her family. She neither took medical advice nor medication prior to coming to our department. Local examination revealed violaceous to brownish irregular hyperkeratotic papules and plaques of different sizes, with well defined margin on lower one third of bilateral labia majora which extended to involve perianal area. There was also a plaque near medial aspect of inner left thigh near groin area (Fig. 1). Systemic examination showed no other abnormality. Biopsy revealed characteristic features of Hailey-Hailey disease (Fig. 2) showing large separation of detached stratum malpighii cells with loss of their intercellular bridge (acantholysis effect) in suprabasal portions. Detached epidermis showed dilapidated brick wall appearance, which was consistent with Hailey-Hailey disease. Immunofluorescence test, due to unavailability, could not be done in our set up. The patient was treated with oral Doxycycline and topical clobetasol propionate 0.05% cream and Tacrolimus 0.1% ointment. A month later follow up examination revealed marked clinical improvement. Patient was then continued with topical tacrolimus.

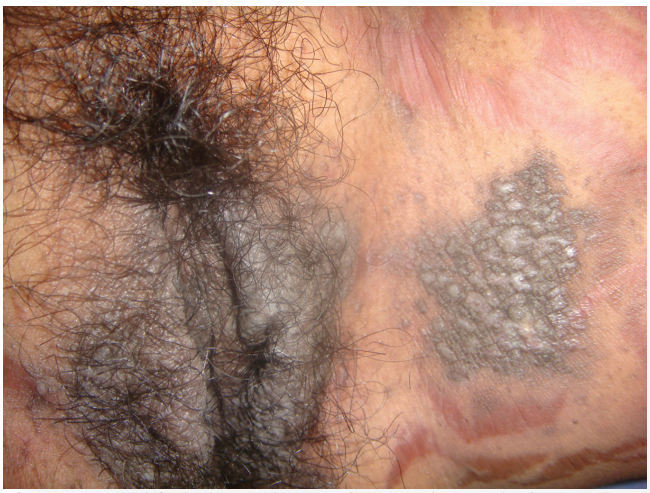

Figure 1. Multiple hyperkeratotic papules and plaque on vulva and near groin area

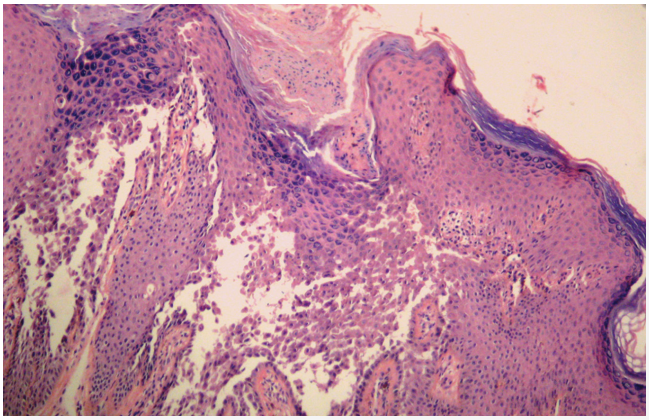

Figure 2. Detached epidermis showing characteristic dilapidated brick wall appearance

Discussion

Hailey-Hailey disease also known as Familial benign chronic pemphigus, was first described in 1939. It is an autosomal dominant acantholytic disorder which clinically presents as recurrent painful or pruritic fragile, vesicles and erosions in intertriginous areas involving axillary folds, groin, submammary region, and neck folds [1]. Patients mostly present with symptoms during the second or third decade of life and suffer from chronic, relapsing outbreaks [2]. Our patient presented with an atypical presentation involving vulva with hyperkeratotic plaques rather than the characteristic vesicle or erosion. Literature review quotes presence of lesion in atypical sites like with symmetrical distribution limited to the upper chest and anterior aspects of the upper arms and neck [3], erythroderma [4], conjunctivae [5] or mucosae [6,7]. The triggering factors like friction, heat, sweating, constrictive clothing, physical trauma, stress and menstruation have been attributed. Our patient also had exaggeration of symptoms during sweating and friction. Characteristic histopathological examination shows widespread suprabasal acantholysis with loss of intercellular bridges, which results in a dilapidated brick-wall appearance and similar picture was also seen in our patient. Recently studies have shown that Hailey-Hailey disease occurs due to the result of mutations in the ATP2C1 gene, which encodes Ca2+/Mn2+- ATPase protein 1 (hSPCA1), which is localized to the Golgi apparatus [1]. Keratinocytes which shows ATP2C1 mutation, have deficient Ca2+signaling, with dysregulated sorting and glycosylation of desmosomal proteins, giving rise to epidermal defects in skin lesions. Patients with Hailey-Hailey disease, a total of 98 ATP2C1 mutations have been reported worldwide. Linkage analysis has localized the gene locus to chromosome 3q21-q24 [8]. Colonization and secondary infections with bacterial, fungal, or viral microorganisms are known to be associated with Hailey-Hailey disease. Squamous-cell carcinoma that is rare can also occur [9]. The frequency of exacerbations may be decreased by wearing light weight clothing and avoiding activities that result in sweating or skin friction. Treatment option includes topical antimicrobials, steroids and intralesional steroids. Systemic therapy includes oral antimicrobials and few case reports describe use of cyclosporin, acitretin and methotrexate. Surgical methods like dermabrasion, CO2 or erbium-YAG laser vaporization and others like 5-aminolevulinic acid photodynamic therapy, botulinum toxin have been used with success. Surgical management with wide local excision of affected skin folds has a high complication rate. Refractory Hailey-Hailey disease may benefit from local electron-beam therapy [3,11-14].

Conclusion

This is very rare disease and no case has been reported from Nepal till date. Histopathology is an important diagnostic tool to diagnose Hailey- Hailey disease. Due to its relapsing and remitting course of the disease there is need to have effective treatment options in future to improve quality of life of the patient with Hailey-Hailey disease.

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TERRA FIRMA-FORME DERMATOSIS. A CASE REPORT

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Abstract
Terra firma-forme dermatosis is a cutaneous discoloration. 'Dirty' brown grey cutaneous patches and plaques that can be rid off by forceful swabbing with alcohol pads characterize it. The pathogenesis has been attributed to abnormal and delayed keratinization. It poses no medical threat. A 40-year-old male patient presented to the Department of Dermatology with a 2-3 month history of persistent pigmented patches on both upper arms. The lesions were not associated with itching or burning sensation. He gives no history of exacerbation on exposure to the sun.

Key words: Terra firma-forme; Duncan dermatosis; isopropyl alcohol

Cite this article:
Anagha Ramesh Babu, Metikurke Vijayashankar: Terra Firma-forme Dermatosis. A case report. Our Dermatol Online. 2013; 4(1): 89-90

Introduction

Terra firma-forme dermatosis is a cutaneous discoloration. 'Dirty' brown grey cutaneous patches and plaques that can be rid off by forceful swabbing with alcohol pads characterize it. The pathogenesis has been attributed to abnormal and delayed keratinization. It poses no medical threat.

Case Report

A 40-year-old male patient presented to the Department of Dermatology with a 2-3 month history of persistent pigmented patches on both upper arms. The lesions were not associated with itching or burning sensation. He gives no history of exacerbation on exposure to the sun. The patient is on treatment for diabetes mellitus since 6 months.

On examination there were brownish-pigmented patches measuring around 6 x 7 cms present on the lateral aspect of both upper arms. The lesions had islands of normal skin (Fig. 1). They could be rubbed off with isopropyl alcohol (70%) over 2 sittings. (Fig. 2) A KOH mount was negative. A 3.5 mm punch biopsy was taken from the lesion.

Histopathological examination revealed:

The epidermis was characterized by hyperkeratosis. Mild increase in melanin and melanin incontinence in the keratinocytes was present in the papillary dermis (Fig. 3). There was also perivascular and periadnexal chronic inflammatory infiltrate. Other features like focal areas of compact whorled orthokeratosis were present (Fig. 4).

Discussion

Terra firma-forme dermatosis (TFFD) is a benign disorder of keratinization characterized by retention hyperkeratosis, presenting as dirt-like plaques, despite normal hygiene. This condition is under-reported in the dermatology literature but may be more common in the general population. This type of dermatosis was first described in the 20th century. It derives its name from the Latin phrase 'terra firma' that means dry land. It has been referred to as 'DUNCAN' DIRTY DERMATOSIS after the physician who described in 1987 [1]. It is characterized by dirt-like muddy brown discoloration, which cannot be removed with just water, requires detergent to do the same. This condition has most often been seen in children, also in adults with equal incidence in males and females. It most commonly involves the neck and trunk followed by limbs, scalp, axillary line and pubic regions [1]. Differential diagnosis includes acanthosis nigricans, Gougerot and Carteaud confluent and reticulated papillomatosis [2], pityriasis versicolor, epidermal nevi, dirty neck syndrome of atopic dermatitis and dermatosis neglecta (DN) [3]. TFFD is distinguished from Dermatosis Neglecta arbitrarily by presence of adequate hygiene, absence of cornflake-like brownish scales and successful eradication of pigmentation with isopropyl alcohol in the former and effective clearance of lesions with soap and water in the latter. However, isopropyl alcohol is operative in both disorders. Histologically, DN is similar to TFFD, except for the absence of whorled hyperkeratosis in DN [3]. Nevertheless, the distinction between TFFD and DN is blurred and there seems to be a considerable clinical and histological overlap between the two disorders.

The diagnosis is made with a single wipe of the affected area using an alcohol-soaked cotton ball. The dermatosis often wipes off with the pad soaked in 70% alcohol [4].

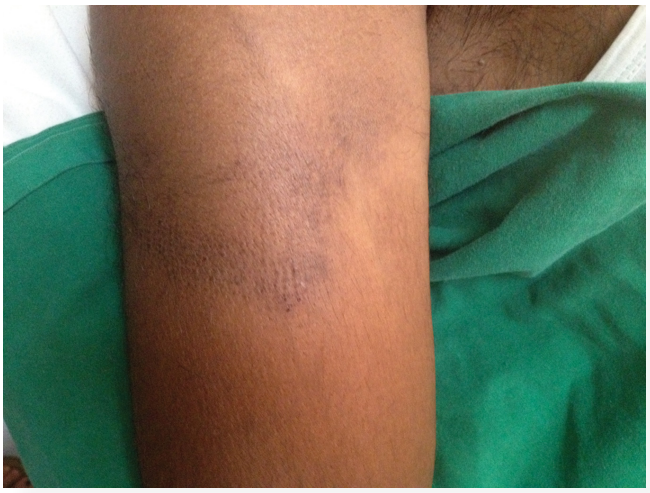

Figure 1. Brownish pigmented patches

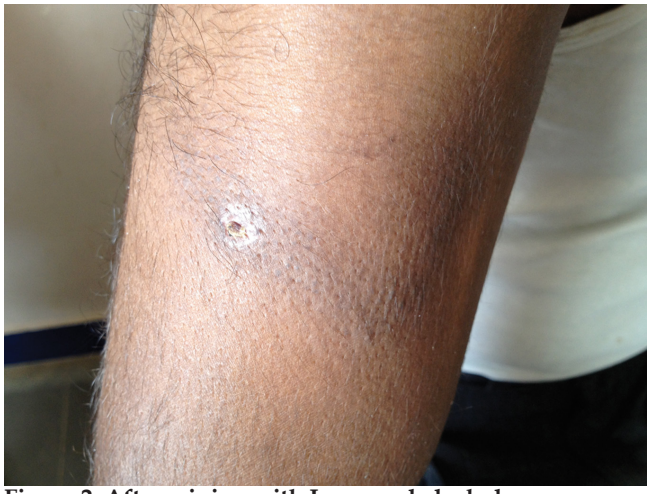

Figure 2. After wiping with Isopropyl alcohol, biopsy site

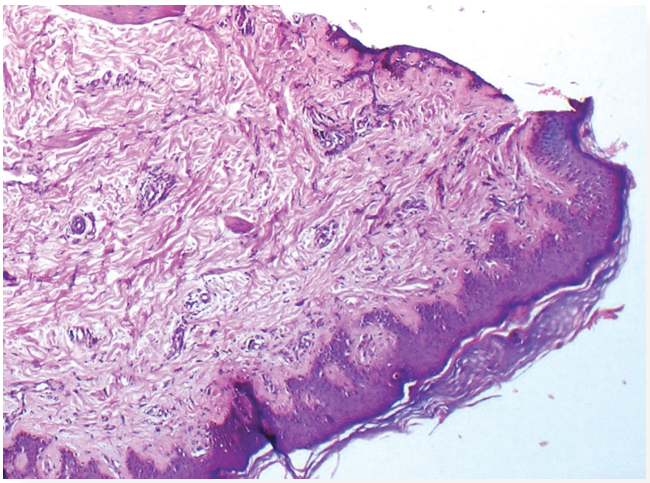

Figure 3. Hyperkeratosis with periadnexal and perivascular inflammatory infiltrate

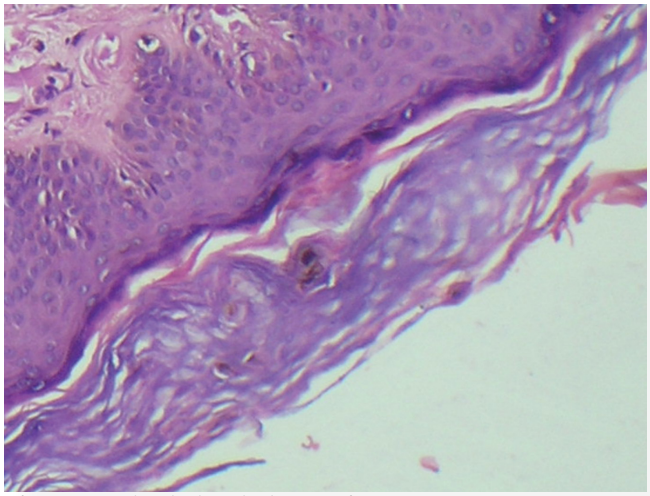

Figure 4. Whorled orthokeratosis

One hypothesis portrays TFFD as a disorder of abnormal and delayed keratinization and incriminates incomplete keratinocyte maturation, melanin retention and buildup and compaction of scales in the pathogenesis. TFFD represents retention, rather than a proliferative hyperkeratosis [3].

Some reports have focused on sunlight exposure as a triggering factor [3].

Existing data does not support a familial predominance or genetic susceptibility [4].

Patient with extensive terra firma forme dermatosis and their families were educated regarding cleaning the skin at home. After removal of pigmentation with isopropyl alcohol, discoloration usually does not recur. However, if it does, one may simply apply alcohol once a week to keep the skin clear [2].

Conclusion

Awareness of Terra firma-forme dermatosis and timely diagnosis prevents unnecessary investigations like biopsy and extensive endocrine evaluation. This cosmetically distressing condition brings relief to the patient after prompt treatment by application of isopropyl alcohol.

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NEURAL REACTIVITY DETECTED BY IMMUNOFLUORESCENCE IN A PATIENT WITH A LOCALIZED BLISTERING DISEASE

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Abstract
Introduction: Multiple clinical etiologies exist for rapidly appearing skin blisters are multiple.
Case report: A 69-year-old male from a rural area of Georgia, USA, was evaluated for the presence of suddenly appearing, localized erythema and edema on his leg with a skin blister. At presentation, the patient was taking multiple medications for other medical issues.
Methods: Skin biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence, indirect immunofluorescence and immunohistochemistry studies were performed.
Results: H&E staining demonstrated a subepidermal blistering process. Within the dermis, a mild, superficial, perivascular and perineural infiltrate of lymphocytes, histiocytes and eosinophils was seen. Direct and indirect immunofluorescence revealed focal dermal perineural and free epidermal nerve fiber staining utilizing antibodies to human Complement/C1q, C3, C4, kappa and lambda light chains. Immunohistochemistry studies revealed IgG, IgE, C3, fibrinogen, albumin and kappa deposition inside and around the blister.
Conclusions: Our case has some clinical and epidemiological features that resemble localized bullous pemphigoid, however, the most interesting findings were the neural reactivity without concomitant diabetes or peripheral neuropathy. Notably, a concomitant leak of ricin was simultaneously detected in same geographic area as the patient. We suggest that ricin environmental toxicity may have contributed to the observed neural reactivity.

Key words: intraepidermal nerve fibers; ricin; blistering agents; direct immunofluorescence

Abbreviations and acronyms: Monkey esophagus (ME), direct immunofluorescence (DIF), indirect immunofluorescence (IIF), immunohistochemistry (IHC), basement membrane zone (BMZ), hematoxylin and eosin (H&E), fluorescein isothiocyanate (FITC), 4',6-diamidino-2-phenylindole (Dapi).

Cite this article:
Ana Maria Abreu Velez, Michael S. Howard: Neural reactivity detected by immunofluorescence in a patient with a localized blistering disease. Our Dermatol Online. 2013; 4(1): 91-94

Introduction

Bullous diseases can be of autoimmune etiology, or caused by medications, diabetes, insect bites, porphyries, and other causes [1-4]. Blistering can be elicited by multiple medications, either prescribed or over-the-counter, as well as natural or synthetic dietary supplements [1-4]. Blisters may be the major clinical feature of the overall disorder; alternatively, blisters may be seen focally in localized areas of a more extensive rash [1-4]. Some of the known blistering diseases may overlap clinically.

Case report

A 69-year-old male was evaluated for blisters of a few days duration, accompanied by pain and itching. On physical examination, the patient displayed a single, intact tense bulla with mild erythema at its base. A second, adjacent site on the abdomen was consistent with a ruptured bulla with a denuded surface. The patient had a past medical history of multiple non-venomous insect bites on the legs, bronquiectasia, and urticaria. The patient was specifically medicated with bisoprolol fumarate 5 mgs orally daily, ipratropim bromide 0,02% inhalation solution 3 times at day via nebulization, clonazepam 0,5 mgs one tablet at day, Nexium™ 40 miligrams one tablet a day, Proair HFA™ (albuterol sulfate; 90mgs base) nebulization aerosol solution 2 puffs every 4 hours as needed, and Xopenex™ 0.63 mg/3ml inhalation nebulization 3 times a day. The patient was living in a rural area and had no clinical history of diabetes or peripheral neuropathy.

Clinically, the patient was diagnosed with bullous pemphigoid and was treated initially with betamethasone 0.05% cream, doxycyclin 100 mg a day and niacinamide; no improvement was achieved on this regimen. Next, the dermatologist prescribed a regimen of 1) prednisone 10 mg a day each morning for 3 weeks, increasing to a dosage of 2.5 mg prednisone every second or third day; 2) Os-Cal Extra D3™ 500 UI a day; and 3) hydroxyzine HCl 25 mg tablets, 1 or 2 tablets at night for itching. The lesions improved after several weeks of this therapeutic regimen.

Methods

Skin biopsies for 1) hematoxylin and eosin (H&E), 2) direct immunofluorescence (DIF), 3) indirect immunofluorescence (IIF) utilizing monkey esophagus (ME) substrate and 4) immunohistochemistry (IHC) stains were performed as previously described [6-9]. An additional sodium chloride salt split skin IIF technique was performed as previously described [4-6]. For the IIF we also used Texas red conjugated armadillo repeat gene deleted in velocardiofacial syndrome (ARVCF) antibody from Progen Germany.

Results

Microscopic and immunofluorescence findings:

Examination of the H&E tissue sections demonstrates a subepidermal blistering disorder (Fig. 1). Within the blister lumen, numerous eosinophils were present, with occasional lymphocytes also seen. Neutrophils were rare. Within the dermis, a florid, superficial, perivascular and perineural infiltrate of lymphocytes, histiocytes and eosinophils was identified. No vasculitis was present. A PAS special stain revealed reinforcement around most dermal nerves, and no fungal organisms. DIF displayed IgG (+++, diffuse dermal perineural); IgA (-); IgM (+++, diffuse dermal perineural); IgD (+, focal dermal perineural); IgE (-); Complement/C1q (+++, diffuse dermal perineural); C3 (+++, diffuse dermal perineural); C4 (+, focal dermal perineural); kappa light chains (+, diffuse dermal perineural); lambda light chains(++, diffuse dermal perineural); albumin(+, focal dermal perineural) and fibrinogen (+, focal dermal perineural) (Fig. 1, 2). Sodium chloride split skin IIF did not reveal significant dermal/epidermal junctional staining.

Discussion

We report a senior patient from a rural area who clinically suddenly developed erythematous plaques and focal blisters. Although clinically his diagnosis was considered to be bullous pemphigoid (BP), the DIF and IIF findings were not representative for that diagnosis. A bullous allergic drug reaction was the second differential diagnosis; however, contrary to most allergic drug reactions, the DIF findings of significant fibrinogen deposition around dermal blood vessels was not found [6]. Notably, BP can cause some neural pathologic sequelae [7]. Our immunologic findings indicated that the primary immunopathologic process was directed against the peripheral and free ending nerves of the skin. Usually reactivity to peripheral nerves can be seen in patients with diabetes and/or peripheral neuropathies, but not with as much immune response to the free epidermal fibers as seen in our case. We believe that our case may represent an allergic drug reaction, overlapping with a possible environmental exposure to a neurotoxic agent.

In the same period as we evaluated this case, our laboratory noted several patients from rural areas of Georgia that exhibited similar neuropathologic features as this patient. We thus reported our series of patients from rural Georgia with both skin blisters and neural reactivity to the US Centers for Disease Control (CDC) in Atlanta, because these findings could occur simultaneously with environmental contamination with ricin, or other neurotoxins [8,9]. Such a possibility is suggested when classical known disease patterns do not fit observed neuropathologic data over multiple patients.

