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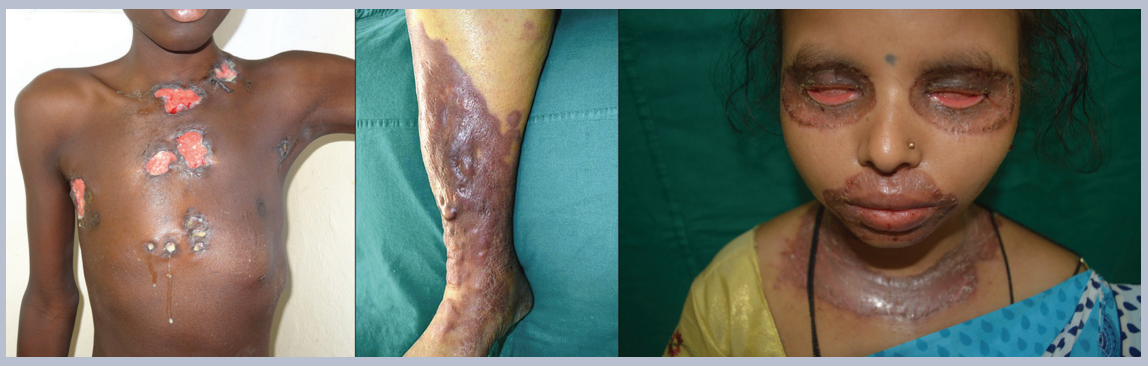

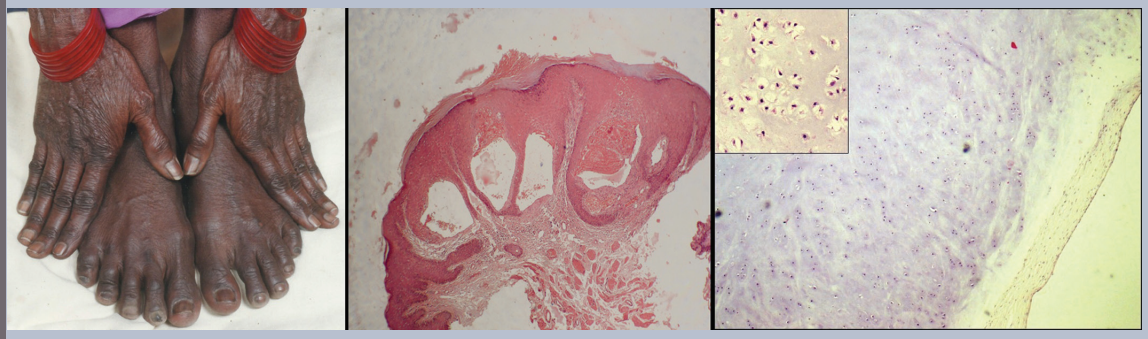

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Editorial Pages

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Original Article

Microwave Thermotherapy: New treatment for cutaneous leishmaniasis

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ABSTRACT

Introduction: Cutaneous leishmaniasis (CL) is an endemic disease with variable therapeutic agents. Microwave radiation has been used in many medical disciplines as therapeutic and diagnostic tools. **Objective:** To evaluate the efficacy of microwave radiofrequency in the treatment of cutaneous leishmaniasis. **Patients and methods:** This is a case, controlled, therapeutic, clinical trial. Thirty five patients completed the study, 18 (51.43%) females and 17 (48.57%) males, with female to male ratio 1.1:1, their ages ranged from 6–60 (26.98±15.22) years and the duration of lesions ranged between 1–6 (2.17±1.44) months. The size of lesions ranged from 1-6.5 (2.87±1.60) cm. Eleven (31.43%) patients had single lesion and 24 (68.57%) patients had multiple lesions. Classical cases of CL were studied and diagnosis was confirmed by histopathological examination. Lesions had been divided in 2 groups, *Group* A: lesions were exposed to a microwave radiation once every two weeks for a maximum of 8 weeks, while *Group B* lesions, received no treatment and left as a control group. Patients were seen every 2 weeks for 8 weeks to reassess the therapeutic effect and to record any side effects. Follow up after cure was carried out for 2-6 months to watch any sign of relapse. **Results:** The total number of lesions were 99;52 (52.53%) ulcerated lesions and 47 (47.47%) dry lesions. In *Group* A, 64 (85.33%) lesions out of 75 showed clinical cure with 1-4 (2.77±0.91) sessions while in *Group B*, 5 (20.83%) lesions out of 24 lesions showed slight healing during the treatment period. No side effects appear in all patients. **Conclusion:** Microwave thermotherapy is highly effective, new therapy for cutaneous leishmaniasis with no harmful side effects.