Ricin represents a significant potential biological toxin because of its stability and worldwide availability as a byproduct of castor oil production. In addition, it may be a potential agent of bioterror [8,9].

We conclude that many conditions can cause blistering diseases; in selected cases, medication reactions and immunologic responses to neurotoxic agents may contribute to overall disease pathophysiology.

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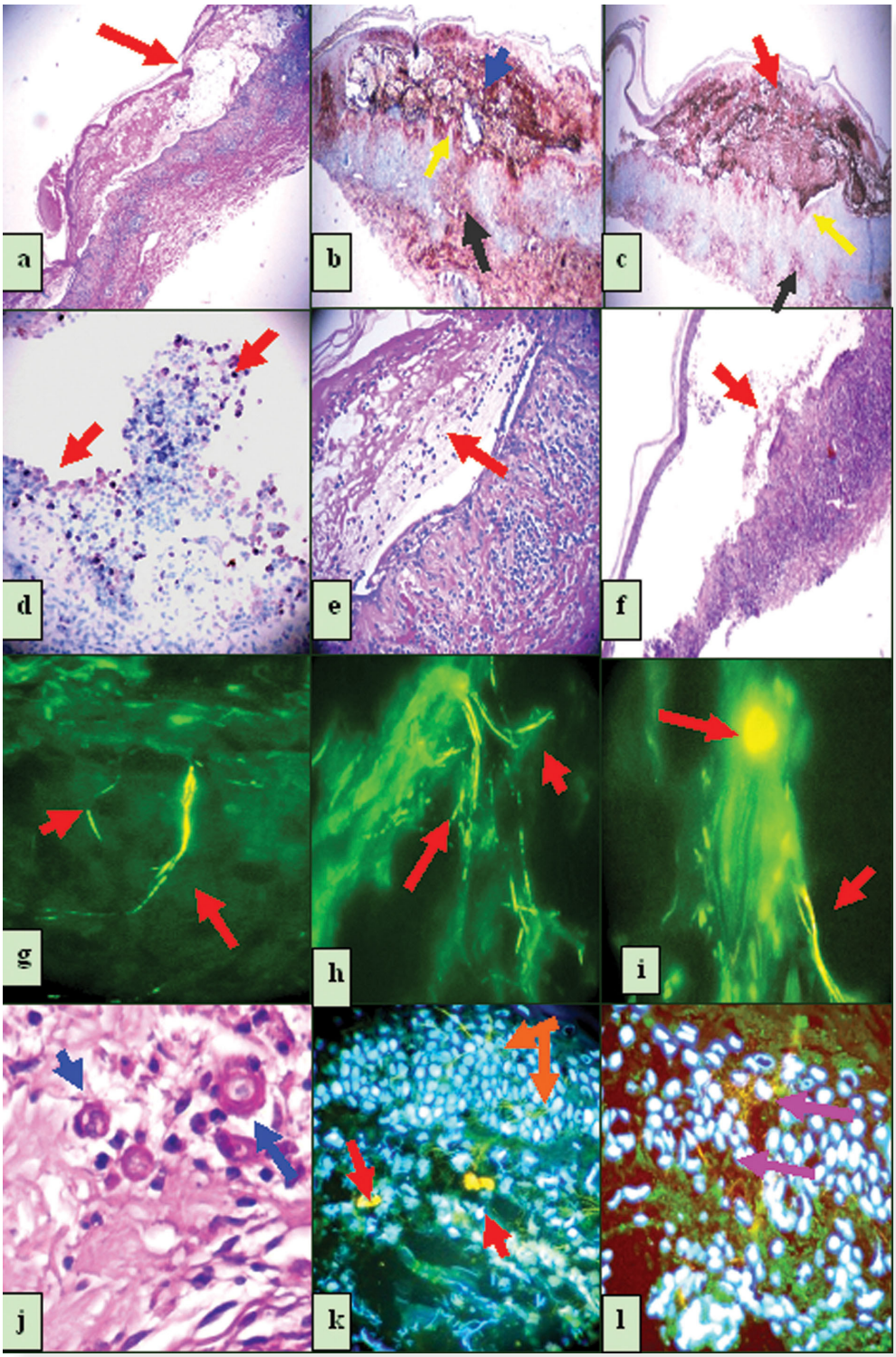

Figure 1. a. H&E showing a subepidermal blister with an intraluminal inflammatory infiltrate (100X). **b**. IHC showing C3 staining inside the blister (brown staining; red arrow), in some areas of the BMZ (brown staining; yellow arrow), and in focal areas of the papillary dermis (brown staining; black arrow). **c.** IHC showing similar pattern of positivity as in **b,** but utilizing anti-human albumin antibody. Note the staining inside the blister lumen (brown staining; red arrow), some staining in focal areas of the BMZ (brown staining; yellow arrow), and in the papillary dermis (brown staining; black arrow). **d.** IHC positive staining using anti-human IgE antibody on some cells inside the blister (dark brown staining; red arrows). **e, f**. H&E at higher magnifications, highlighting the blister contents (red arrows). **g** and **h**. DIF positive staining using FITC conjugated anti-human C1q against several neurovascular bundles in the dermis (yellow/green staining; red arrows). **i.** Similar to **g** and **h**, but at higher magnification (400X). **j.** PAS positive staining around the dermal neurovascular packages(blue arrows). **k**. Anti-human kappa antibody FITC conjugated showing positive staining in the neurovascular packages of the upper dermis (yellow staining; red arrows), please notice some thin fibers in the epidermis (green-yellow staining; orange arrow). **l.** Additional positive staining of thin neural fibers in the epidermis, but in this case using FITC conjugated anti-human IgG (green staining; fuchsia arrows).

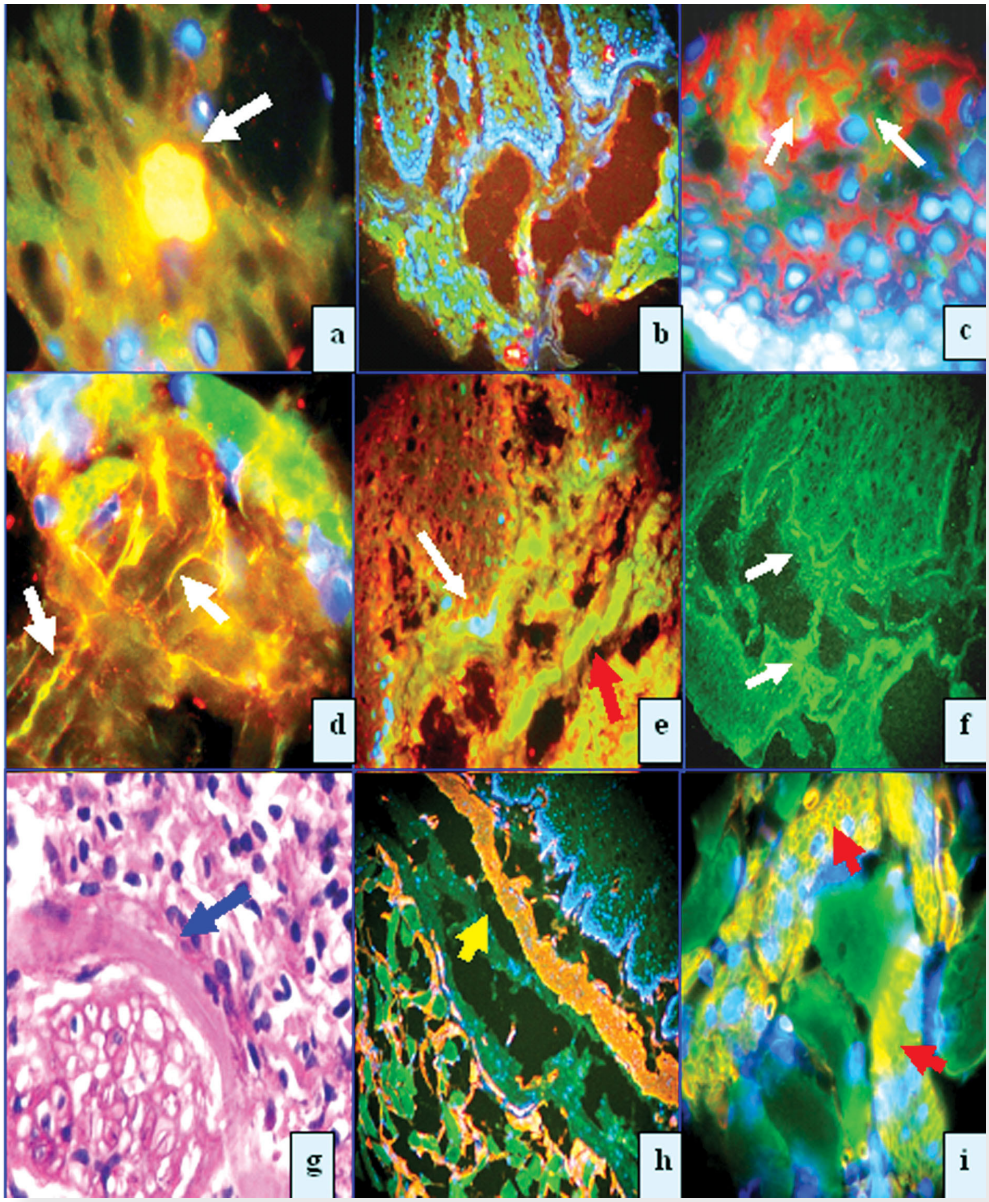

Figure 2. a. Double IIF staining utilizing FITC conjugated anti-human IgG antibody and Texas red conjugated anti-ARVCF antibody on monkey esophagus, and showing positive staining of a neural structure (flower-shaped structure; orange-yellow staining, white arrow)(100X). **b.** Double staining IIF on ME, showing positive stain with FITC conjugated anti-human kappa antibody (green staining; white arrow) and Texas red conjugated PPG 9.5 antibody(red staining) showing positivity in neural structures in the epithelium and BMZ (white arrows). **c.** IIF positive staining of neural structures on ME using FITC conjugated anti-human C4, and showing positive nerves in the epithelium (green staining, white arrows). The red staining between the cells is Texas red conjugated p0071 (100x). The nuclei of the epithelial keratinocytes are counterstained with Dapi (light blue staining). **d.** IIF on ME, demonstrating positive staining with FITC conjugated anti-human-C1q against several neural structures in the BMZ and beneath it (yellow-green staining; white arrows). **e.** IIF on ME, demonstrating positive staining with FITC conjugated anti-human-IgG against a neurovascular plexus in the epithelium (green staining; white arrow), and in the endomysium (green staining; red arrow). We also used Texas red conjugated armadillo repeat gene deleted in velocardiofacial syndrome (ARVCF) antibody, showing staining between the epithelial cells of the monkey esophagus (red staining). **f.** Similar to e, but using only the FITC conjugated anti-human IgG antibody (green staining; white arrows). **g.** PAS stain, showing some perineural staining and indicating the immune response occurs at this level (blue arrow; 400X). **h.** IIF on ME. Here we used Texas red conjugated anti-collagen IV antibody to address whether neural fibers crossed the endomysium collagen fibers (orange staining; yellow arrow) and the BMZ (blue staining). We were able to confirm that, as showing in higher magnification in **i** using a FITC conjugated anti-human kappa antibody, that nerves indeed tangentially cross the endomysium (yellow staining; red arrows).

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LITIGATION AGAINST DERMATOSURGEONS AND COSMETOLOGISTS AND CONSUMER PROTECTION ACT

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Abstract
The concept of beauty has acquired new dimensions due to the increasing awareness in general public about the aesthetic procedures. The problems between the patient and the cosmetologists arise when the patients expectations become very high and unrealistic. The classical concept of doctor – patient relationship born in the golden days of family physicians has undergone drastic change due to dramatic advancement in medical technology, availability of sophisticated imaging system, high tech electronics and preponderance of new diseases. However, the accountability of the doctors under the law of professional negligence has emerged as a debatable issue among the medical fraternity all over the country after the enactment of the consumer protection act, 1986, which has not only changed the law of medical negligence1, but created an inexpensive and speedy remedy against medical malpractice.

Key words: dematosurgeon; consumer protection act; negligence; medical insurance; compensation; cosmetologist; malpractice

Cite this article:
Neerja Puri, Ashutosh Talwar: Litigation against dermatosurgeons and cosmetologists and consumer protection act. Our Dermatol Online. 2013; 4(1): 95-97

Introduction

The dermatosurgeons and cosmetologists owe duty of care towards their patients. Failure to show due care or skill in medical treatment resulting in death, injury or pain of the patient gives rise to a cause of action in negligence [1]. A charge of professional negligence against a cosmetic surgeon is serious. It stands on a difficult footing to a charge of negligence against the driver of a motor car.The consequences are far more serious. It affects his professional status and reputation. With the best will in the world, things sometimes go amiss in surgical operations or medical treatment. A dermatosurgeon is not to be held negligent simply because something goes wrong. He is only liable when he falls below the standard of a reasonably competent practitioner in his field so much so that his conduct may be deserving of censure or inexcusable. A dermatosurgeon or cosmetologist will be judged by the standard of an average practitioner of the class to which he belongs or holds himself out to belong.

Failure to exercise due skill in diagnosis as a result of which wrong treatment is given, is held to amount to negligence [2]. A competent dermatosurgeon must know which case is beyond his skill. It is the bounden duty of the dermatosurgeon either to call in a more skillful person or to advise the removal of the patient to a place where skilled treatment is available. The dissatisfaction of the patients following dermatosurgery stems from inadequate communication between patient and the dermatosurgeon during the preoperative stage. The expected chances of success and failure, the risk and benefit of the procedure, the hazards and complications of the particular surgery should be explained to the patient before obtaining the consent for surgery. Under the general principles of tortuous liability the cosmetologist who caused injury or damage by negligence is bound to pay compensation. Taking a look at the above fallacies, it is advisable for a dermatosurgeon to get himself insured under the medical indemnity scheme of any of the national general insurance companies [3]. All this will help him to free from the heavy tensions of sudden financial load if any. Failure to obtain the history of the patient, may result in omission to make proper clinical examination leading to inappropriate therapy resulting in tragic end of the patient. The patient should be enquired about the drug history before the surgery because many drugs have serious complications if continued during the operation [4]. The duty of the dermatosurgeon is to observe the patient during postoperative stage in order to check abnormalities in pulse rate, blood pressure, respiration, urine output, temperature and consciousness level. It is important to monitor the fluid balance of the patient during postoperative period. The development of haematoma or wound infection is very common after emergency. Failure to diagnose and treat haematoma may contribute negligence [5].

Discussion

With the immense strides in technology health care has emerged as a profitable sector attracting investors from varied background in our country and the dermatosurgeons get to spend less and less time with their patients. Owing to lack of time,the dermatosurgeons and cosmetologists communicate adequately with the patients. As a result, the patient dissatisfaction is on the rise. Naturally, the dissatisfied patients are resorting to legal remedy [6]. Like other professionals the cosmetologists are liable to pay damages for their negligence under the law of torts. Unlike foreign countries the instances of award of damages in India are few and far between. The reason is obviously the low level of awareness of rights, the exorbitant court fees and the unending court procedures. A glance at the emerging scenario of the country indicates that our consumer courts are doing justice by giving adequate compensation to the genuinely affected patients and by dismissing the false and frivolous complaints with exemplary costs against committed cosmetologists. According to our apex court, a determination about deficiency in medical service is to be made by applying the same test as in an action for damages for medical negligence. One of the most important aspects of any profession is the degree of excellence, which a person practising that profession can give in his results. It is not at all expected that each and every dermatosurgeon would deliver the goods in the same expertise. There are so many aspects and factors that determine the relative competence of an individual in a group, vocation or a particular line of personalised and highly skilled practice. But what is important is that one acts, conducts himself and discharges his duties in such a manner as would be expected from a prudent contemporary in a similar situation having access to similar facilities. In a doctor – patient relationship, the patient is entitled to services from the doctor in such a degree of professional skill and expertise as would be expected from such a medical man of similar qualifications and standard [7]. In case the service availed is that from one who claims to be or is a qualified specialist, then the degree of skill required to be exercised is more. The dermatosurgeon must exercise the methods founded on scientific principles. It is pertinent to mention that the number of cases being filed before the redressal agencies under the consumer protection act relating to the cosmetologists are ever increasing. At the same time, in some cases the hospitals and nursing homes have filed complaints. The national consumer disputes redressal commission, which is sitting at New Delhi and the other state consumer disputes redressal commissions have delivered appreciable judgements on the basis of allegations made out in different cases in the light of provisions of the act [8]. These bodies are required to decide disputes while observing the fundamental principles of natural justice and have power to grant certain specific reliefs provided under section 14 of the act. In appropriate cases, the compensation or damages are also awarded. And it does not end here. There are penalties for non-compliance of the orders passed. So, you see the system, though simple on one hand, is doubtlessly effective and authoritative. Regarding 'Compensation', simply on hearing this word, spontaneously blood rushes in our bodies to claim the maximum, as it is apparently unearned. But it is not so. Damages, compensation and other incidental reliefs are based upon certain well-settled principles. There is compensation for other wrongs where loss suffered by party can be calculated in terms of money. The consumer protection act has also provided for granting of compensation or damages to an aggrieved consumer, but there is no table as such. Each case has its own peculiar circumstances and at best the quantum of penalty or fine etc is tried to be made commensurate with the degree of dereliction. Outflowing and incidental loss is also covered. Besides this, interest is also awarded and the costs of litigation may be awarded in addition to the above. Compensation to the aggrieved patients in consumer protection act is decided according to prescribed procedure. It is not at all inevitable that the court would grant a certain amount of money, because the same is claimed. The forums have to see first whether there was negligence or deficiency in service. Then, it is to be confirmed that the aforesaid negligence resulted in the loss to the patient. The nature and degree of loss is also vital i.e. the gravity of the injury caused and the span of period it would subsist. Furthermore, what implications would arise in the day to day life of the patient which includes financial loss, mental agony and social embarrassment etc. The age of the person, the source of income and the amount of income, further prospects in the career, the detriment caused due to the alleged disability, other diseases a patient is suffering from, history of chronic ailments and the concept of contributory negligence and extenuating circumstances which govern the formula to liquidate a sum of money as compensation. The expenses already incurred by the patient are also taken into account. In a nutshell, it depends on the peculiarity of facts and circumstances of each case and not by hard and fast rule. An error of judgement can be excused and reasonable degree of care and skill is expected but if the person professes to be specialist in the field, then a highest degree of skill is mooted. A dermatosurgeon charged with negligence can clear himself if he shows that he acted in accordance with general and approved practice [9]. It is not required in discharge of his duty of care that he should use highest degrees of skill, since each and every individual may never acquire the same. Even deviation from normal professional practice in peculiar and special circumstances is not necessarily evidence of negligence. As regards the standard of care required for the dermatosurgeon, it can be stated that a mistaken diagnosis is not necessarily a negligent diagnosis. A dermatosurgeon can only be held liable in this respect if the diagnosis is so palpably wrong as to prove negligence, that is to say if his mistake is of such a nature as to, imply an absence of reasonable skill and care on his part, regard being had to the ordinary level of skill in the profession [10].

Conclusion

In addition to the guidance given in the code of ethics, the certain other duties of a dermatosurgeon and cosmetologist should also be remembered :To use the necessary skill, care, judgement and attention in the treatment of his patients. He has full liberty to adopt any of the accepted theories of medicine or surgery in which he honestly believes. Also there is considerable scope for him in exercising his judgement and discretion, as medical science is not an exact science [11,12]. Dermatosurgeon must remember that he owes a duty towards his patients, whether there is any contract with the patient or not.

As soon as a dermatosurgeon agrees to treat a patient, relationship is legally established, it neither guarantees a cure nor an assured improvement for the treatment given by him. To conclude, the dermatosurgeon should follow the IADVL approved standards of care in dermatosurgery and should not show any negligence while carrying out the procedures. Also, the cosmetic procedures should never be done free of cost, rather it should be charged heavily. This is to compensate for the harassment and mental agony a dermatologist has to face later in the court of law.

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SEBORRHEIC DERMATITIS BY *DEMODEX FOLLICULORUM*

DERMATITIS SEBORREICA POR *DEMODEX FOLLICULORUM*

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Male patient, 28 years old, presents bilateral dermatitis with rosacea-rash on the nasal dorsum, accompanied by intense itching, scaling and burning for about four months. He did not refer an important personal medical history (Fig. 1-3). According to the topography and morphology, seborrheic dermatitis was diagnosed and then we procedure with the direct microscopic examination. We took a sample of scaly skin of the injured area for soaking with potassium hydroxide solution (KOH) to 10%. With this procedure, we observed adult specimens of *Demodex folliculorum* and revealed a density of 5 *Demodex* per field (Fig. 4-7). Photographs were taken with the consent of the patient. The publication of the photographs was authorized by the patient.

The *Demodex folliculorum* is a mite that is between 0.3 to 0.4 mm long [1]. It is the most common ectoparasites on humans. Their food source is sebum, concentrating mainly on the cheeks, cheekbones, forehead, nose and eyelids. The density in normal skin is less than five per cm^2, but the presence of 5 or more mites in $1cm^2$ has clear implications pathological [2.3]. Described various clinical forms of *Demodex* infestation in humans, called Demodicosis such as seborrheic dermatitis, pityriasis folliculorum, rosacea demodicosis like [4]. Seborrheic dermatitis is a chronic and inflammatory dermatosis with unknown etiology and many associated factors. The *Demodex folliculorum* plays an important role in the etiology of this disease, since the number of mites is significantly higher in patients with seborrheic dermatitis [5].

The importance of suspecting *Demodex folliculorum* infestation in cases of seborrheic dermatitis and the importance of direct microscopic examination with KOH, allows the observation and quantification of *Demodex folliculorum*.

Paciente varón de 28 años de edad, acude por una dermatosis bilateral con erupción de tipo rosácea en el dorso nasal, acompañado de intenso prurito, descamación y sensación de quemazón de cuatro meses de evolución. No refirió antecedentes patológicos personales de importancia (Fig. 1-3). De acuerdo a la topografía y morfología, se diagnosticó dermatitis seborreica y se le indicó el examen microscópico directo. Se tomó una muestra de escamas de la zona lesionada para su maceración con solución de hidróxido de potasio (KOH) al 10%. Con este procedimiento se observaron ejemplares adultos de *Demodex folliculorum* y se reveló una densidad de 5 *Demodex* por campo (Fig. 4-7). Se tomaron fotografías previo consentimiento del paciente. La publicación de las fotografías fue autorizada por el paciente.

El *Demodex folliculorum* es un ácaro que mide entre 0,3 a 0,4 mm de largo [1]. Es el ectoparásito más común en el ser humano. Su fuente de alimento es el sebo, concentrándose principalmente en las mejillas, pómulos, frente, nariz y párpados. La densidad en piel normal es menor a cinco por cm^2, pero la presencia de 5 o más ácaros en $1cm^2$ tiene implicancias patológicas claras [2,3]. Se han descrito diversas formas clínicas de infestación por *Demodex* en humanos, denominadas Demodicosis como la dermatitis seborreica, pitiriasis folliculorum, demodicosis rosácea like [4]. La dermatitis seborreica es una dermatosis inflamatoria y crónica, con una etiología desconocida y muchos factores asociados. El *Demodex folliculorum* juega un rol importante en la etiología de esta enfermedad, ya que el número de ácaros es significativamente superior en los pacientes con dermatitis seborreica [5].

Se destaca la importancia de sospechar la infestación por *Demodex folliculorum* en los casos de dermatitis seborreica y la importancia del examen microscópico directo con KOH, permite la observación y cuantificación de *Demodex folliculorum*.

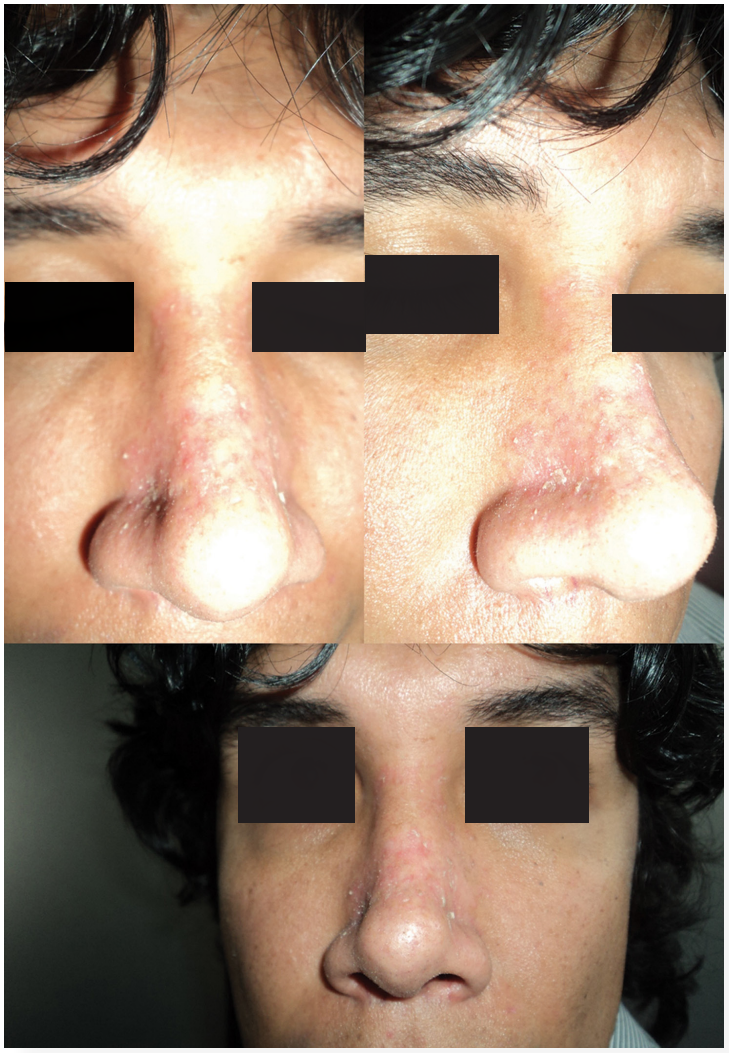

Figure 1-3. Male patient, 28 years old, presents bilateral dermatitis with rosacea-rash on the nasal dorsum

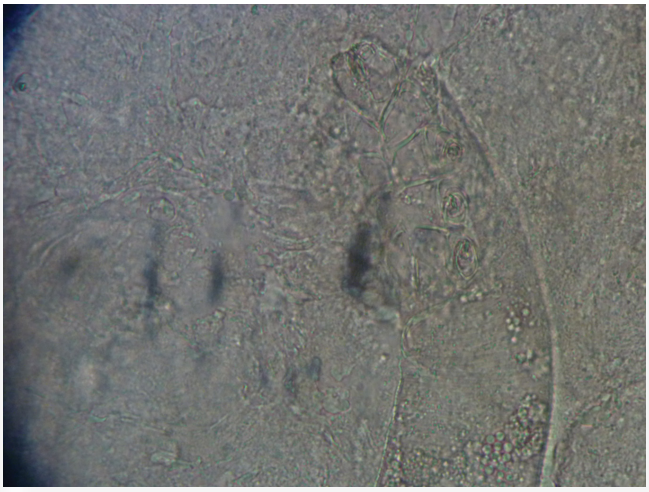

Figure 4. Photomicrography. Demodex folliculorum adult. Side view

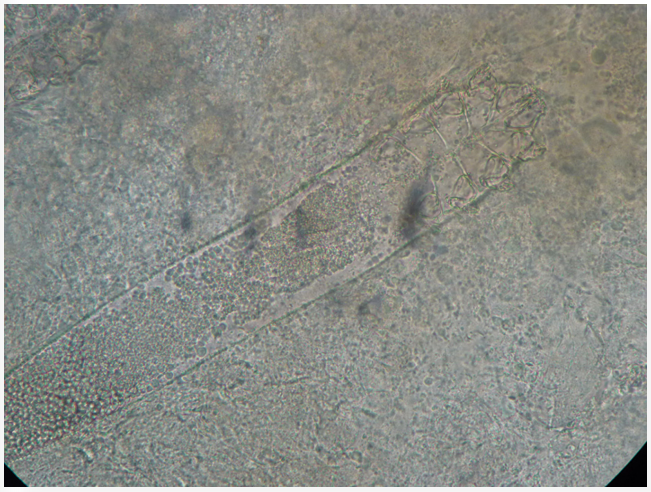

Figure 5. Photomicrograph. Demodex folliculorum adult, ventral view showing the gnathosoma or cephalothorax, podosoma with four pairs of legs and opisthosoma or abdomen striatum

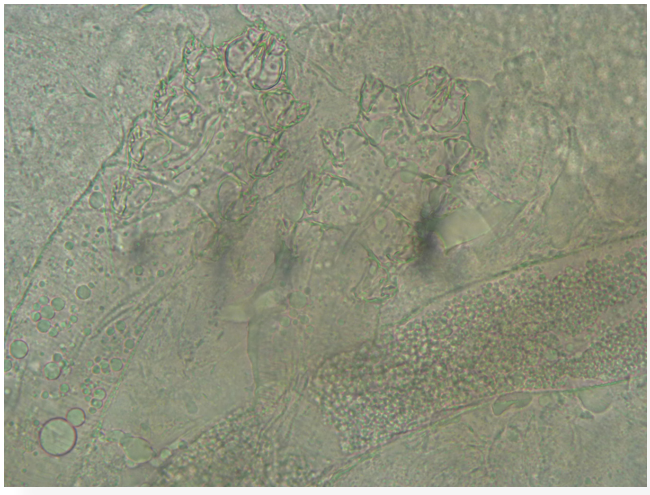

Figure 6. Typical clustering of Demodex folliculorum. Ventral view

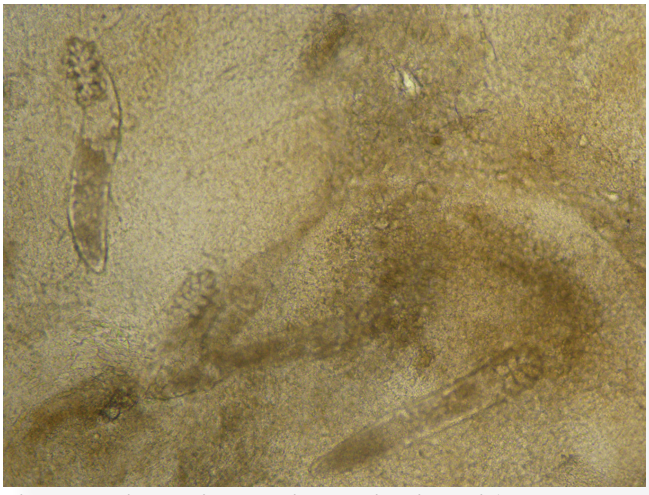

Figure 7. Direct microscopic examination with KOH: 5 Demodex per field (10X)

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REVERSIBLE HYPOPIGMENTATION OF HAIR SECONDARY TO VITAMIN B12 DEFICIENCY

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Ramesh Y Bhat, Chaitanya Varma: Reversible hypopigmentation of hair secondary to Vitamin B12 deficiency. Our Dermatol Online. 2013; 4(1): 101-102

Sir

Vitamin B12 deficiency affects all age groups and involves hematological gastrointestinal and central nervous systems. Mucocutaneous manifestations are rare, especially in children. We present a child with reversible hypopigmentation of hair because of vitamin B12 deficiency. A 3 year old male child born of third degree consanguineous marriage presented with history of lethargy, and increasing hyperpigmentation over the knuckles and feet. On examination child was observed to have pallor, sparse lusterless hypopigmented hair (Fig. 1, 2), angular stomatitis and hyperpigmentation over the hands and feet. Anthropometry was normal for age. Systemic examination was normal. Blood counts showed a low hemoglobin (10gm/dl), a reticulocyte count of 3% with the peripheral smear showing macrocytes (Mean cell volume, MCV=120fl) and anisopoikilocytosis. Bone marrow aspirate showed hyperplastic marrow with features of megaloblastic anemia. Serum electrolyte levels were normal. Serum vitamin B12 level was low (109.7pg/ml) and Folate level was normal (20Mcg/ml). Child was given a single dose of Vitamin B12 injection (1000microgram) followed by 1000 micrograms of oral Vitamin B12 daily. Since the child was a vegetarian a diet rich in Vitamin B12 was also adviced. On follow up child showed remarkable improvement in general condition, was active, playful and interactive. Pallor had disappeared and the hyperpigmentation over the limbs had significantly lightened. The hypopigmented hair had been replaced with dark healthy hair. The blood picture showed normalizing of hemoglobin levels with a good reticulocyte response.

Skin hyper pigmentation, vitiligo, angular stomatitis, and hair changes are some of the muco cutaneous manifestations associated with vitamin B12 deficiency [1]. A study done by Aaron et al. reported that 19% of the patients with Vitamin B12 deficiency had skin hyperpigmentation but only 9% of them had hair changes [2]. Reversible hypopigmentation of hair in the pediatric age group due to Vitamin B12 deficiency has very rarely been reported in medical literature unlike reversible hyperpigmentation of skin [3,4]. Unresolving pigmentation of the skin or hypopigmentation of hair should make the treating pediatrician consider treatment with Vitamin B12.

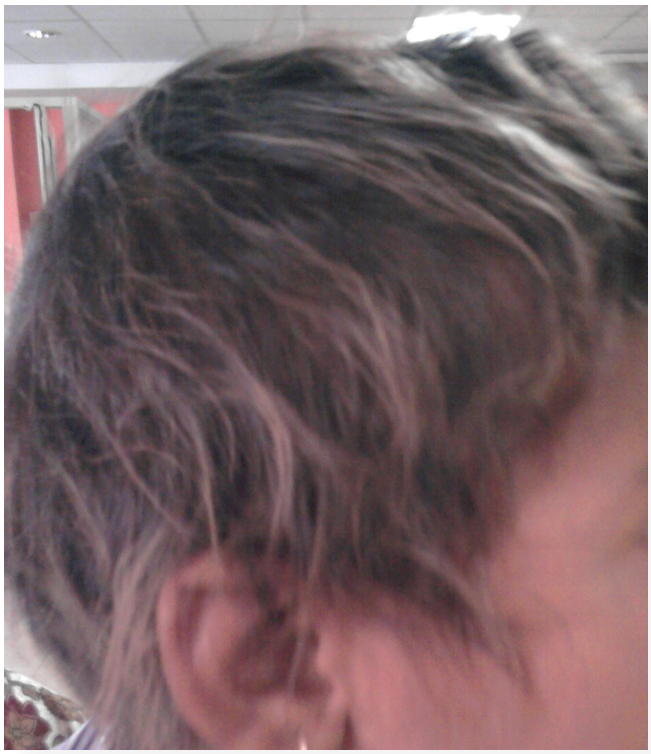

Figure 1. Sparse hypopigmented hair

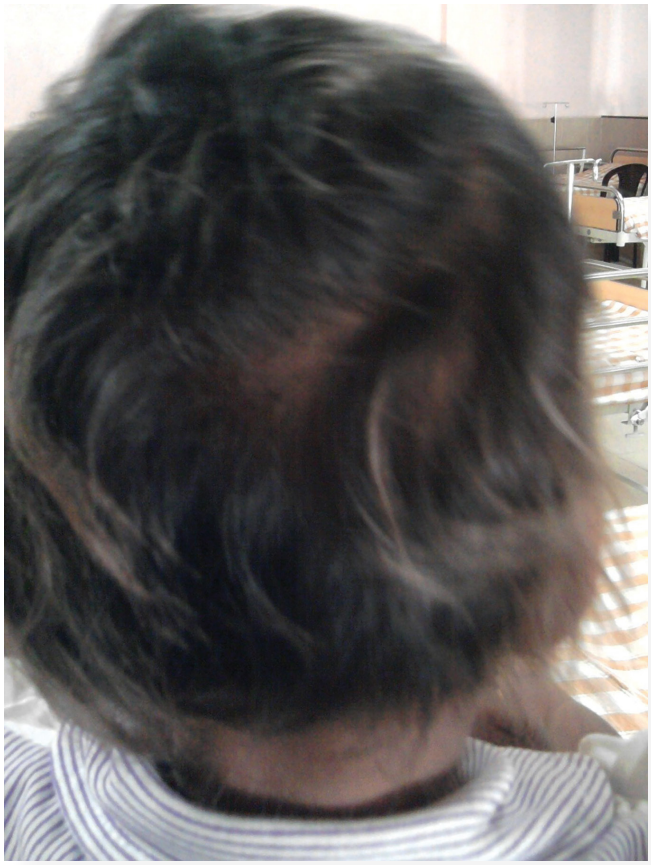

Figure 2. Sparse hypopigmented hair

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ADULT URTICARIA PIGMENTOSA WITH TRANSITORY DISAPPEARANCE OF LESIONS DURING ENOXAPARINUM TREATMENT

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Sir

We present a case of adult urticaria pigmentosa: maculo-papular type- with temporary disappearance of the lesions during treatment with Enoxaparinum.

History

A 52-year-old female pacient, with a 20 years history of asymptomatic, erythematous-to-brown macules and papules on the trunk, neck, buttocks and extremities, presented in our department a few months ago searching for a diagnosis (Fig. 1). Her medical problems were: an arterial hypertension (controled with Indapamidum) and osteoporosis (with no medication for).

Physical Examination

Scattered, erythematous, edematous papules and brown macules were present on the neck, chest, abdomen, back, extremities and buttocks. The face, palms, soles, and genitals were spared.

Lab

A complete blood count, basic metabolic profile, hepatic and lipid panels were within normal limits and we excluded systemic involvement. A bone density study showed osteoporosis. Serum tryptase levels, 24 hour urinary N-methylhistamine, N-methylimidazoleacetic acid and prostaglandin D2 metabolites excretion werewithin normal limits.

Skin biopsy cofirmed the diagnosis of generalized cutaneous mastocytosis (Urticaria pigmentosa) (Fig. 2A-D).

The patient left the Dermatology Unit with no medication, but she called us, a few weeks later for a new appointment. She described and we confirmed the dissapearance of the cutaneous lesions during the last weeks, while she was hospitalised for a hip fracture and treated with Enoxaparinum 40mg s.c/daily for 14 days.

The patient refused a new biopsy and we saw her again three months later, she again showed the characteristic brownish-red skin lesions of Urticaria pigmentosa, exactly as at the first appointment. The lesions had begun to appear very soon after she had stopped taking Enoxaparinum (Fig. 3).

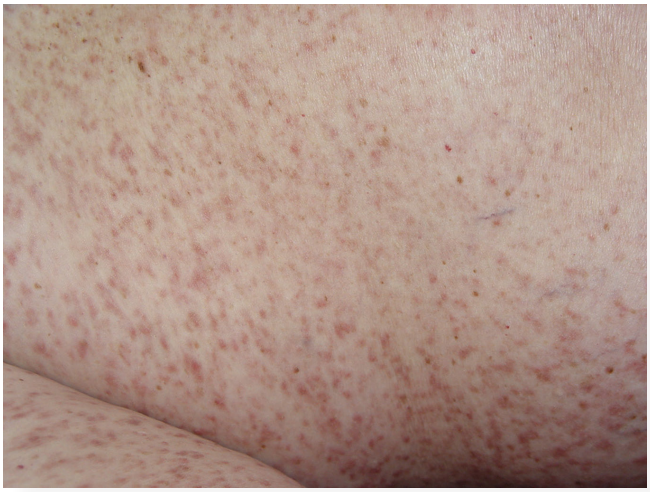

Figure 1. Yellow-tan to reddish-brown macules and slightly raised papules scattered over the trunk and extremities

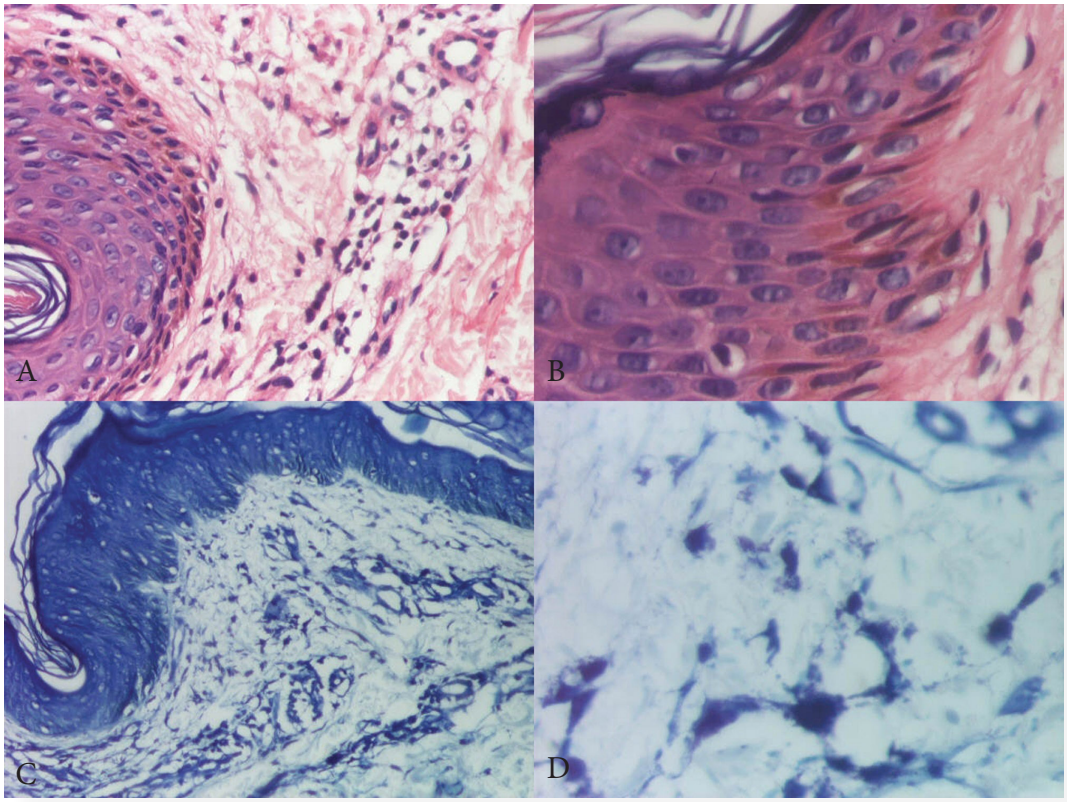

Figure 2.A. Sparse infiltrate with mast cells perivascular. (HE stainx200); B. Hyperpigmentation of the basal layer of the epidermis. (H&E stainx400); C. Mast cells in the papillary dermis. (Giemsa stain x100); D. Round and spindle-shaped mast cells. (Giemsa stain x400)

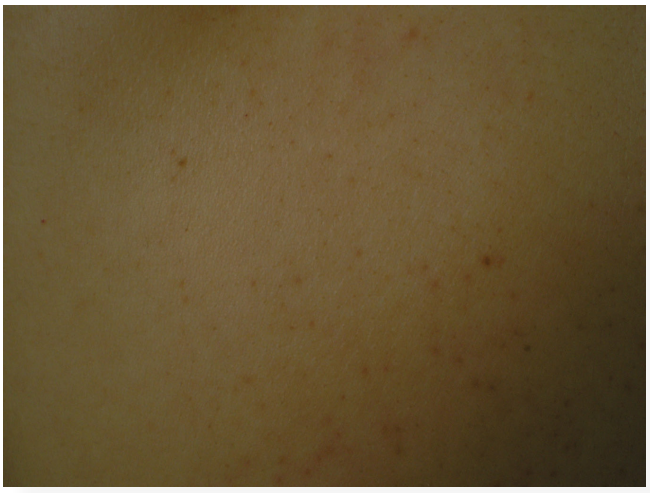

Figure 3. A slight hyperpigmentation scattered just in a few places on the trunk

Discussions

In the mast cell granules, tryptase is stored in complex with negatively charged heparin proteoglycans. Apart from the critical role of heparin proteoglycan in storage of tryptase in the secretory granules, heparin has been implicated in the autocatalytic processing of protryptase into mature tryptase monomer (Sakai). It has been known for a long time that heparin is required for stabilization of the mature tryptase tetramer (Schwartz).