Key words: Cutaneous leishmaniasis; Thermotherapy; Microwave

INTRODUCTION

Cutaneous leishmaniasis (CL) is considered as an endemic disease causing a major health problem in Iraqi population and the causative organism is *Leishmania Tropica* [1]. The disease could be very disfiguring, especially involving cosmetically important areas like the face including the nose, lips and around the eyes [1].

Cutaneous leishmaniasis is a self limiting disease however, it may take several months –years in order to achieve spontaneous resolution and this has a great psychological and cosmetic impact on patients [2]. Hence treatment is mandatory in most cases to shorten the duration of the disease and to minimize complications like scarring [1], so the type of therapy could be topical or systemic which is indicated in multiple-numerous lesions, a child that couldn't be treated locally, cases that failed to respond to topical therapy and immune compromised patients [3].

There are many varieties of systemic therapies; its response might vary according to the country of the disease, serotypes of the parasite and its virulence and the patients immunity [4]. Of these systemic treatments are: sodium stibogluconate [1], zinc sulphate [1], azithromycin [5], dapsone [6], chloroquine [7] and many others. While the indication for topical therapy is single or few lesions in non-critical areas [3]. Many topical therapies are used such as, intralesional sodium stibogluconate [8], intralesional zinc sulphate [8], intralesional hypertonic

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chloride solution [9], intralesional metronidazole [10], electrotherapy [11], cryotherapy [12], photodynamic therapy [13] and heat therapy using infrared [14], laser [15] and radiofrequency [16].

The response to therapy whether systemic or topical needs at least one month, as when the parasites are killed we need weeks to have resolution of inflammatory tissues [17]. Microwave radiation is a band of electromagnetic radiation between infrared and short wave with a wavelength ranging from as long as one meter to as short as one millimetre and frequencies between 300 MHZ & 300 GHZ. Microwave radiation agitate water molecules in the surrounding tissue, producing friction and heat, thus inducing cellular death via coagulation necrosis, so this makes it an effective method of tissue heating [18]. It has been used in treatment of many medical conditions especially rheumatic disease [19].

As the aim of many topical therapies is to raise the temperature of lesions to a certain degree in order to kill the parasite, like heat therapy using infrared, accordingly we planned to use microwave thermotherapy in treatment of cutaneous leishmaniasis.

PATIENTS AND METHODS

This is a case controlled therapeutic study that was carried out in the Department of Dermatology and Venereology-Baghdad Teaching Hospital, Baghdad, Iraq, during December 2011 - March 2012. *Thirty eight patients* with cutaneous leishmaniasis were enrolled in this study. Three patients with 6 lesions were lost for unknown reason and regarded as defaulted cases. A history was taken from each patient regarding the followings: age, gender, address, number of lesions and their duration, history of previous therapy, also family history, pregnancy and lactation and history of fracture with internal fixation. Close physical examination was performed including site, size, induration, type of the lesion and regional lymph nodes.

Patients with the following criteria were excluded from this study

Those who received any anti–leishmanial treatment for one month and less, chronic diseases like diabetes mellitus, peripheral neuropathy, lesions close to eyes and testes, patients with pacemaker or implantable metals in the treated area, patients with sporotrichoid lesions and pregnancy and lactation.

Ethical approval was given by the Scientific Committee of the Scientific Council of Dermatology and Venereology, Iraqi Board for Medical Specializations. After full explanation to each patient about the nature of therapy and the number of courses given to each patient, formal consent was taken from each patient. The diagnosis was clinical and confirmed by histopathological examination. In patients; with multiple lesions, one lesion was left untreated as a control, especially in hidden areas. While patients with single lesions, control lesion in other cases was considered as a control for these patients.

This is the first study using microwaves, hence we designed a special approach to define the tissue temperature induced by a microwave diathermy device (Elettronica, Pagani, RX 250 and Frequency 2450 MHZ, Italy) according to three variables which are the intensity, time of exposure and the distance from the device to the lesion. So we have used a two steps method: using two different media, chicken meat and water, exposed to microwave radiation in different intensities, measuring the temperature by a chemical thermometer. Accordingly we found that 100 watt intensity, 1 cm distance and 2-4 minutes the time of exposure raise the temperature to around 42C° *in water* and *44 C° in chicken meat.*

Assessment

The degree of erythema was assessed by the change in intensity of the color and the size of the lesion. Induration of the lesion was determined by taking the diameter of regular lesions, while in irregular one, multiple diameters were measured using a tape measure and the mean was calculated. The response to therapy was graded according to Sharquie's scale [2]:

- *Slight: decrease in erythema and indurations of the lesion,*
- *Mild: reduction in the size of the lesion 30%,*
- *Moderate: reduction in the size of the lesion of 30-60 %,*
- *Marked: reduction in the size of the lesion >60%,*
- *Total clearance of the lesion*

Both marked improvement and total clearance were considered as a cure [2].

Lesions had been divided into two groups:
Group A: Lesions were exposed to microwave radiation. Re-adjustment of time of exposure was determined according to the pain threshold (Sharquie's method) exposure is continued until the patient no more

tolerate the pain of heating and then suddenly the pain vanish, this is called the critical point, when we stop the exposure to microwave, this ranged between 2-4 minutes. The number of sessions was determined by the response to therapy and were given every 2 weeks for a maximum of 8 weeks.

Group B: Lesions in this group received no treatment and left as control group.

Follow-up

Patients in two groups were seen every 2 weeks for 8 weeks and on each visit the scoring was re-assessed to estimate the degree of the response and record any local and systemic side effects. Photos were taken in a standardized way according to place, light exposure and distance by using SONY® Cyber shot camera super steady shot+ iso3200, 8.1 Mega pixels. After complete cure follow up was carried out for 2-6 months to monitor any sign of relapse.

RESULTS

Thirty five patients completed the present study, 18 (51.43%) females and 17 (48.57%) males, with female to male ratio 1.1:1, their ages ranged from 6–60 years with a mean ± SD 26.98±15.22 years. The total number of lesions was 99 with 52 (52.53%) ulcerated lesions and 47 (47.47%) dry lesions and the duration of lesions ranged between 1–6 months with a mean ± SD 2.17±1.44 months. The size of lesions ranged from 1- 6.5 cm with a mean ± SD 2.87 ±1.60 cm. Eleven (31.43%) patients had single lesion and 24 (68.57%) patients had multiple lesions. The most common site affected by the disease was the upper extremities 61 (61.62%), then the lower extremities 31 (31.31%), while the trunk was affected in 7 (7.07%).There was no regional lymphadenopathy.

Group A: Seventy- five lesions were treated, 64 (85.33%) lesions showed a cure with number of sessions ranged from 1-4 with a mean ± SD of 2.77±0.91 sessions Table 1. Forty four (68.75%) lesions had complete clearance with 1-4 sessions with a mean ± SD of 2.2+0.83 session (Fig. 1). While 20 (31.25%) lesions had marked response. Six (8%) lesions out of 75 lesions had moderate response with 4 sessions, 3 (4%) lesions had mild response with 4 sessions, while 2 (2.66%) lesions showed slight response with 4 sessions Table 2.

This study revealed that the ulcerated lesions had a quicker response than dry lesions, where 33 (86.84%) ulcerated lesions out of total 38 lesions had clinical cure with 1-4 sessions of therapy, and 31 (83.78%) dry lesions out of total 37 lesions had clinical cure with 1-4 sessions of therapy.

Table 1: The score of response in all treated lesions

Score of response	No of lesions	Percentage	No of sessions
Slight	2	2.67	4
Mild	3	4	4
Moderate	6	8	4
Clinical cure	64	85.33	1-4
Total	75	100	Mean+SD=2.77+0.91

Table 2: Number of sessions of therapy in patients with complete clearance

No. of session	No. of lesion	Percentage
1	5	11.36
2	6	13.64
3	27	61.36
4	6	13.64
Total	44	100

Mean±SD=2.2+0.83

There was no statistical significant difference between ulcerated and dry lesions (χ^2=0.26 and p-value=0.6).