Small heparine molecules, as is Enoxaparinum, in excess, could block/interfere with H-receptors family in a way that would prevent further degranulation of mastocytes.

This case report is the first observation in the literature regarding the transitory favorable effect of Heparine administration on the evolution of adult urticaria pigmentosa lesions. Further studies are needed to confirm or not our observation.

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CHONG HAI TAY AND THE SYNDROME WHICH BEARS HIS NAME

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Tay's syndrome, a rare autosomal recessive disorder, characterized by icthyosiform erythroderma, trichothiodystrophy, brittle hair and nails, intellectual impairment, decreased fertility, short stature, progeria-like facies and photosensitivity [1-3]. There is no specific treatment for this genetic disorder. However, some authors reported control of ichthyosis in a case of Tay's syndrome by topical application of tazarotene [3].

This syndrome is reported first by, Dr. Tay Chong Hai in Singapore in the year 1969 [4]. Dr Tay reported it in 2 brothers and a sister, with first-cousin parents of Chinese extraction. One of the children had hypogammaglobulinemia, and one died at age 2 months of intestinal obstruction. Erythroderma was particularly striking at birth.

Chong Hai Tay, was born in 1932 (Fig. 1). He is the first Singapore physician to have a disease named for him in the Western medical literature [5]. He authored more than hundred scientific articles. He wrote also poems. He established the National Arthritis Foundation in 1984, and was chairman for 14 years.

Figure 1. Chong Hai Tay

He is currently in private practice and a consultant physician and rheumatologist at Mt. Elizabeth Hospital, Gleneagles Hospital, Mt. Alvernia Hospital and East Shore Hospital. Dr Tay was the first editor of The Scientific Victorian [5]. Among his many other scientific contributions, he also, reported ten patients who were presenting with acute polyarthritis and hypereosinophilia of unknown causation [6].

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ERNST HANHART (1891-1973) AND THE SYNDROME WHICH BEARS HIS NAME

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Richner-Hanhart syndrome (RHS) is a rare autosomal recessive disease associated with high serum tyrosine levels .RHS is caused by the deficiency of tyrosine aminotransferase enzyme (TAT) [1-5]. It is listed in Online Mendelian Inheritance of Man as (tyrosinemia type II) (OMIM #276600). It is a disorder of amino acid metabolism which characterized by ocular changes, painful palmoplantar hyperkeratosis, and mental retardation. Serum tyrosine increases resulting in the deposition of tyrosine crystals in the cornea and in corneal inflammation [5].

It is mapped to gene16q22.2 .Patient with RHS may present with complaints of bilateral photophobia and tearing, which started during the infancy period. RHS should be suspected in patients demonstrating dermatologic signs, especially palmoplantar keratosis, associated with bilateral pseudodendritic corneal lesions unresponsive to antiviral therapy [1].

Patients are often misdiagnosed as having herpes simplex keratitis. However, serum and urine tyrosine levels confirm, usually, the diagnosis. A low tyrosine and phenylalanine diet permitted good control of the disease with a complete resolution of the oculo-cutaneous symptoms in a month. The importance of an early diagnosis of this syndrome to avoid the risk of mental retardation was emphesized [3].

This syndrome is reported first by Richner [6] in 1938 and Hanhart [7] in 1947.

Dr. Hermann Richner, was a Swiss dermatologist, born September 6, 1908, Zürich [8].

Ernst Hanhart (1891-1973), was a Swiss internist and human geneticist [9] (Fig. 1). After qualifying in medicine from the University of Zurich in 1916.He worked under professors Otto Nägeli (1871-1938) and Wilhelm Löffler (1887-1972). Hanhart became interested in human genetics and became a specialist in hereditary disorders [9].

He was appointed professor at the University of Zurich in 1942 and was a founding member of the Swiss Society of Genetics [9].

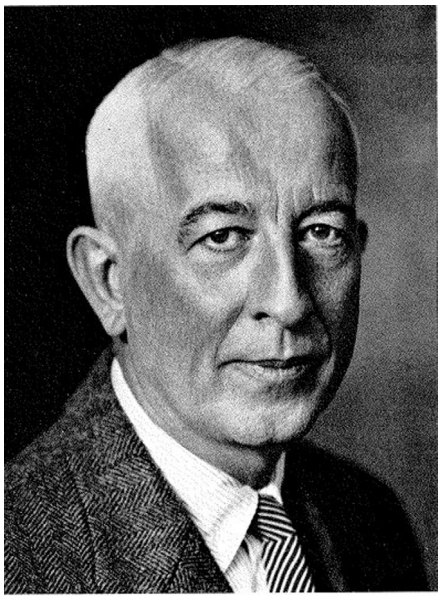

Figure 1. Ernst Hanhart (1891-1973).
Courtesy of Prof. Dr. med. Anita Rauch University of Zurich, Institute of Medical Genetics.

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ERICH URBACH (1893-1946) AND THE MEDICAL EPONYMS WHICH BEAR HIS NAME

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Erich Urbach (1893-1946) is an Austrian-American dermatologist and allergy specialist [1-3] (Fig. 1). He made great contributions and publications in medicine and there were many medical conditions named after him. Table I shows listed these eponyms.

Urbach was born on 29 July 1893, in Prague. He graduated from the University of Vienna under Wilhelm Kerl (1880-1945) in 1919 [1-3].

He worked at the Breslau skin clinic under Josef Jadassohn, and at the skin department of the Vienna Rothschild hospital under Hans Königstein. In 1929, he was habilitated (achieved the highest academic qualification) for skin and venereal diseases at the University of Vienna, becoming Dozent. He was subsequently an assistant physician at the II skin clinic with Wilhelm Kerl [1-3].

He migrated to USA in 1938 to become an associate in dermatology at the University of Pennsylvania. From 1939, he was Chief of the allergy department of the Jewish Hospital, Philadelphia [1-3]. He died in 1946, from coronary thrombosis.

From, Table I, one can see that, the name of Erich Urbach, were linked to different medical conditions. However, all of these eponyms faded with time and being replaced by other terms. The eponyms linked to his name are no longer used in the current medical literature. Nevertheless, many dermatologists remember „Urbach'', because of the synonym for Lipoid proteinosis; „Urbach-Wiethe disease'', which is sometimes used to refer to this disease.

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Figure 1. Erich Urbach (1893-1946). Courtesy, National Library of Medicine

The eponym	Remarks
Extracellular cholesterinosis of Kerl-Urbach	Historically, this used to be a variant of Erythema Elevatum Diutinum [4,5]; the other variant is "Crocker-Williams Type" [6].
Oppenhein-Urbach disease	Also called "Oppenhein-Urbach syndrome", and "Urbach's syndrome". This was a name for necrobiosis lipoidica diabeticorum [7-10]. Moriz Oppenheim (1876-1949), is an Austrian dermatologist.
Urbach-Königstein technique	Also called, "Urbach-Königstein method or reaction". It is a diagnostic procedure for demonstrating antibodies in allergics [11]. Allergen administered percutaneous, cutaneous or intracutaneous causes a local reaction, which will develop into a blister when a cantharidal dressing is placed on it. Hans Königstein (1878-1954) is an Austrian physician.
Urbach-Wiethe disease	Also called "Rössle-Urbach-Wiethe syndrome" [12,13]. But the name is Lipoid proteinosis. It is rare autosomal recessive genodermatosis, characterized by the deposition of hyaline material in the skin and mucosa, causing generalized thickening and scarring (hyalinosis cutis et mucosae) [1]. Camillo Wiethe (1888-1949), is an Austrian otologist. Robert Rössle (1876-1956), is a German pathologist.

Table I. Medical eponyms named after Erich Urbach

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EPONYMS IN DERMATOLOGY LITERATURE LINKED TO AUSTRALIA

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The nomenclature in medicine including dermatology is not totally perfect. One can see many non-precise names and even misnomers.

For examples in acanthosis nigrican there is neither acanthosis neither nigricans (pigmentation), in pyogenic granuloma, there is neither pyogenic (infection) neither granuloma, and so on and so forth.

One more example is „Buruli ulcer'', which honours neither the one who discovered it, nor the place from which it was first described, nor even any significant clinical feature, and thus has no justification for „naming rights" [1].

One author suggested that this disease be named after its main clinical feature, namely undermined subcutaneous ulcers: hence „ulcerans disease" or „ulcerans infections", both of which are simple, descriptive and accurate [1].

For the eponymic type of nomenclature, there have always been arguments as to who should receive primacy of recognition with regard to nomenclature of a new disease or syndrome. Until now, some health care providers like eponyms while many others do not.

Some argue that, the „possessive use of an eponym should be discontinued, since the author neither had nor owned the disorder". Yet, eponymic terms are widely used and very unlikely to be removed from medical literature.

These eponymic terms are originated from different countries around the world. In Table I [2-6], we elaborated on a selected eponyms in dermatology literature linked to Australia.

Australia is the world's area, with a population of 22.7 million. It ranks highly in many international comparisons of national performance, such as quality of life, health, education, economic freedom, and the protection of civil liberties and political rights [1]. The name Australia is derived from the Latin australis, meaning „southern".

Australia has the fourth highest life expectancy in the world after Iceland, Japan and Hong Kong. It has the highest rates of skin cancer in the world [1].

Among many other good things, Australia is remembered in dermatology for Australasian journal of Dermatology, an important dermatology resource, which is being published since 1951 [7]. This current title started in 1967. It was published as „Australian Journal of Dermatology'', from 1951-1966.

Eponyms in dermatology literature linked to Australia	Remarks
Munro microabscesses [2,3]	Munro microabscesses are composed of degenerated polymorphonuclear leukocytes in the horny layer and are seen in psoriasis and seborrheic dermatitis. It is named after William John Munro (1863–1908), (Fig. 1), an Australian dermatologist. It is different from Spongiform pustules of Kagoj which are multilocular pustules in the upper stratum malpighii within a sponge-like network made up of flattened keratinocytes. They are seen in psoriasis, Reiter's disease, geographic tongue and rarely in candidiasis. Spongiform pustules of Kagoj is named after Franz (Franjo) Kogoj (1894-1983), a Slovenian–born physician. Munro was born in Sidney, and graduated in Arts from Sidney University in 1880. He proceeded to Edinburgh, where he graduated in Medicine in 1884 and was admitted to the Royal College of Surgeons, London. He returned to Glebe, Sidney, where he engaged in general practice until 1896. The distinguishing features of psoriatic Munro's microabscess have been described earlier by several authors before Munro (1898), first of all presumably by Ernst Kromayer in 1890. Those authors might make, also, a note of spongiform pustule of Kogoj (1927).

Table I. Selected Eponyms in dermatology literature linked to Aaustralia

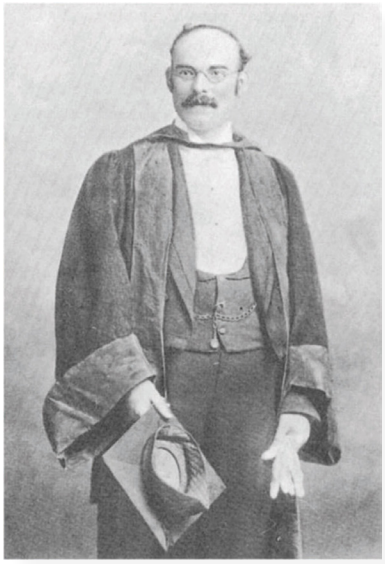

Figure 1. The legend reads, "William John Munro in the robes of a medical doctor upon graduation from Edinburgh in 1884". Reproduced from Reference number 2

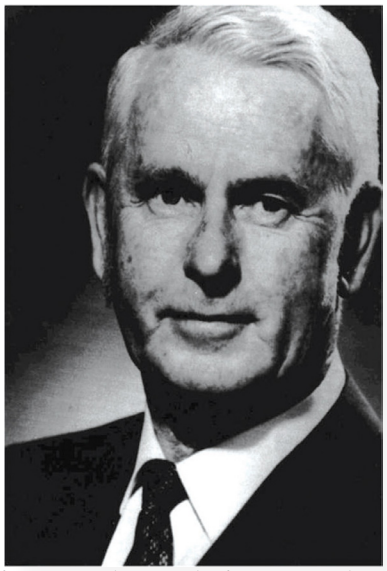

Figure 2. John P. O'Brien. Reproduced from Reference number 4

Eponyms in dermatology literature linked to Australia	Remarks
O'Brien's actinic granuloma [4,5]	O'Brien's actinic granuloma is a rare skin disease. Controversy continues over whether it should be considered a specific condition or a form of granuloma annulare located in sun-exposed areas. It is named after John P. O'Brien (Fig. 2). John P. O'Brien was born on May 27, 1914 in Mosman, Sydney, New South Wales, Australia. He was the foundation president of the Australasian Society of Dermatopathology, a founding member of the College of Pathologists (Australia) and its president from 1969–1971.
Searls ulcer [1]	This is another synonym for Buruli ulcer Named after Australian practitioner, John Robert Searls (1905-1971). Buruli ulcer is a chronic debilitating skin and soft tissue infection that can lead to permanent disfigurement and disability. It is caused by the *Mycobacterium ulceran*s bacterium. It is the third most common mycobacterial disease of the immunocompetent host, after tuberculosis and leprosy. The disease was so named after Buruli County in Uganda (now called Nakasongola District), because of the many cases that occurred there in the 1960s. Also known as the Bairnsdale ulcer after Bairnsdale Country town in Victoria, Australia. Also known as Daintree ulcer, and Mossman ulcer. *Mycobacterium ulcerans* has many synonyms. One of these is that used by the Mapi people in northern Uganda, but it is too much of a mouthful for general use, although it is aptly descriptive of its clinical pattern: "the ulcer that heals in vain". Similarly, the people of the Sepik District of Papua New Guinea refer to it as the "sik bilong wara Sepik". Shattock used the term "tropical ulcer type 2". Albert Cook, a missionary doctor in Uganda, may have noted ulcerans cases in 1896, but they were first formally described in the late 1930s by Dr J.R. Searl, a general practitioner in rural Victoria, Australia, when he and his colleague, D.G. Alsop, noticed a group of patients around the town of Bairnsdale, with indolent ulcers that were resistant to the usual forms of therapy. The causative organism was isolated in 1948 by MacCallum in the Bairnsdale region of Victoria. The disease was described widely throughout Australia, but for several decades it was known as the "Bairnsdale ulcer" and or "Searl's ulcer". "Buruli ulcer" or "Buruli disease", after the Mengo District in Buganda, came into use only in the 1960s. There are many other geofocal synonyms for Mycobacterium ulcerans infections, reflecting its focal association with bodies of water, such as "Kumusi ulcer" and "sik bilong wara Sepik" in Papua New Guinea, from where many of the early reports came. Reports from the Congo (now DRC) go back as far as 1942. In the Congo it is known as the "Tora ulcer", the "Kasongo ulcer" and the "Kakerifu ulcer". This later name, Janssens claimed, should be the African synonym as that was the area from which the first African case was described, also by a general practitioner, Dr Lubicz. In Mexico it was named the "Mexican ulcer".

Table I. Selected Eponyms in dermatology literature linked to Australia (continued)

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EPONYMS IN DERMATOLOGY LITERATURE LINKED TO CANADA

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Canada is a North American country with a population of approximately 33.4 million as of 2011. Per capita income is the world's ninth highest, and Canada ranks sixth globally in human development [1].

There are several eponyms in dermatology which are linked to Canada. In Table I [2-11], we listed selected eponyms in dermatology literature which are linked to Canada.

Numerous activities related to dermatology have occurred in Canada. The Canadian Dermatology Association, which published the well-known periodical, The Journal of Cutaneous Medicine and Surgery, was founded in 1925. The Canadian Dermatology Foundation was established in 1969 and The Canadian Dermatology Nurses Association was founded on 1997.

As a testimony of its Excellency in dermatology teaching, there are several specialized fellowships in Canada, in different subspecialties of dermatology. These fellowships accept candidates from all over the world.

There are also important educational resources in dermatology which are based in Canada. Just an example is, Dermanities (www.dermanities.com), which was launched in 2002 by Benjamin Barankin and David J. Elpern.

The city of Vancouver, in Canada will host the 23rd World Congress of Dermatology in 2015.

Eponyms in dermatology literature linked to Canada	Remarks
Birt–Hogg–Dube´ syndrome [2-4]	It is an autosomal dominant trait characterized by multiple fibrofolliculomas and extracutaneous cancer proneness. It is named after three Canadian doctors, Arthur Robert Birt (dermatologist) (Fig. 1), Georgina Hogg (pathologist), (Fig. 2), and Jim Dube´ (endocrinologist). Between 1964 and 1972, Arthur Robert Birt was professor and head of the department of dermatology at the University of Manitoba, where he proved a popular and effective teacher. In recognition of Dr. Birt's achievements, the University of Manitoba made him emeritus professor of medicine (dermatology) in1977. Birt–Hogg–Dube´ syndrome, is actually first reported in 1975, by a German dermatologist, Otto Paul Hornstein and his coworker, Monika Knickenberg and sometimes called Hornstein-Knickenberg-Syndrom. That is why a recent paper suggested that the term „Hornstein-Birt-Hogg-Dubé syndrome" appears to be appropriate. Otto Paul Hornstein was born 1926 in Munich. He was the former director of the Department of Dermatology, University of Erlangen-Nuremberg.
Cullen's sign [5,6]	Cullen's sign is described as superficial edema with bruising in the subcutaneous fatty tissue around the peri-umbilical region. It is also known as peri-umbilical ecchymosis. The sign was named after Thomas S. Cullen (1868–1953), (Fig. 3), a Canadian Gynecologist who researched gynecological disease including uterine cancer and ectopic pregnancy, and became a Professor at John Hopkins Hospital. He first described the sign in 1918 after a case of a ruptured extra uterine pregnancy.

Table I. Selected Eponyms in dermatology literature linked to Canada

Figure 1. Arthur Robert Birt. Reproduced from Reference 3.

Figure 2. Georgina Hogg. A curtesy of „Dr David Rayner,Walter Mackenzie Health Sciences Centre, Edmonton, Alberta, Canada"

Figure 3. Thomas Stephen Cullen (1868-1953). A courtesy of National Library of Medicine

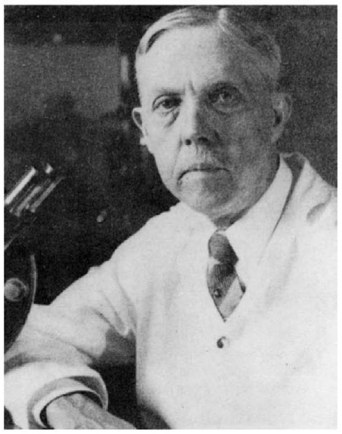
Eponyms in dermatology literature linked to Canada	Remarks
Hunter syndrome [7]	Hunter syndrome, also known as mucopolysaccharidosis (MPS) II, is one of at least 10 defined mucopolysaccharidoses. It is named after, Charles A. Hunter (1873-1955), a Scottish-Canadian physician. Dr. Charles Hunter, in Manitoba, Canada, first described Hunter syndrome in 1917 when he documented short stature, unusual facial features, hepatomegaly, deafness, heart disease, and nodular skin lesions in two brothers. Cutaneous features of this syndrome are firm, hypopigmented to skin-colored papules and nodules generally found on the back, particularly near the scapulae, as well as on the chest, neck, arms, or thighs. These occur generally before 10 years of age in both the mild and severe forms of Hunter syndrome.
Masson's neuronevus and Masson's pseudoangiosarcoma [8]	Masson's neuronevus was used to refer to the neurotized nevus. Masson's pseudoangiosarcoma or the Masson lesion are the other names for intravascular papillary endothelial hyperplasia. These were named after Claude L. Pierre Masson (1880-1959), (Fig. 4), French-born Canadian pathologist. He was the chair of anatomic pathology at the hospital and medical school at Strasbourg, France. In 1927, while he was 46 years old, Masson resigned his position at Strasbourg and accepted the position of chief of anatomic pathology at the University of Montreal Medical School. Pierre Masson died at the age of 79 years. He is buried, as he wished, at the cemetery of Notre-Dame-des-Neiges, atop Mont Royal, where today one has a grand view of the University of Montreal.  **Figure 4. Claude L. Pierre Masson (1880-1959). Reproduced from Reference 8**

Table I. Selected Eponyms in dermatology literature linked to Canada (continued)

Eponyms in dermatology literature linked to Canada	Remarks
Osler's nodes and Osler-Weber-Rendu syndrome [9]	Osler's nodes are painful, red, raised lesions found on the hands and feet. They are associated with a number of conditions, including infective endocarditis. Osler-Weber-Rendu syndrome or Osler-Weber-Rendu disease are another names for Hereditary hemorrhagic telangiectasia which is a familial syndrome characterized by multiple telangiectasia of the skin, and of the oral, nasal and gastrointestinal mucous membranes. The above conditions and some other medical conditions are named after Sir William Osler. Osler was a Canadian physician, (1849-1919), (Fig. 5) a native of Canada who at the age of 35 came to USA for 21 years and then moved to the England for the final 14 years. Frederick Parkes Weber (1863-1962) was English physician. Henri Jules Louis Marie Rendu (1844-1902) was a French physician.  **Figure 5. William Osler (1849-1919). A courtesy of National Library of Medicine**
Senear-Usher syndrome [10]	This is eponym for what is also known as pemphigus erythematodes. It is named after the American dermatologist, Frances Eugene Senear (1889–1958) and the Canadian dermatologist, Barney David Usher (1899–1978). Usher, (Fig. 6), is the first Canadian dermatologist to have his name eponymically attached to a disease. He was born and received his early medical education in Montreal and his MD from McGill University in 1922. In 1926, in collaboration with Senear, Usher published the classic report on pemphigus erythematodes.  **Figure 6. Barney David Usher (1899–1978). Reproduced from Reference 10**

Table I. Selected Eponyms in dermatology literature linked to Canada (continued)

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EPONYMS IN DERMATOLOGY LITERATURE LINKED TO SWEDEN

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Sweden is the third largest country in the European Union by area, with a total population of about 9.4 million [1].
There are several medical eponyms originated from this country. In Table I [2-8] we listed selected eponyms in dermatology literature linked to Sweden.
The Online Wikipedia, referred to interesting facts about the scientific advancement of this country.
Sweden tops other European countries in the number of published scientific works per capita. It ranks in the top five countries with respect to low infant mortality. It also ranks high in life expectancy [1].
Swedish inventors hold a total of 33,523 patents in the United States as of 2007, according to the United States Patent and Trademark Office. As a nation, only ten other countries hold more patents than Sweden [1].
The Nobel Prize is well-known all over the world. It is instituted by Alfred Bernhard Nobel (1833-1896) (Fig.1), who was a Swedish chemist, engineer, innovator, and armaments manufacturer. He was the inventor of dynamite.
Dermatologists around the world is also remembering Sweden for, Acta Dermato-Venereologica, which is an international peer-review journal for clinical and experimental research in the field of dermatology and venereology published in Sweden since 1920.

Eponyms in dermatology literature linked to Sweden	Remarks
Boeck-Schaumann disease [2,3]	This eponym with other eponyms like Besnier-Boeck-Schaumann disease, Boeck's sarcoid, sarcoidosis Boeck, and Schaumann syndrome are now largely replaced by the term „sarcoidosis". Cæsar Peter Møller Boeck (1845-1917), was a Norwegian dermatologist. Together with Boeck, the English physician, Jonathan Hutchinson (1828-1913), and the French physicians, Ernest Besnier (1831-1909), and Henri Tenneson (1836-1913) were all pioneers in sarcoidosis work, even though the connections between them were made clear many years later. Boeck coined an instantly acceptable term, sarkoid, and perhaps most important, he accurately and lucidly depicted the classic histologic features of this characteristic granuloma. So, history justifies the term, „Boeck's sarcoidosis". Boeck's compatriot, Ansgar Kveim (1892-1966), presented, in 1941, the Kveim reaction for diagnostic use. The swede, Jörgen Schaumann (1879-1953), demonstrated early the generalized character of the disease. Jörgen Nilsen Schaumann (1879-1953) (Fig. 2), was a Swedish dermatologist. His name is also lent to Schaumann bodies (see below). Schaumann was also an accomplished artist.

Table I. Selected Eponyms in dermatology literature linked to Sweden

Figure 1. Alfred Bernhard Nobel (1833-1896). With a kind permission from The Nobel Foundation

Figure 2. Jörgen Nilsen Schaumann (1879-1953). A courtesy of the South Swedish Society for the History of Medicine. Also available online from, www.medicinhistoriskasyd.se

Eponyms in dermatology literature linked to Sweden	Remarks
Löfgren's syndrome [4]	In 1952, a Swedish clinician, Sven Löfgren (1901-1978) (Fig. 3), described the combination of erythema nodosum, polyarthritis, fever, and bilateral hilar lymphadenopathy, called Lofgren's syndrome, the most usual form of acute sarcoidosis. It is usually self-limiting, with a generally good prognosis. Given its multi-systemic nature and unspecific manifestations, clinical presentations of this acute-onset form of sarcoidosis can be missed and mistaken for cellulitis or other rheumatic conditions, especially in an ED setting. This is further complicated by the existence of variants, where some patients present with bilateral hilar lymphadenopathy and periarticular inflammation of the ankles without erythema nodosum. The treatment for Löfgren's syndrome is primarily conservative, with NSAIDs and bed rest recommended. Some patients also require corticosteroids as second-line therapy.

Figure 3. Sven Halvar Löfgren (1910-1978). Available from, the Dictionary of Swedish National Biography, www.nad.riksarkivet.se

Table I. Selected Eponyms in dermatology literature linked to Sweden (continued)

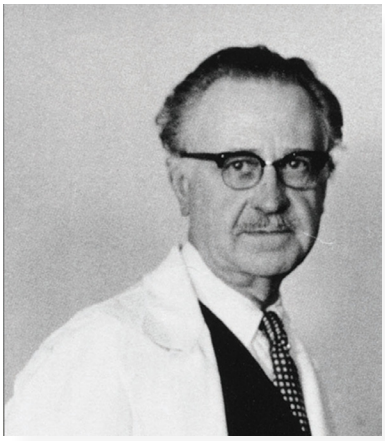
Eponyms in dermatology literature linked to Sweden	Remarks
Schaumann's bodies [5,6]	Calcium-containing inclusion bodies found in the cytoplasm of giant cells in sarcoidosis, berylliosis and uncommonly, in Crohn's disease and tuberculosis. These bodies were first described by the German physician Oscar von Schüppel (1837-1881) in 1871, and by Max Askanazy (1865-1940) in 1921 as Kalkdrusen. But it is named for Jörgen Nilsen Schaumann (1879-1953), a Swedish dermatologist. It is to be mentioned that, a number of cytoplasmic structures/inclusions can be identified within the granulomas of sarcoidosis, including asteroid bodies, Schaumann's bodies, calcium oxalate crystals, and Hamazaki-Wesenberg bodies; the last two of these can cause difficulties in differential diagnosis. Hamazaki-Wesenberg bodies (alternatively termed yellow-brown bodies, yellow bodies, Hamazaki corpuscles) are structures of unknown significance, which have been periodically documented in the sinuses of lymph nodes in numerous anatomic locations and myriad medical conditions, including appendicitis, cirrhosis, lymphoid tumours, colon carcinoma and numerous others, most famously sarcoidosis. Initially described by Hamazaki in 1938 in mesenteric lymph nodes, 6 and later noted by Menne in 1952 in 70% of mesenteric lymph nodes removed during appendectomies.
Sjögren's syndrome [7]	Sjögren syndrome (SS) is a chronic autoimmune disease - an inflammatory exocrinopathy - affecting mainly postmenopausal women (80–90%) or younger women after artificial menopause. It is named for, Henrik Samuel Conrad Sjögren (1899-1986) (Fig. 4), a Swedish ophthalmologist. SS is also known as, Gougerot-Houwer-Sjögren syndrome, Gougerot-Sjögren syndrome, Sjögren disease and von Mikulicz-Gougerot-Sjögren syndrome. In 1925, Henri Gougerot (1881-1955), a French dermatologist, described three cases of salivary gland atrophy associated with dry eyes, mouth and vagina. Houwer (1927) and Wisssmann (1932) noted the joint occurrence of keratoconjunctivitis sicca and arthritis. Sjögren in 1933 published the complete disease picture.Sjögren described his syndrome in 1933 in his doctoral thesis „Zur Kenntnis der keratoconjunctivitis sicca". Jan Mikulicz-Radecki (German: Johann von Mikulicz-Radecki) (1850-1905), was a Polish-Austrian surgeon. His name is also associated with one of the eponyms of this syndrome.  **Figure 4. Henrik Samuel Conrad Sjögren (1899-1986). A courtesy of the South Swedish Society for the History of Medicine**
Sjögren-Larsson syndrome (SLS) [8]	It is a rare autosomal recessive condition comprising congenital ichthyotic hyperkeratosis, spastic diplegia, mild to moderate mental retardation, and retinopathy. It is named for Karl Gustaf Torsten Sjögren (1896-1974) and Tage Konrad Leopold Larsson (1905-1998). Karl Gustaf Torsten Sjögren (1896-1974) (Fig. 5), a Swedish psychiatrist and geneticist, was a pioneer of modern Swedish psychiatry. Among his many contributions to medicine, he is credited for describing several medical conditions, which were later named after him, including Graefe-Sjögren syndrome, Marinesco-Sjögren syndrome, and Sjögren-Larsson syndrome (SLS). During his work on juvenile amaurotic idiocy,Sjögren forged collaboration with Tage K.L. Larsson, a statistics lecturer at the University of Lund. Their study on the combination of oligophrenia, congenital ichthyosis, and spastic disorders in 1957 established the clinical and genetic profile of a new disease entity, later known as Sjogren-Larsson syndrome (SLS). The incidence of SLS in Sweden is 1 in 100,000, rising to 1 in 10,000 in the northwest region of Vasterbotten.

Table I. Selected Eponyms in dermatology literature linked to Sweden (continued)

Figure 5. Karl Gustaf Torsten Sjögren (1896-1974). Image is provided by the Center for History of Science, the Royal Swedish Academy of Sciences. Permission For republication is granted by Norstedts, Sweden

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EPONYMS IN DERMATOLOGY LITERATURE LINKED TO SWITZERLAND

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There are many diseases in medicine which are named after scientists. These so-called „eponyms" have become quite commonplace in medical literature and offer important historical insight.
These eponyms originated from different countries around the world.
In Table I [1-18]. I listed selected eponyms in dermatology literature linked to Switzerland.
Switzerland is situated in western Europe. Its current population is estimated to be 8 million people.
It is known for many people around the world by its productions of many good and beautiful things. For examples, high quality hand watches.
Many scientific contributions in medicine came also from Switzerland.
The well-known whonamedit website, (www.whonamedit.com), listed till now more than 100 scientists from Switzerland for whom many medical conditions were named.
In addition, many scientists from Switzerland win Nobel Prize in its different branches. As a matter of fact, when it comes to Nobel Prize winners per capita, Switzerland is head and shoulders above the competition.
The first winner from Switzerland in Physiology or Medicine is Emil Theodor Kocher (1841-1917), (Fig. 12), for his work in the physiology, pathology and surgery of the thyroid. He was awarded in 1909.
Many scientists from Europe were also teaching medicine in Switzerland. For example Jacob Henle (1809-1885), a German scientist for whom, Henle's Layer of the Internal Root Sheath, was named. Also, Johann Lukas Schönlein (1793-1864) a German scientist, who made important medical discoveries. All were made during his years in Zurich, the so-called typhoid crystals in patients' stools (1836), „peliosis rheumatica" (1837), and-most important-the causative agent of favus (1839), a fungus later named Achorion schoenleinii [19].
Henoch-Schönlein purpura is named for him and for his former student from Germany Eduard Heinrich Henoch (1820-1910). Trichophyton schönleinii is still acceptable term, named for him.
Also, there are scientists from outside Switzerland who had medical training in Switzerland like the famous American dermatologist, Marion Baldur Sulzberger (1895-1983).
On the other hand there are scientists from Switzerland who continued their researches and career outside Switzerland. Willy Burgdorfer is an example. Burgdorfer, (Fig. 13), is an American scientist born and educated in Basel, Switzerland. He is an international leader in the field of medical entomology. He is famous for his discovery of the bacterial pathogen that causes Lyme disease, a spirochete named Borrelia burgdorferi in his honor. He isolated the bacterium in 1982 [20].
It is to be mentioned that some of the eponyms linked to Switzerland are no longer in common use in medicine. For example, Rickettsia mooseri is an old name for Rickettsia typhi, the causative agent of murine typhus. It is named for Hans Mooser, a Professor of bacteriology in Zurich.
It is, also, a well-known and not uncommon phenomenon, that eponyms often become associated with names of people who are not, in fact, identical with the person who first described or discovered a given state or circumstance. This applies to eponyms linked to Switzerland. The du Bois sign is an example. Neither was Charles du Bois the first person to describe the shortened fifth finger in cases of congenital syphilis, nor did he devise the sign's currently accepted description (Tabl. I).
Lastly, it is needless to say that eponyms originated from a given country provide just an inclusive and not a conclusive idea about its overall scientific contributions.

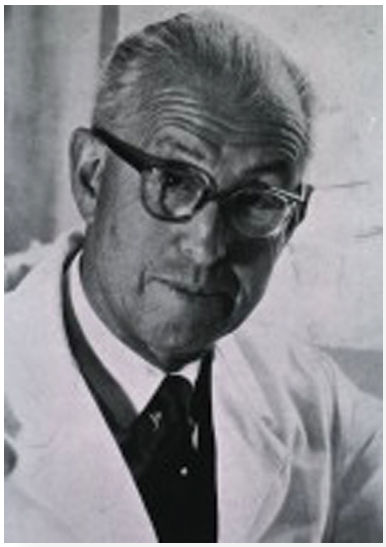
Eponyms in dermatology literature linked to Switzerland	Remarks
Bloch-Sulzberger syndrome (BSS) [1-3]	BSS is another name for Incontinentia pigmenti (IP). IP is an x-linked dominant condition that affects skin, teeth, eyes and may also have neurological problems. IP is more commonly used term than BBS. Garrod reported the first probable case of incontinentia pigmenti in 1906 and described it as a peculiar pigmentation of the skin in an infant with mental deficiency and tetraplegia. Subsequently, Bloch and Sulzberger further defined the condition in 1926 and 1928, respectively, as a clinical syndrome. Bruno Bloch (1878-1933), (Fig. 1) is a Swiss dermatologist. His name is also linked to „Bloch's reaction" or more commonly named „Dopa stain", which is, a dark staining observed in fresh tissue sections to which a solution of dopa has been applied, presumably due to the presence of dopa oxidase in the protoplasm of certain cells. Marion Baldur Sulzberger (1895-1983), was one of the most famous American dermatologists. He had received his training in dermatology in Zurich (Switzerland) from 1926 to 1929.  **Figure 1. Bruno Bloch (1878-1933). With kind permission of The Alumni Association of the Medical Faculty of the University of Basel / Switzerland**
Fanconi anemia [2,4]	It is one of the rare hereditary diseases characterized by genetic defects of DNA repair mechanisms, which share many clinical features such as growth retardation, neurological disorders, premature ageing, skin alterations including abnormal pigmentation, telangiectasia, xerosis cutis, pathological wound healing as well as an increased risk of developing different types of cancer. It is named for, Guido Fanconi (1892-1979), (Fig. 2); a Swiss paediatrician. His name is also linked to Fanconi syndrome (osteomalacia, aminoaciduria, hyperphosphaturia, glycosuria and aciduria).  **Figure 2. Guido Fanconi (1892-1979). A courtesy of National library of Medicine**

Table I. Selected Eponyms in dermatology literature linked to Switzerland

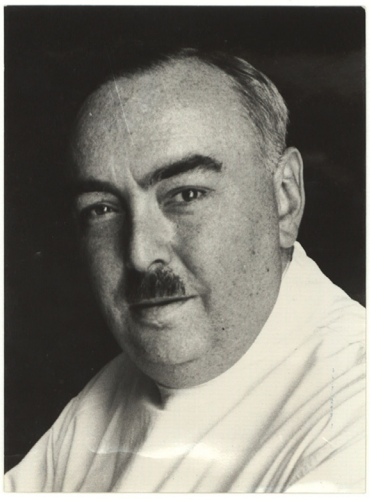
Eponyms in dermatology literature linked to Switzerland	Remarks
Franceschetti-Klein syndrome [5]	Franceschetti-Klein syndrome is another name for what is currently widely known as Treacher Collins syndrome. It is a rare disorder of craniofacial Development. The term mandibulofacial dysostosis is used to describe the clinical features. It is named after Edward Treacher Collins (1862-1932), the English surgeon and ophthalmologist who described its essential traits in 1900. In 1949 Franceschetti and Klein described the same condition on their own observations as mandibulofacial dysostosis. Adolphe Franceschetti (1896-1968), (Fig. 3), was a Swiss ophthalmologist. David Klein (1908-1993), was a Swiss human geneticist and ophthalmologist. There is confusion as to the correct eponymic term for This condition. Treacher Collins syndrome is the termcommonly used in Britain and USA, while Franceschetti-Klein syndrome is used in continental Europe. George Andreas Berry in 1889 first described an Abortive form with colobomata of the lower eyelids. In1900, Treacher Collins presented two similar patients. Franceschetti and Zwahlen in 1944 and Franceschetti and Klein in 1949 published extensive reviews of the condition in which they expanded the phenotype, employing the designation „mandibulofacial dysostosis". Adolphe Franceschetti created a department of human genetics at his clinic. This was headed by David Klein and became the origin of the first institute of human genetics in Switzerland. Franceschetti published more than 500 articles, and his name is attached to some 10 syndromes. David Klein was a leading figure in the organization of the British Ophthalmological Society as well as in theInternational council of ophthalmology and was elected president in 1927.  **Figure 3. Adolphe Franceschetti (1896-1968). A courtesy of Library, university of Basel, Switzerland**
Horner syndrome [6]	This syndrome is characterized by drooping of the eyelid (ptosis) and constriction of the pupil (miosis), sometimes accompanied by decreased sweating of the face on the same side. It occurs due to a defect in the sympathetic nervous system. It is named after Johann Friedrich Horner (1831-1886), (Fig. 4), a Swiss doctor who laterBecame an ophthalmologist. He was the founder of modern scientific Swiss ophthalmology.  **Figure 4. Johann. Horner (1831-1886). A courtesy of National library of Medicine**

Table I. Selected Eponyms in dermatology literature linked to Switzerland (continued)

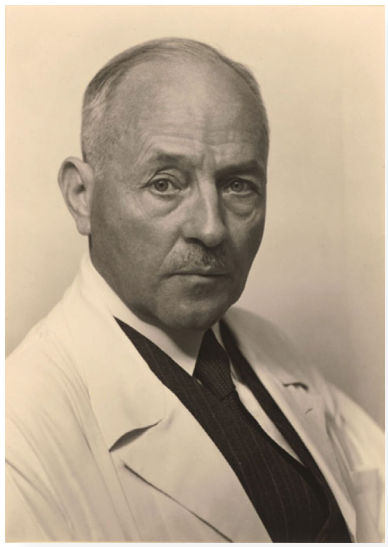
Eponyms in dermatology literature linked to Switzerland	Remarks
Jadassohn-Tieche nevus [7,8]	This term was once used for a blue nevus. It is named after Max Tièche (1878-1938), (Fig. 5), a Swiss physician and Joseph Jadassohn (1863-1936), a German dermatologist.  **Figure 5. Max Tièche (1878-1938). A courtesy of Archives of the Institute for the History of Medicine, University of Zurich, Switzerland**
Laugier-Hunziker syndrome (LHS) [9]	LHS is a rare acquired disorder characterized by diffuse macular hyperpigmentation of the oral mucosa and, at times, longitudinal melanonychia. Laugier-Hunziker syndrome was first described in 1970 by Laugier (from France) and Hunziker (from Switzerland).
Lutz-Miescher syndrome (LMS) [10,11]	LMS was an old name for Elastosis perforans serpiginosa (EPS). It is no longer used. LMS is named for Wilhelm Lutz and Alfred Guido Miescher. Wilhelm Lutz (1888-1958), (Fig. 6), was a Swiss dermatologist. Alfred Guido Miescher (1887-1961), (Fig. 7), was an Italian-born Swiss dermatologist. The first recognizable description of EPS was provided by Fischer in 1927 but was offered as an example of Kyrle disease. Jones and Smith also described elastosis perforans serpiginosa in 1947 but mistook it for porokeratosis of Mibelli. In 1953, Lutz recognized the features of EPS as those of an unknown disease and termed the condition keratosis follicularis serpiginosa. Miescher believed the condition was unique and termed it elastoma intrapapillare perforans verruciform.  **Figure 6. Wilhelm Lutz (1888-1958). With kind permission of The Alumni Association of the Medical Faculty of the University of Basel/ Switzerland**  **Figure 7. Alfred Guido Miescher (1887-1961). A courtesy of Archives of the Institute for the History of Medicine, University of Zurich, Switzerland**

Table I. Selected Eponyms in dermatology literature linked to Switzerland (continued)

Eponyms in dermatology literature linked to Switzerland	Remarks
Miescher's cheilitis [12]	Miescher's cheilitis is another less commonly used name for Granulomatous cheilitis. Miescher's cheilitis is named for Alfred Guido Miescher. Granulomatous cheilitis or cheilitis granulomatosa is a monosymptomatic form of the Melkersson–Rosenthal syndrome (MRS). MRS is characterized by a triad of symptoms, typically with an onset in childhood or youth. It comprises recurrent facial paralysis (in 30% of cases), chronic edema of face and lips and fissured tongue (lingua plicata). MRS was described by Melkersson in 1928 and, Rosenthal in 1931 emphasized that lingua plicata (fissured tongue) is commonly related. However, there are several earlier descriptions of the condition-by Paul Hübschmann (1894), Lothar von Frankl-Hochwart (1891) and Grigorii Ivanovich Rossolimo (1901). Ernst Gustaf Melkersson (1898-1932) was born and educated in Sweden. Later, he worked at the medical department of the Gothenburg Sahlgrenska sjukhuset. Curt Rosenthal (1892-1937), was born in Germany and worked at the University of Breslau psychiatry and neurology clinic. The designation Melkersson's syndrome was suggested to honor Melkersson, who had died so young, but the term Melkersson–Rosenthal syndrome has now been generally accepted.
Naegeli-Franceschetti-Jadassohn syndrome (NFJS) [13]	It is a rare symptom complex out of the spectrum of ectodermal dysplasia. The main clinical findings are absence of dermatoglyphs, reticularor mottled hyperpigmentation, hypohidrosis and nail dystrophy. NFJS is named after Oskar Naegeli, Adolphe Franceschetti and Josef Jadassohn. Oskar Naegeli (1885-1959), (Fig. 8), was a Swiss dermatologist. Adolphe Franceschetti (1896-1968), was a Swiss ophthalmologist. Josef Jadassohn (1863-1936), was a German dermatologist.  **Figure 8. Oskar Naegeli (1885-1959). A courtesy of Archives of the Institute for the History of Medicine, University of Zurich, Switzerland**
Richner-Hanhart syndrome [14].	It is a rare autosomal recessive disease characterized by ocular changes, painful palmoplantar hyperkeratosis, and mental retardation. This syndrome is reported first by, Dr. Hermann Richner, Swiss dermatologist, born September 6, 1908, in Zürich. Ernst Hanhart (1891-1973), (Fig. 9), was Swiss internist and human geneticist.  **Figure 9. Ernst Hanhart (1891-1973). A courtesy of Archives of the Institute for the History of Medicine, University of Zurich, Switzerland**
Secretan's syndrome [15]	It is an edema of the limbs due to factitious factors like self-inflicted trauma with a hard object. In 1916, Henri-Francois Secretin (1856-1916), (Fig. 10), a Swiss physician, reported this condition.

Table I. Selected Eponyms in dermatology literature linked to Switzerland (continued)

Figure 10. Henri-Francois Secretin (1856-1916). With kind permission from, http://www.secretan.info/

Figure 11. Alfred Vogt (1879-1943). A courtesy of National library of Medicine

Eponyms in dermatology literature linked to Switzerland	Remarks
The du Bois sign [16]	The du Bois sign is a common but generally very unclearly defined term. It was possible to show that the origin of the term is based on the observations made by the Swiss dermatologist Charles du Bois in connection with congenital syphilis in 1926. The du Bois sign was defined as a shift in the volar skin crease of the distal joint of the fifth finger in the proximal direction as compared with the intermediate joint of the ring finger by Rene´ Hissard in 1932. Charles du Bois (1874–1947), was the Director of the Dermatological Syphiligraphic Clinic of the Medical Faculty in Geneva. This sign is sometimes wrongly attributed to Paul Dubois (1795–1871), a French gynecologist. The du Bois sign is a description of a brachydactylic condition of the fifth finger. This characteristic should not be seen as being of particular clinical significance on its own. If at all, the du Bois sign may be of limited use for diagnosing congenital syphilis, but only in combination with other symptoms or by way of supplementary evidence. Some authors suggested that this term to be replaced with brachymesophalangia 5 (BMP 5).
Vogt–Koyanagi–Harada syndrome [17,18]	It is characterized by uveitis, poliosis, vitiligo, and meningitis. Named for Alfred Vogt, Yoshizo Koyanagi, and Einosuke Harada. Yoshizo Koyanagi (1880–1954), was a Japanese ophthalmologist. In recognition of Koyanagi's outstanding contribution and publications, the government conferred on him the posthumous Decoration of the Second Order of the Sacred Treasure. Einosuke Harada (1892–1946), was a Japanese ophthalmologist. Harada started to practice in the city of Nagasaki in 1930, where his hospital was destroyed by the atomic bomb on August 9, 1945; although he survived the bomb, Harada died before he could restart his practice. Alfred Vogt (1879-1943), (Fig. 11), was one of three ophthalmologists from the German-speaking part of Switzerland who had an exceptional impact on ophthalmology during the 20th century; the other two were Hans Goldmann (1899-1991) and Franz Fankhauser (1924-). Vogt is known for his natural gift of observation, his extraordinary memory for facts, and an enormous working capacity.

Table I. Selected Eponyms in dermatology literature linked to Switzerland (continued)

Figure 12. Emil Theodor Kocher (1841-1917). A courtesy of National library of Medicine

Figure 13. Willy Burgdorfer. Reproduced with permission from; http://www.medicalecology.org/diseases/lyme/lyme_disease.htm

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THE FADING EPONYM OF „VERNEUIL'S DISEASE"

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Eponyms are one type of nomenclature in medical literature. In dermatology, in particular, there are many existing eponyms and many are added with times [1,2].
However not all the eponyms in dermatology preserve its place in the literature. As some of them are already replaced by descriptive names or by other types of nomenclature and some are in their ways to lose its uses.
In this communication, we shall highlights on one of the fading eponyms in dermatology which is Verneuil disease.
Verneuil's disease is a previous name for hidradenitis suppurativa. The term „Verneuil's disease" is no longer in common usage in dermatology literature.
Verneuil's disease is named after Aristide Auguste Stanislas Verneuil (1823-1895), (Fig. 1), who was a French physician and surgeon [3,4].
In addition to Verneuil disease , there are other medical conditions named after Aristide Auguste Stanislas Verneuil. These include Calvé-Kümmell-Verneuil disease or Kümmell-Verneuil's disease [5,6], which is the posttraumatic vertebral body necrosis. This disease can occur as a rare but serious complication several months or even years after a spinal trauma. Jacques Calvé (1875-1954), is a French orthopedic surgeon. Whereas Hermann Kümmell (1852-1937), was a German surgeon.
Verneuil's neuroma (plexiform neuroma) is another eponym linked to Aristide Auguste Stanislas Verneuil, but is no longer used in the current medical literature.
Hidradenitis suppurativa is a common skin disease [7-11]. Clinical manifestations include painful nodules, abscesses, sinus tracts, and ropelike hypertrophic scars in the apocrine gland-bearing areas [9]. Treatment is both medical and surgical: wide-spectrum antibiotics and excisions tailored to the extent of involvement [9].
It was first described as a distinct entity in 1839, when Velpeau reported a patient with superficial abscess formation in the axillary, mammary, and perianal regions [11]. In 1854, Verneuil associated the suppurative process with the sweat glands [10], and the condition was given its current name. Not having performed any histopathologic studies himself, Verneuil conceded that his conclusion was based purely on the characteristic distribution of the condition [11].
Aristide Auguste Stanislas Verneuil studied medicine in Paris [4], where his instructors were Jacques Lisfranc de St. Martin (1790–1847), Pierre-Antoine-Ernest Bazin (1807–1878), Charles-Pierre Denonvilliers (1808–1872) and Joseph-François Malgaigne (1806–1865) [4].
In 1887 he replaced Leon Athanese Gosselin (1815–1887) at the „Académie des Sciences" [4].
The scientific activities of Verneuil were numerous but among others he is best known for contributions made in the development of wound dressing, and is credited for introducing forcipressure in treatment of hemorrhage [4].

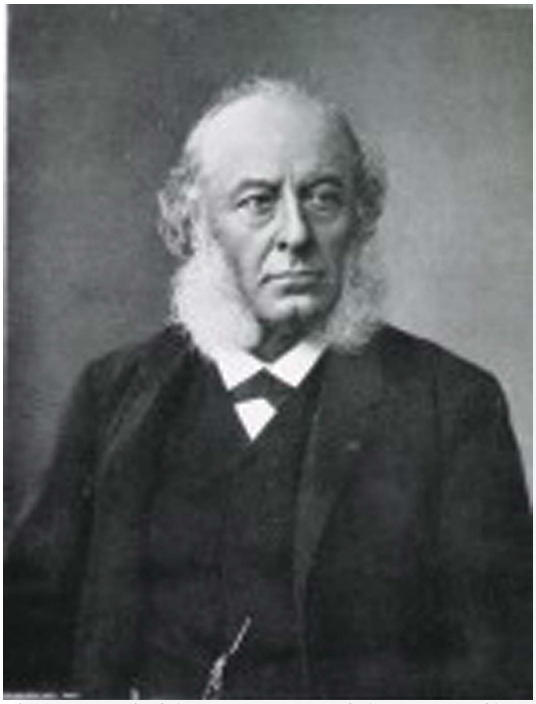

Figure 1. Aristide Auguste Stanislas Verneuil (1823-1895). A courtesy of The National library of Medicine

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DERMATOLOGY EPONYMS – SIGN – LEXICON – (H)

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Abstract
Eponyms are used almost daily in the clinical practice of dermatology. And yet, information about the person behind the eponyms is difficult to find. Indeed, who is? What is this person's nationality? Is this person alive or dead? How can one find the paper in which this person first described the disease? Eponyms are used to describe not only disease, but also clinical signs, surgical procedures, staining techniques, pharmacological formulations, and even pieces of equipment. In this article we present the symptoms starting with (H). The symptoms and their synonyms, and those who have described this symptom or phenomenon.

Key words: eponyms; skin diseases; sign; phenomenon

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HAIR COLLAR SIGN

Congenital scalp lesions surrounded by a ring of dark hair (Fig. 1, 2). Most of the scalp lesions were single and located at the vertex or parietal areas. They were most commonly composed of heterotopic neural tissue [1]. The hair collar sign may be a marker for cranial dysraphism and spine abnormalities.

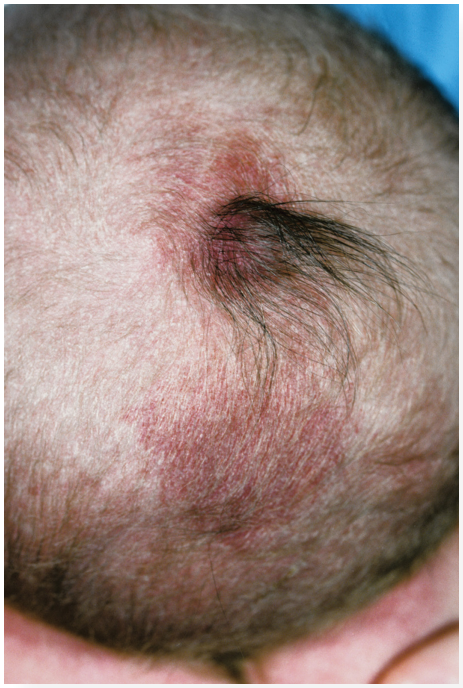

Figure 1. Hair collar sign - close up

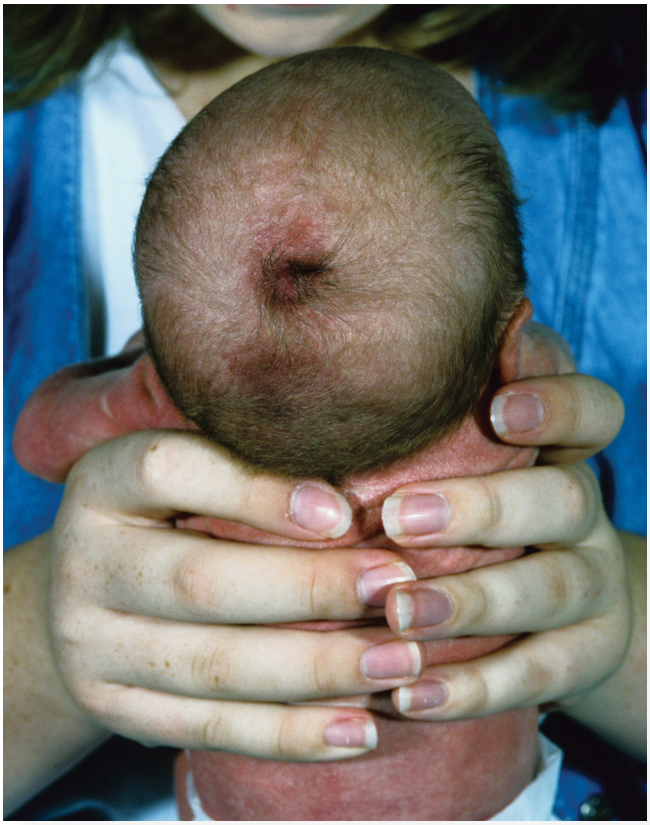

Figure 2. Hair collar sign - back of head

HAIR EATERS SIGN

Nodular growth of hair due to fungous spore in association with alopecia furfuracea. Also called tinea nodosa [2].

MALCOLM ALEXANDER MORRIS

English dermatologist, 1849-1924 (Fig.3, 4).

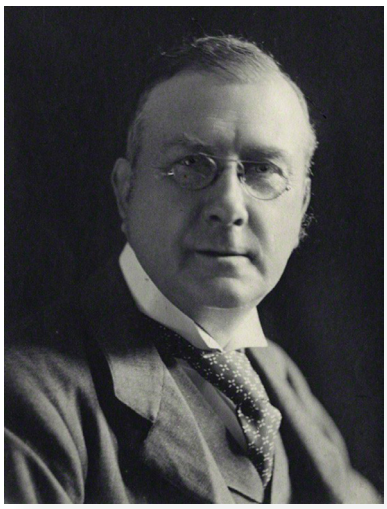

Figure 3. Malcolm Alexander Morris

Figure 4. Book of Malcolm Alexander Morris. Available online from; http://archive.org/details/ringworminlighto00morr

WALTER BUTLER CHEADLE

1835-1910 (Fig. 5). Walter Butler Cheadle was educated at Gaius College, Cambridge, graduating M.B. in 1861 and then studied medicine at St. George's Hospital, London. He interrupted his studies in 1861 to join Lord Milton on an expedition to explore Western Canada (1862-1864), and to go to China. On returning home, with Milton, he published a book on his adventures, The North-West Passage by Land, which gained a lot of attention.

He continued his medical studies and received his doctorate in 1865, became assistant at the St. Mary's Hospital in 1866 and from 1869 he was for 23 years at the Hospital for Sick Children, Great Ormond Street, where he was dean of the medical faculty from 1869 to 1873. He was an ardent advocate of women in the study of medicine.

Cheadle published the first observation on acute rachitis after J. O. L. Möller, calling the disease «infantile scurvy». He distinguished scurvy from rickets in 1878.

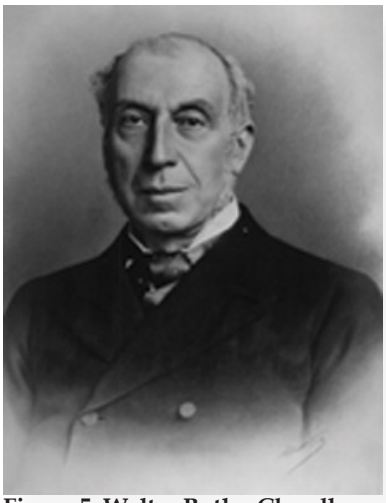

Figure 5. Walter Butler Cheadle

HAIR IN THE EYE SIGN

Inflamed and thickened eyelids which curl in upon themselves, inverting the eyelashes, which begin to scratch the cornea causing a frosted glass appearance and blindness. An indication of infection by zoonotic Chlamydia trachomatis transmited by the fly known as Musca sorbens. Also known as **Frosted Glass sign** [3].

HAIR PULLING SIGN (trichotillomania)

A dopamine or serotonin related abnormality that causes a sufferer to pull out ones hair, including bodily hair and eyelashes [4].

HALSTERN'S SIGN

Endemic syphilis. Endemic syphilis is also known as sibbens (Scotland), radseyege (Scandinavia), siti (Gambia), therlijevo (Croatia), njovera (Southern Rhodesia), frenjak (Balkans), and nonvenereal endemic syphilis (Bejel) [5].

HAND-AND-FOOT SIGN

A trophoneurotic affection charakterized by ulceration of the hands and feet [6].

HANTAAN SIGN

Rapid fever, kidney failure, severe back pain, and bleeding rash which progresses to death in 15 percent of victims. Caused by a zoonotic hantaviral infectious process known as hemorrhagic fever which renal syndrome [7].

HANGING GROIN SIGN

Chronic cutaneous onchocerciasis (onchodermatitis) causes pruritus, a papular rash, scarring, and lichenification (Fig. 6). Over time, affected skin may begin to sag, leading to terms such as „hanging groin." In severe cases is classified as "mild local elephantiasis" [8].

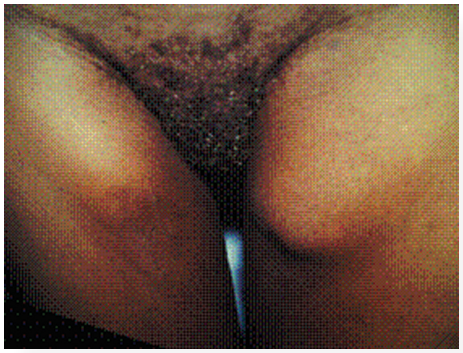

Figure 6. Hanging groin sign

HARLEQUIN FETUS SIGN

Ichtyosis congenita [9] (Fig. 7). The author of „harlequin fetus" was Samuel Wilks. Disease described: François Henri Hallop, Hermann Werner Siemens and Elliott Kaufman [10-12].

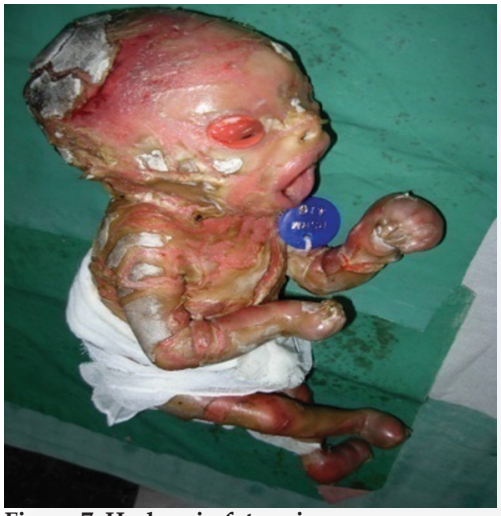

Figure 7. Harlequin fetus sign

SAMUEL WILKS

Sir Samuel Wilks, 1st Baronet (1824-1911) was a British physician and biographer (Fig. 8). In 1842 he entered Guy's Hospital to study medicine. After graduating MB in 1848 he was hired as a physician to the Surrey Infirmary (1853). In 1856 he returned to Guy's Hospital, first as assistant physician and curator of its Museum (a post he held for nine years), then as physician and lecturer on Medicine (1857). From 1866 to 1870 he was Examiner in the Practice of Medicine at the University of London and from 1868 to 1875 Examiner in Medicine at the Royal College of Surgeons. Among his major discoveries, Wilks recognised ulcerative colitis in 1859, differentiating it from bacterial dysentery. His work was confirmed later (1931) by Sir Arthur Hirst. Wilks also firstly described trichorrhexis nodosa (the formation of nodes along the hair shaft), in 1852. Wilks described the first case of myasthenia gravis, in 1877. He was a collaborator and biographer of the „Three Great", contemporary physicians who worked at Guy's Hospital, Dr. Thomas Addison, the discoverer of Addison's disease, Dr. Richard Bright, discoverer of Bright's disease and Dr. Thomas Hodgkin, discoverer of Hodgkin's lymphoma [10].

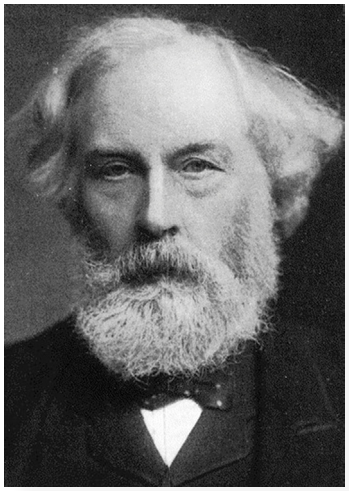

Figure 8. Samuel Wilks

FRANÇOIS HENRI HALLOPEAU

French dermatologist, 1842-1919 (Fig. 9). He became externe des hôpitaux de Paris in 1863, interne in 1866. He received his doctorate in 1871 and became Médecin des Hôpitaux de Paris in 1877, 1878 professor agrégé at the faculty.

Hallopeau was chef de service at the Hôpital Tenon from 1880, and from 1881 to 1883 at the Hôpital Saint-Antoine. From 1884 he was physician to the Hôpital St. Louis, where he abandoned neurology to concentrate his efforts on dermatology, giving clinical lectures. From 1893 he was a member of the Académie de Médecine, and secretary general of the Société Française de dermatologie et de syphiligraphie, of which he had been co-founder in 1890 [11].

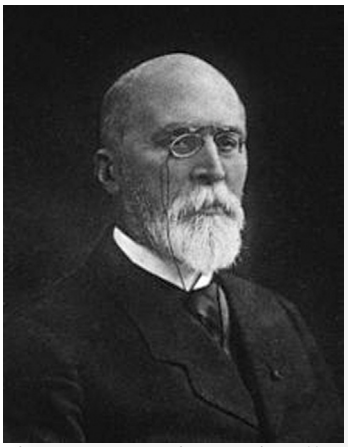

Figure 9. François Henri Hallopeau

HERMANN WERNER SIEMENS

German dermatologist, (1891-1969). Siemens studied at Munich and Berlin, receiving his doctorate from the latter university in 1918. He worked for a brief period of time under Josef Jadassohn (1863-1936) in Breslau (Poland), and in 1921 entered the university dermatological clinic in Munich. Here he was habilitated for dermatology in 1923, becoming ausserordentlicher professor in 1927, and in 1929 was called to Leiden as ordinarius. Besides his main speciality Siemens concerned himself extensively with Vererbungspathologie [12].

HARRISON'S SIGN

A transverse depression located at the xiphisteriol junction and mid-axillary lines, over the diaphragm (Fig. 10). A sign of rickets. Also called Haqrrison's sulcus [13].

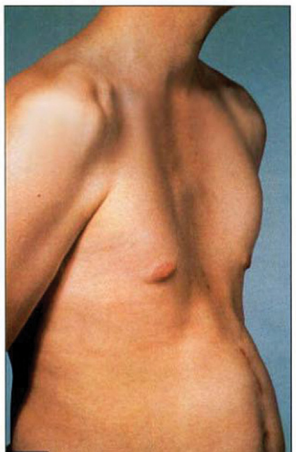

Figure 10. Harrison's sign

EDWARD HARRISON

English physician, 1766-1838. Edward Harrison studied in Edinburgh, and then in London under the Hunter brothers – John Hunter (1728-1793) and William Hunter (1718-1783). He obtained his doctorate at Edinburgh in 1784, visited Paris, and subsequently practiced for thirty years in Horncastle in Lincolnshire, where he founded, among other things, a dispensary and the Lincolnshire Benevolent Society. He was also in charge of an infirmary for crooked spines, and was a member of the Royal Society. He died while on the way to Marlborough.

HATA SIGN

Increase in severity of an infectious disease when a small dose a chemotherapeutical remedy is given [14].

Figure 11. Sahachiro Hata

SAHACHIRO HATA

Japanese bacteriologist, 1873-1938 (Fig. 11). Developed the Arsphenamine drug in 1909 in the laboratory of Paul Ehrlich. completed his medical education in Kyoto. He studied epidemic diseases under the famous Dr. Kitasato Shibasaburō at Kitasato's Institute for the Study of Infectious Diseases in Tokyo, and later studied immunology at the Robert Koch Institute in Berlin. While in Germany, he took the opportunity to learn about chemotherapy at the German National Institute for Experimental Therapeutics in Frankfurt, where he assisted Paul Ehrlich in the discovery of arsphenamine, which proved effective in curing syphilis.

It was called Salvarsan 606 because it was the 606th drug that Ehrlich tried. After his return to Japan, he helped found the Institute now Kitasato University, of which he became a director. He also lectured at Keio University [15].

HAVERHILL SIGN

Rat bite fever with peripheral rash frem the zoonotic bacterium *Sterptobacillus moniliformis* (Fig. 12, 13). Also called epidemic arthritis erythema [16].

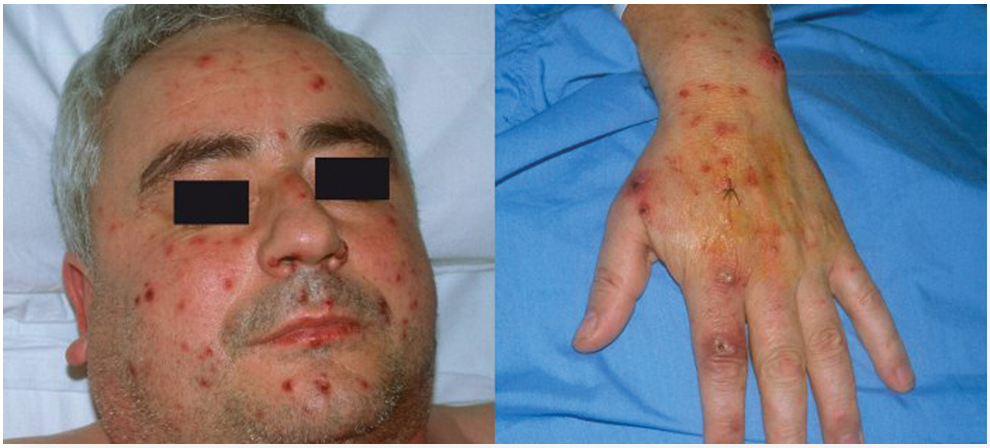

Figure 12. Haverhill sign. Lesiones polimorfas, purpúricas y necróticas, con elementos pustulosos en zonas acras

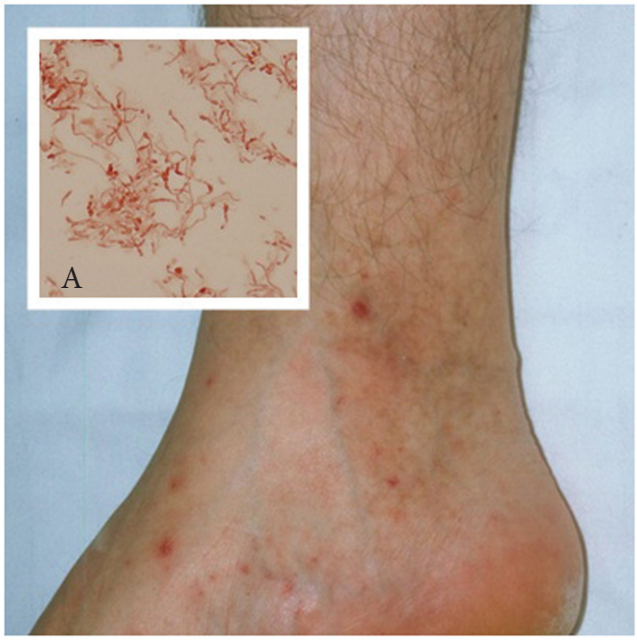

Figure 13. Haverhill sign. Mínimas lesiones purpúricas en las piernas, sugestivas de vasculitis séptica.
a)Tinción de Gram. Se observa un bacilo gramnegativo pleomorfo

HEADLIGHT SIGN (Perinasal pallor)

Lateral extension of intraepidermal component Infantile atopic dermatitis: involvement of the cheeks. The nose is spared [17].

HECKER'S SIGN

Speechless from patsy on the tongue, an early indication of the Black Death, due to infection with the Bubonic plaque bacterium *Yersinia pestis* [18].

JUSTUS FRIEDRICH CARL HECKER

German phatologist and medical writer, 1795-1850 (Fig. 14).

He particularly studied disease in relation to human history, including plague, smallpox, infant mortality, dancing mania and the sweating sickness, and is often said to have founded the study of the history of disease. Justus studied medicine at the University of Berlin, graduating in 1817 and becoming a Privatdozent and then (in 1822) Extraordinary Professor. In 1834, he became the university's „ordinary professor" for the History of Medicine.

Figure 14. Justus Friedrich Carl Hecker

HECHT SIGN

Rumpel-Leede phenomenon [19] (Fig. 15).

ADOLF FRANZ HECHT

Austrian paediatrician, 1876-1938 (Fig. 16). He was a lecturer and tit. a.o. Univ. pediatrics at the Medical School of the University of Vienna. He had already completed his medical studies in Vienna and graduated as MD on 05/19/1899 univ, then assisted at the Heidelberg Children's Hospital and at the General Policlinic in Vienna. In 1915 he qualified as a professor of Pediatrics and was a lecturer at the Children's Hospital at the Medical Faculty of the University of Vienna.

He was persecuted in Nazi racial discrimination, 1938, his Venia legendi revoked and he on 22 April 1938 deprived of his office and expelled from the University of Vienna [20].

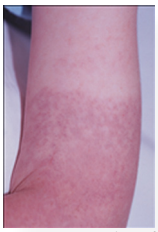

Figure 15. Hecht sign

HECTIC TONGUE SIGN

A smooth red tongue seen in cases of prolonged suppuration [21].

HEKTOEN'S SIGN

When antigens are introducted into the animal body in allergic states, there may exist an increased rahge of new antibody production which may include production of antibodies concerned in previous infections and immunizations.

LUDVIG HEKTOEN

Figure 17. Ludvig Hektoen

American phatologist, 1863-1951 (Fig. 17). Hektoen published widely and served as editor of a number of medical journals. In 1942, Hektoen received the American Medical Association's Distinguished Service Medal for his life's work. He attended the Monona Academy in Madison, Wisconsin and graduated with a B.A. degree in 1883 from Luther College in Decorah, Iowa. He entered the College of Physicians and Surgeons in Chicago, receiving his M.D. degree in 1888. Between 1890 and 1895, he studied abroad in Upsala, Prague and Berlin. In 1898, Hektoen became professor of Pathology at Rush Medical College and in 1901, professor and head of the Department of Pathology at the University of Illinois, Chicago. From 1904 until 1941, he was editor of The Journal of Infectious Diseases. In 1926 he became editor of the Archives of Pathology, serving until 1950 [22].

HENNEBERT'S SIGN

In the labyrinthitis of congenital syphylis, compression of the air external auditory canal produces a rotatory nystagmus to the diseased side; rarefaction of the air in the canal produces a nystagmus to the oppoiste side. Also known as Pneumatic sign or test [23].

CAMILLE HENNEBERT

Belgian otologist, 1867-1954. His year of death is also given as 1958. Camille Hennebert was affiliated with the Université Libre de Bruxelles. He published extensively. His name is associated with: Hennebert's fistula syndrome, Hennebert's syndrome.

HENOCH'S SIGN

Henoch's purpura [24].

EDOUARD HEINRICH HENOCH

German paediatrician, 1820-1910 (Fig. 18). After graduating in doctor of medicine in 1843 with the dissertation De atrophi cerebri, Henoch went for an educational journey to Italy and Switzerland. In 1844 he became assistant at the Berlin University Policlinic, an outpatient clinic headed by his uncle, Moritz Heinirich Romberg (1795-1873). In addition to his duties at the Poliklinik, Henoch worked as an Armenarzt, a doctor for underprivileged persons. This position gave young doctors the chance to gain practical experience. In December 1849 he completed his postgraduate training in internal medicine, qualifying him for a lecturing license. He was habilitated as Privatdozent in 1850. In the first edition of his main work, Vorlesungen über Kinderkrankheiten, he argued against modern bacteriology, calling it Bakterienschwindel (Swindle of Bacteria). He later changed his opinion. In his text he also mentioned social factors as influential in childhood diseases. In 1889, Henoch received a medal of high distinction, the Rothe Adlerorden. For his 70th birthday in 1890, he was presented a Festschrift (commemorative volume) with 24 articles written by colleagues and edited by Adolf Baginsky (1843-1918). The same year, Henoch wrote an article for the Klinisches Jahrbuch (Clinical Yearbook), in which he placed his scientific statement. He demanded separation of internal medicine and paediatrics, establishment of hospitals for children at the universities, and obligatory examinations for students in paediatrics. Henoch's name is perpetuated in medical history chiefly through his description of the connection between purpura and abdominal pains - Henoch's purpura.

Henoch was also the first to describe purpura fulminans, which is sometimes called Henoch's Purpura II (misnomer) [25].

Figure 18.
Adolf Franz Hecht

HERTOGH'S SIGN
Lateral thinning of eyebrow hair; atopic dermatitis, hypothyroidism [26,27].

HERTOGHE EUGÈNE LOUIS CHRÉTIEN
Belgian physician, (1860—1928). Became vice-president of the Belgian Medical Society and one the world's foremost thyroid experts. Hertoghe taught of the importance of diagnosing and treating the milder forms of low thyroid. He gave remarkably detailed descriptions of the many problems that could be caused by low thyroid function. Before any thyroid tests became available, Hertoghe taught doctors how to diagnose and treat all forms of this condition. He explained what to look for and what listen for in order to identify this illness. Eugene Hertoghe also offered remarkable examples of how patients could improve with treatment. He reported that problems as diverse as hair loss, mental illness, dry skin, and digestive problems could all be caused by hypothyroidism and could be reversed with proper treatment. Hertoghe also noted that low temperature was the most consistent finding of hypothyroidism [28].

HEUBNER'S SIGN
Syphilitic endarteritis of the cerebral vessels [29].

JOHANN OTTO LEONHARD HEUBNER

Figure 19. Johann Otto Leonhard Heubner

German paediatrician, 1843-1926 (Fig. 19). He was a student of Karl Reinhold August Wunderlich (1815-1877), to whom he was assistant at the clinic for several years in Leipzig even before he obtained his doctorate in 1867. After graduation he continued his studies in Vienna, and was habilitated for internal medicine at Leipzig in the autumn of 1868. He became professor extraordinary at the University of Leipzig in 1873, and in 1876 was made director of the district policlinic, a position he held until 1891. From this time Heubner turned his attention to paediatrics, and began investigating children's diseases in order to publish his findings, particularly on important infectious diseases of childhood. He built a children's ambulatory connected to the policlinic, and later a private children's hospital. In 1894, he went to Berlin as director of the university children's clinic and policlinic at the Charité, succeeding Eduard Heinrich Henoch (1820-1910). Here, the same year, he became ordentlicher etatsmässiger professor of paediatrics at the Friedrich Wilhelm Universität. In 1898, with Max Rubner (1854-1932), he made the initial investigation on food requirements for normal and ill-nourished children which formed the foundation of later investigations in this area. He warned against too prolonged sterilisation of milk and whilst in Leipzig recognised Behring's discovery of diphteria antitoxin and was one of the first to use it in treatment. By means of lumbal puncture, in 1896 he succeeded in discovering the agent of cerebral meningitis, as he isolated meningococci from the cerebrospinal fluid [30].

HIDE BOUND SIGN
Diffuse symetric scleroderma in which the whole skin is so hard as to suggest a frozen corpse, the face when involved is ghastly and gorgonized [31].
„ ...Diffuse symmetric scleroderma, or hide-bound disease, is quite rare, and presents itself in two phases: that of infiltration (more properly called hypertrophy) and atrophy, caused by shrinkage. The whole body may be involved, and each joint may be fixed as the skin over it becomes rigid. The muscles may be implicated independently of the skin, or simultaneously, and they give the resemblance of rigor mortis. The whole skin is so hard as to suggest the idea of a frozen corpse, without the coldness, the temperature being only slightly subnormal. The skin can neither be pitted nor pinched. As Crocker has well put it, when the face is affected it is gorgonized, so to speak, both to the eye and to the touch. The mouth cannot be opened; the lids usually escape, but if involved they are half closed, and in either case immovable. The effect of the disease on the chest-walls is to seriously interfere with the respiration and to flatten and almost obliterate the breasts; as to the limbs, from the shortening of the distended skin the joints are fixed in a more or less rigid position..." [32].

HENRY RADCLIFFE CROCKER
English dermatologist, 1845-1909 (Fig. 20). Crocker started his working life as an apprentice to a general practitioner, before going to London to attend the University College Hospital medical school. Working as a resident medical officer with William Tilbury Fox, Crocker began a lifelong career in dermatology. With his 1888 book Diseases of the Skin: their Description, Pathology, Diagnosis and Treatment, he became known as a leading figure of dermatology. In 1870 he became a student at University College Hospital medical school in London. He worked part time as a drug dispenser in Sloane Street. As an undergraduate student, Crocker won gold medals in materia medica, clinical medicine and forensic medicine, as well as a university scholarship.

After receiving his Membership of the Royal College of Surgeons (MRCS) qualification, Bachelor of Science degree and then in 1875 his MD, Crocker obtainied a position as resident obstetric physician and physician's assistant at University College Hospital. He then held posts at the Brompton Hospital for Consumption and Diseases of the Chest and Charing Cross Hospital before returning to University College Hospital as resident medical officer. He worked under dermatologist William Tilbury Fox, and began to develop his own dermatological career as assistant medical officer in the hospital's dermatology department. At this time, the practice of specialising in medicine was somewhat frowned upon in the United Kingdom (although more popular in continental Europe), but Tilbury Fox and Crocker were credited with bringing some structure to the field of dermatology. Although a specialist, in his clinical work, he emphasised the value of treating the whole patient. [1][2] His research concentrated on the epidemiology of skin diseases and histology, noting the importance of microscopic inspection of skin cells. During his career, he was the first to describe or name diseases such as granuloma annulare and erythema elevatum diutinum. In 1888, Crocker published Diseases of the Skin: their Description, Pathology, Diagnosis and Treatment, a textbook that helped to establish him as a leading figure in dermatology [33].

Figure 20.
Henry Radcliffe Crocker

HIGOUMÉNAKI'S SIGN

A tumefaction at the inner third of the right clavicle (Fig. 21); seen in congenital syphilis. It's an end result of neonatal periostitis. Also known as Higoumenaki's sign. Sign has been described by Georgios Higoumenakisa in 1927 on the pages of the Greek journal Πρακτικά Ιατρικής Εταιρείας Αθηνών (Reports of the Medical Society of Athens) [34].

GEORGE HIGOUMENAKIS

(1895–1983) was a Greek dermatologist born in Iraklion of Crete (Greece) (Fig. 22). He studied medicine at the Medical School of the National University of Athens. He then chose to become a dermatologist and went to France to fulfil his desire. He was a student of Gaston Milian, a famous syphilologist, at the Hospital St. Louis. He returned to Greece in 1924, became a member of the Medical Society of Athens and began practicing medicine privately. He became a director of the Department of Dermatology at the hospital „Evaggelismos" and practiced medicine successfully until the 1940s [34].

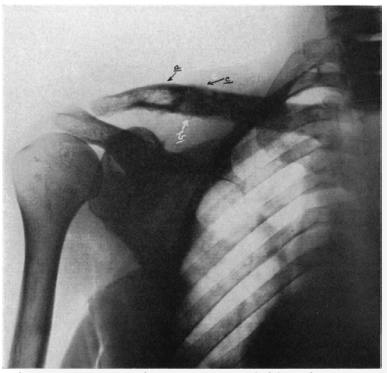

Figure 21. Higouménaki's sign

Figure 22.
George Higoumenakis

HIVP SIGN

(Painful acute necrotizing ulcerative gingivitis) (Fig. 22), also known as ulceromembranous gingivitis, Vincent's infection, Vincent's War sign, Trench Mouth sign, and ANUG sign, LGE sign, NUP sign [18].

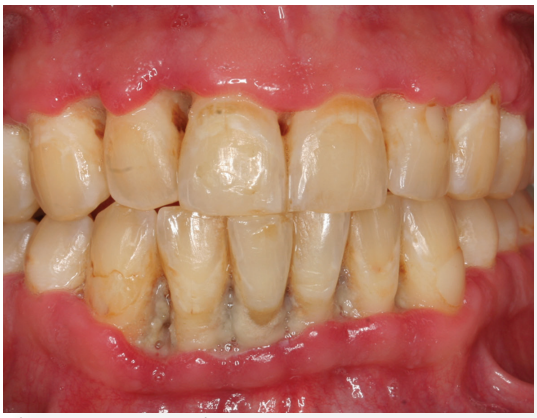

Figure 22. HIVP sign

HENRI VINCENT

French physician, 1862-1950. His name is associated with Vincent's Disease or Vincent s Angina. It is also widely known as Trench Mouth, due to an outbreak in soldiers in trenches during World War One. *Borrelia vincentii* used to be spread out worldwide, but is now mainly in countries that are not very developed.

HODARA'S SIGN

A kind of trichorrhexis nodosa seen in women in Constantinopole [35].

MENAHEM HODARA

Jewish Turkich dermatologist, 1869-1926 (Fig. 23, 24). Histopathology of the skin doctor who is an expert Ottoman Turkey. Defines a skin disease known by his name. Came from a Jewish family. In 1890, the military medical school (School of Medical School-i scrumptious i) was sent to

Hamburg for specialized training after graduating. Worked for a while in Vienna, and in 1906 he returned to Istanbul. Kasımpaşa Navy Central Hospital (today Naval Hospital) Emraz-i dermatology (skin), and zühreviye (Sexually transmitted diseases) was appointed physician. During this task both medicine and scientific research and experiments, then the palace getirldiği continued intensively. Trichorrhexis nodosa is a kind of the „Hodara Disease" of the international medical literature describing the input. Salicylic acid, krizarobin and iodine, in conjunction with student Hulusi Behçet süblimenin explored the effects on the skin. Several moles, freezing and melting of infants hip histo-patolojisiyle, „piedra" he described the first known disease. Bacteriology expert Fuad Omar Bey and skin mikozlarını examining the skin and skin fungal disease aspergillosis led to the detection of cases. The results of his research were published in French and German in Europe. Celebrity look-a dermatology specialist in Unna, Hodara'yı „The German and French medical literature enriches people publications as" definitions [35].

Figure 23. Dr. Menahem Hodara 1895 in Istanbul with his wife Estrella Ner and three of their eight children Betty, Elise and Victor. Al. IJEF.
To: Enrico Isacco's Sephardic photographic library. Collection Estelle Dora

Figure 24. Menahem Hodara
To: Enrico Isacco's Sephardic photographic library. Collection Estelle Dora

HOOF AND MOUTH SIGN

Fever, vomiting, and painful oral lesions similar to the herpetic type. Caused by contact exposure to cattle and pigs that are infected with the zoonotic Foot-and-Mouth disease aphthovirus. There is high morality in young animals which can have devastating censequences as it spreads through foot supply animals. Humans may be carrier hosts and quarantine recommended [36].

(article about Foot-and-Mouth disease: "Outbreak of Hand, Foot and Mouth disease in northeastern part of Romania in 2012" will be published in issue 2.2012 (April) in Our Dermatology Online)

HOMAN'S SIGN

Dorsiflexion of foot leads to pain in the calf. Ss a sign of deep vein thrombosis (DVT) [37].

JOHN HOMANS

American surgeon, 1877-1954 (Fig. 25). John Homans worked on experimental hypophysectomy with Harvey Williams Cushing (1869-1939) at Johns Hopkins. Homans, Cushing and Samuel James Crowe (1883-1955) in 1910 presented the first evidence of the relationship between the pituitary and the reproductive system. Homans later became interested in peripheral vascular disease. Homans worked on peripheral vascular disease, helping to popularise the ligation of the saphenofemoral junction for treatment of varicose veins, and advocating ligation of the superficial femoral vein to stop migrating clots causing pulmonary embolus. He described the sign which bears his name in 1944 and reported the first instance of deep venous thrombosis occurring in flight in 1954 in a doctor who had flown between Boston and Caracas. He was also interested in lymphoedema, developing the Homans operation for this condition. [38].

Figure 25. John Homans

HUNTERIAN ULCER SIGN

Primary sypohilitic chancre, an ulcer with sloping edges which differs from the punchen out ulcel in teritiary syphilis (Fig. 26) [39].

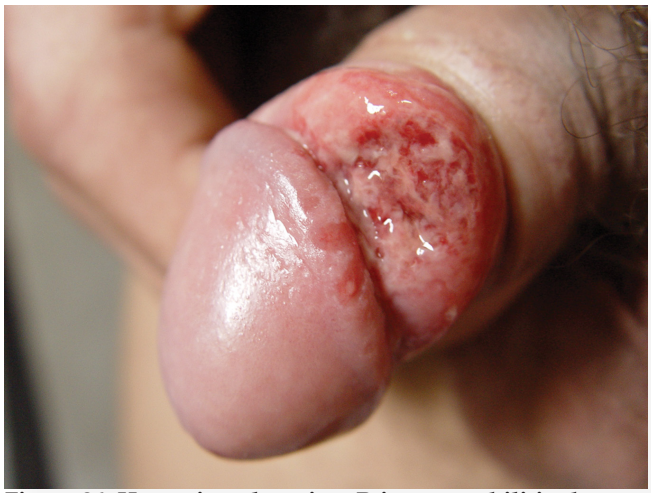

Figure 26. Hunterian ulcer sign. Primary syphilitic chancre

JOHN HUNTER

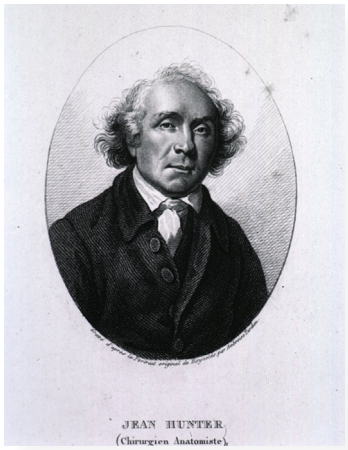

Figure 27. John Hunter

Scottish surgeon, 1728-1793 (Fig. 27). He was an early advocate of careful observation and scientific method in medicine. He was commissioned as an Army surgeon in 1760 and was staff surgeon on expedition to the French island of Belle Île in 1761, then served in 1762 with the British Army in the expedition to Portugal.[12] Contrary to prevailing medical opinion at the time, Hunter was against the practice of ‚dilation' of gunshot wounds. This practice, which involved the surgeon deliberately expanding a wound with the aim of making the gunpowder easier to remove. Hunter left the Army in 1763. Hunter was elected as Fellow of the Royal Society in 1767. At this time he was considered the authority on venereal diseases. In May 1767, he believed that gonorrhea and syphilis were caused by a single pathogen. Living in an age when physicians frequently experimented on themselves, he inoculated himself with gonorrhea, using a needle that was unknowingly contaminated with syphilis. When he contracted both syphilis and gonorrhea, he claimed it proved his erroneous theory that they were the same underlying venereal disease. He championed its treatment with mercury and cauterization. He included his findings in his Treatise on the Venereal Disease, first issued in 1786. In 1776 he was appointed surgeon to King George III [40].

HUTCHINSON'S SIGN

Interstitial keratitis and a dull red discoloration of the cornea. A sign of inherited syphilis.

Sir JONATHAN HUTCHINSON

English surgeon and pathologist, 1828-1913 (Fig. 28). In 1851 he studied ophthalmology at Moorfields and was an ophthalmologist to the London Ophthalmic Hospital. He was also venereologist to the Lock Hospital, physician to the City of London Chest Hospital, and general surgeon to the London and Metropolitan Hospitals. From 1859 to 1883 he was surgeon to the London Hospital, and he also worked at the Blackfriars Hospital for Diseases of the Skin, being elected to the staff in 1867 and becoming senior surgeon. Hutchinson developed a special interest in congenital syphilis, which was common in London in his time, and he was responsible for delineating the natural history of the disorder. It is said that he saw more than one million patients with syphilis in his lifetime. Hutchinson had a vast clinical experience and he published his observations in more than 1,200 medical articles. Despite his busy practice he produced the quarterly Archives of Surgery. For a brief period of time he was the editor of the British Medical Journal.

In England the term morbus Hutchinson-Boeck has been used for benign lymphogranulomatosis, now commonly known as Boeck's sarcoid.

In January 1869, a 58 year-old coal-wharf worker, John W, attended Jonathan Hutchinson at the Blackfriars Hospital complaining of purple skin plaques, which had gradually developed over the preceding two years, somewhat symmetrically on his legs and hands. They were neither tender nor painful and did not ulcerate. Hutchinson considered that the skin lesions were in some way related to the patient's gout.

His name is associated with: Bernard-Horner syndrome (Claude Bernard), Hutchinson's angina, Hutchinson's dehidrosis, Hutchinson's disease, Hutchinson's facies, Hutchinson's freckle, Hutchinson's mask, Hutchinson's melanotic disease, Hutchinson's patch, Hutchinson's prurigo, Hutchinson's pupil, Hutchinson's sign 2 (Sir Jonathan Hutchinson), Hutchinson's teeth, Hutchinson's triad, Hutchinson-Gilford disease [41].

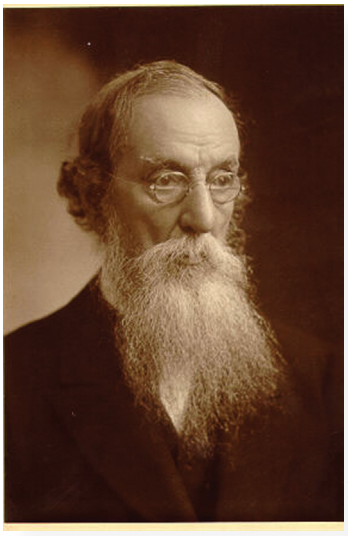

Figure 28.
Sir Jonathan Hutchinson

HUTCHINSON'S INCISORS SIGN

There are depressions or notching of the incisal edges of the labial surfaces of the permanent incisors. A sign of congenital syphilis (Fig. 29-31) [42]. Also called **Hutchinson's teeth sign** and **Screwdriver sign**.

HUTCHINSON'S TEETH SIGN

see Hutchinson's Incisors sign

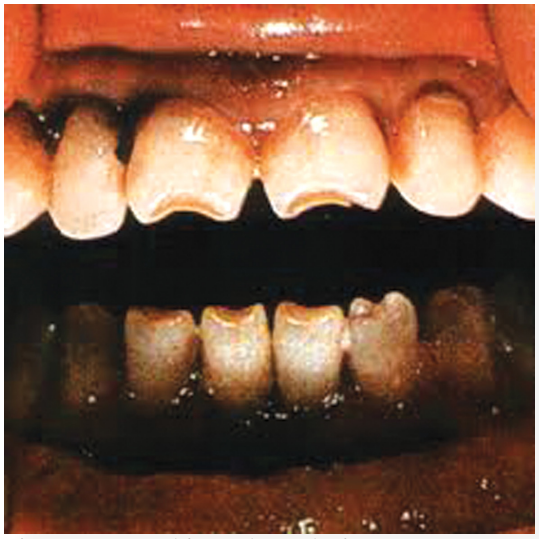

Figure 29. Hutchinson's teeth sign

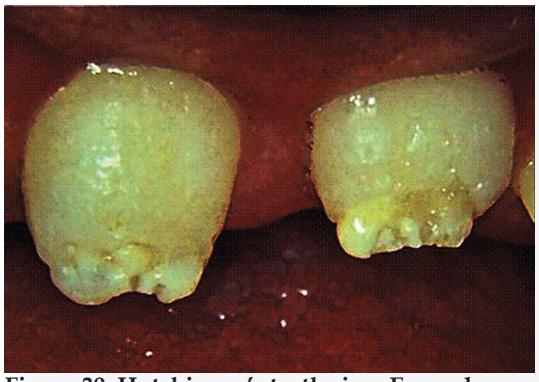

Figure 30. Hutchinson's teeth sign. Enamel hypoplasia of maxillary central incisors [42]

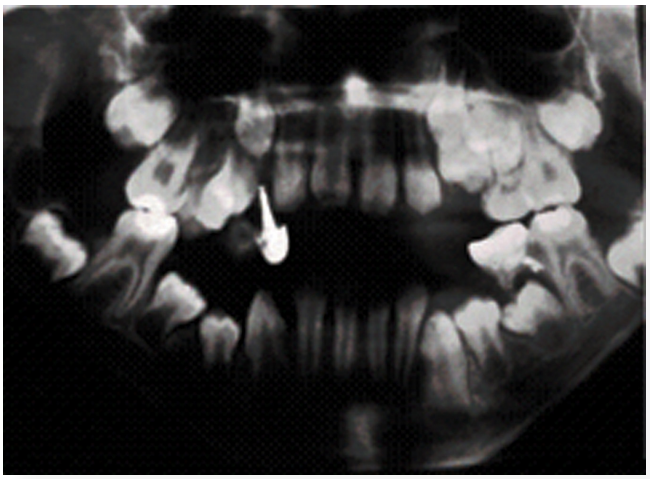

Figure 31. Hutchinson's teeth sign. Panoramic radiograph: presence of restorations in posterior teeth and absence of some deciduous teeth that it is not common to see in this patient's age [42]

HUTCHINSON'S TRIO SIGN

The precence of interstitial keratitis, notched teeth, and otitis occurring together. A sign of inherited syphilis [43]. The Triad is characterized by three signs: 1) deformation of teeth as a result of direct influence pale спирохеты on tooth rudiments of a fruit or on the bodies regulating growth of teeth. Changes concern the top central cutters, is more rare — lateral and central bottom (a barrel-like form, semi-lunar defects of cutting edge); 2) parenchymatous keratity; 3) the progressing relative deafness arising owing to a degeneration of a preddvernoulitkovy nerve, lying in a stony part of a temporal bone (syphilitic лабиринтит). The triad belongs to symptoms of late congenital syphilis. At one patient two can be observed only or one of signs, meet all three less often. The triad is described for the first time by J. Hutshinson in 1858.

HUTCHINSON'S SIGN 2

Sign that refers to „the tip of the nose" lesion that occurs in some cases of herpes zoster involving the nasociliary nerve (Fig. 32, 33). Hutchinson Sign in herpes zoster will at times presage the development of serious ocular involvement [44].

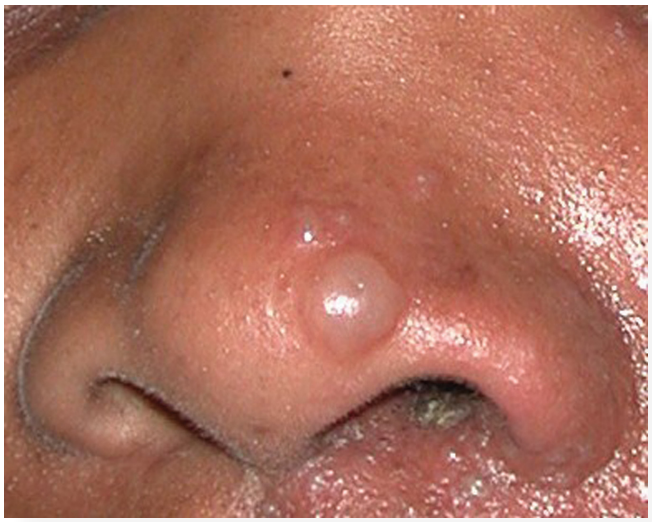

Figure 32. Hutchinson's sign 2

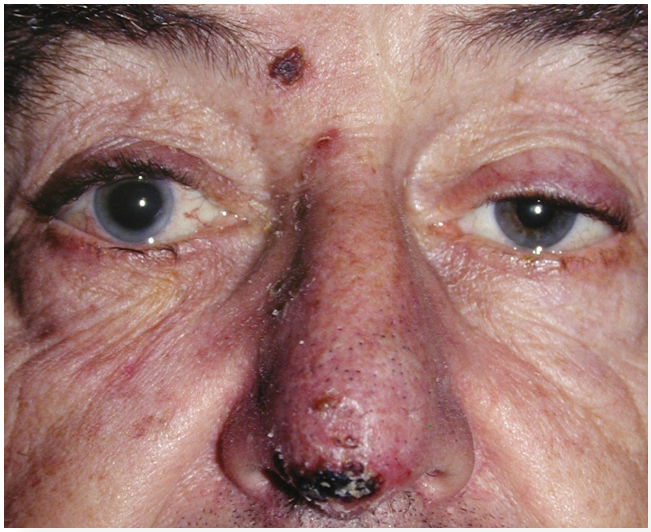

Figure 33. Hutchinson's sign 2

HUTCHINSON'S NAIL SIGN

Hutchinson's nail sign is an important clinical clue to subungual melanoma and is characterized by extension of brown or black pigment from the nail bed, matrix, and nail plate to the adjacent cuticle and proximal or lateral nail folds (Fig. 34) [45].

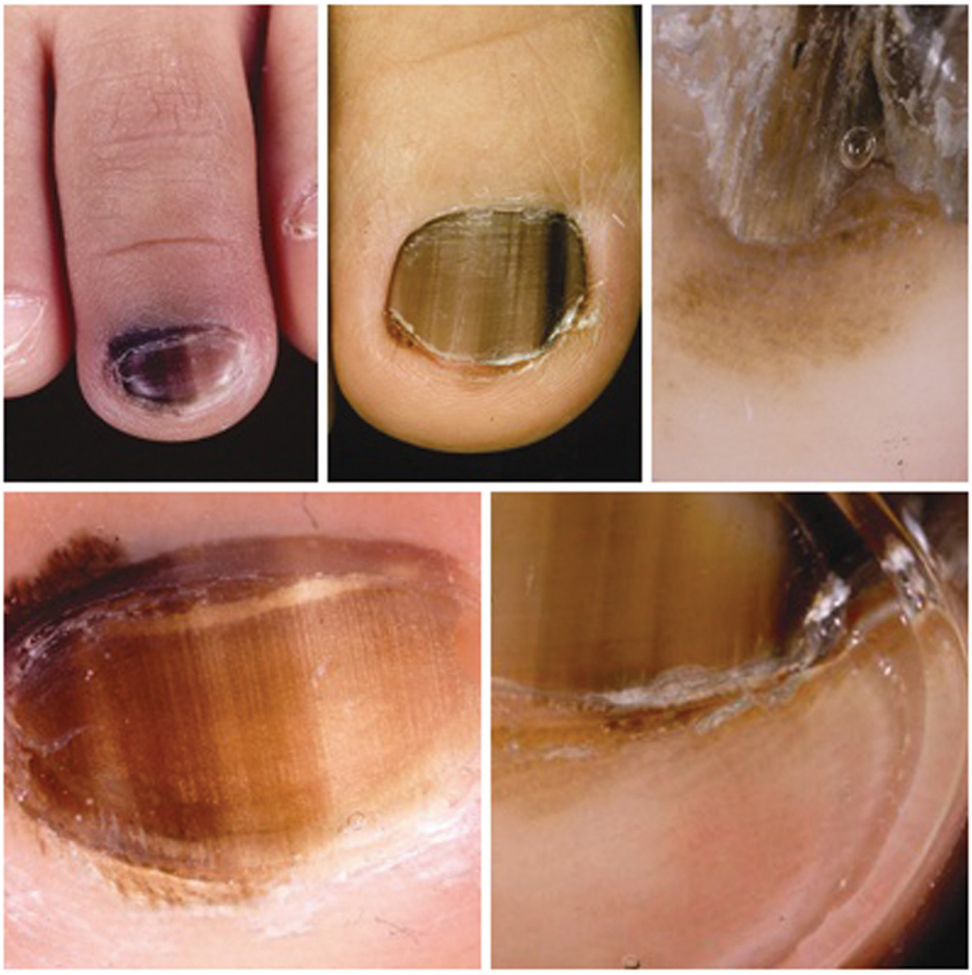

Figure 34. Hutchinson's nail sign

HUXHAM'S SIGN

Green saliva (Huxham – in 1773). Change of colour of the saliva in jaundice.

"…There are some early notices of a change of colour of the saliva in jaundice,^ and one of the best of these we owe to so excellent an observer as John Huxham. A gentleman 40 years old, jaundiced, took overnight, with some other medicines, gr. viii. of calomel. The next day a very green saliva poured out of the man's mouth, exactly like green bile, but' thinner. This flow of green saliva lasted 40 hours, and very nearly equalled two quarts in amount. The green colour of the saliva

passed into yellow, which lasted another 40 hours and then the salivation disappeared as suddenly as it came on. Huxham does not think it due to the mercury, on account of the smallness of the dose; the patient had before been salivated, apparently without mercury…" [46-48].

JOHN HUXHAM

English surgeon, 1672–1768 (Fig. 35). A provincial doctor notable for his study of fevers. In 1750 Huxham published his Essay on Fevers and in 1755 received the Copley Medal for his contribution to medicine. In 1723, James Jurin, one of the secretaries of the Royal Society, asked for volunteers to keep daily records of their observations of the weather including readings of the barometric pressure, temperature, rainfall, and direction and strength of the wind. Their observations were to be submitted annually to the secretaries of the society for collation and analysis. In 1724 Huxham began to keep such records and, from 1728 on until 1748, he noted monthly the prevalence of epidemic diseases. These records he published in two volumes. He was elected Fellow of the Royal Society in 1739.

Huxham was perhaps the first in England to classify the disease Influenza. He is also associated with diagnosis of scurvy and for a recommended cure of drinking cider [49].

HYDROCHLORIC SIGN

Burning pains in outh and throat with vomit containing while lumps of mucous and altered brown or black blood. Stain on skin and mucous membranes appear grayish-white and clothing is stained bright red. A sign of poisoning with htdrochloric acid [50].

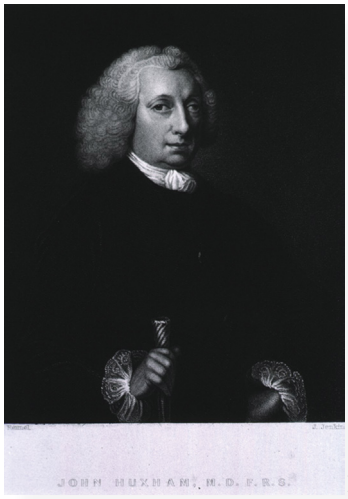

Figure 35. John Huxham

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Dr. Michael E. Doyle
to information about Dr Hertoghe Eugène Louis Chrétien
http://www.gotodrdoyle.com

Mr. Enrico Isacco (to Figure 23 and 24)
Enrico Isacco's Sephardic photographic library.
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We are pleased to extend a warm welcome to the 23RD World Congress of Dermatology (23RD WCD), to be held in Vancouver, Canada from June 8-13, 2015. Held under the auspices of the International League of Dermatological Societies, the 23RD WCD will be the largest international gathering of dermatologists and people dedicated to skin health from all sectors. Our vision for the world's premier dermatology conference includes celebration, innovation, and inclusiveness. Our award-winning world class Vancouver Convention Centre will serve as one of the most beautiful venues to ever host the WCD. Strategically situated on the waterfront in the heart of downtown Vancouver, participants will enjoy spectacular views of the harbour and mountains as they move between their sessions. This unique convention centre is within walking distance of a spectacular variety of accommodation, dining, shopping, tourist attractions, and transportation.

We look forward to celebrating with you in Vancouver, where the world of dermatology will gather in 2015.

Dr. Jerry Shapiro and Dr. Harvey Lui
President and Secretary-General

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