Group B: Five (20.83%) lesions out of 24 lesions showed slight healing during the treatment period.

Follow – up after cure for 2-6 months showed no features of relapse in any patient. Regarding the side effects, no local or systemic side effects were reported. There was no local or systemic infections. About 71% of patients had erythema and crustation after treatment and this was considered as a normal reaction to microwave radiation. In all cured lesions there was minimal or no scarring, while post- inflammatory hyperpigmentation was noted that gradually resolved over time. No leukoderma at the site of treatment was obvious in any case.

DISCUSSION

Treatment of leishmaniasis is essential in many cases especially those lesions on cosmetically important sites. There are many systemic and topical therapies that are used effectively in treating cutaneous leishmaniasis, however, researchers are always looking for new treatments using new devices in order to achieve possibly better results especially in cases where other treatments have failed to clear the lesions.

Microwave radiation has been used in medicine to treat many medical conditions like, rheumatic

disease, cardiac arrhythmias, tumour ablation and dermatological conditions like: plaque psoriasis, axillary hyperhidrosis [19].

The aim of the present study is to use microwave radiation in treatment of cutaneous leishmaniasis by raising the temperature of the lesions to around 41°C in order to kill the leishmania parasite [16].

The present work had achieved a high success rate of (85.33%) in clearance of cutaneous leishmaniasis.

The therapy was tolerable, easy to use without side effects, leaving no obvious scarring and with good cosmetic results.

Comparing the response rate using a microwave device with other forms of radiofrequency, it showed that ThermoMed Model 1.8 used by *Aronson, et al* had a less rate of responsiveness (73%). This study had used it locally giving heat at 50 C for 30 seconds through a portable, battery-operated, localized current field radio-frequency generator, produces a 6.78-mHz frequency, applied with a handset that includes an applicator gauge with 2 electrodes (i.e. bipolar device) that are placed onto the diseased skin. Wide range of complications were noted in *Aronson, et al* study particularly infection, blistering and oozing [16].

Monopolar microwave device in our study avoids the invasive approach of the skin tissue so reduces the chances of infection, hence this microwave device was superior regarding the septic complications, in addition, there was no need for neither local anaesthesia nor antibiotics or dressing as a pre treatment regimen.

Also when the response to microwave therapy was compared with other modes of physical therapies like, infrared [14] it gives (70%) response rate, but it is a painful method of treatment, CO_2 laser [15] (93.7%), although it achieves a high response rate, it is not cost effective and followed by persistent erythema and post inflammatory hyper pigmentation. Cryotherapy [12] (78%) may cause blistering and leukoderma.

In addition, comparing the microwave responsiveness in this study with chemical modes of therapy like, intralesional sodium stibogluconate [8] (94%), intralesional hypertonic sodium chloride solution [9] (96%), intralesional zinc sulphate [8] (97.8%) and intralesional metronidazole [10] (87%), all the above drugs are given through an invasive method and might

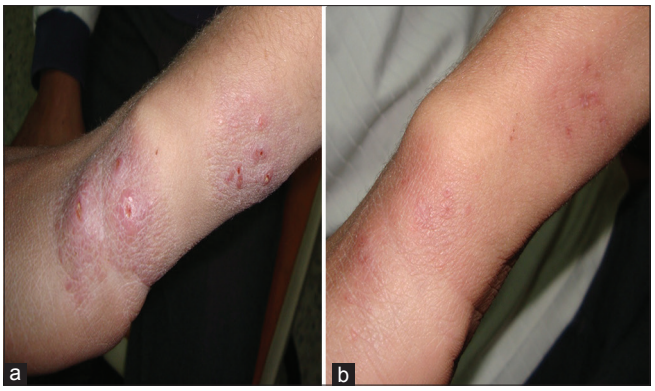

Figure 1: Thirteen years old male with cutaneous leishmaniasis. A. Before treatment. B. After one session

be associated with some side effects. While microwave therapy proved to be an effective regimen without any disturbing side effects.

In conclusion, microwave thermotherapy is highly effective new treatment of cutaneous leishmaniasis. We strongly recommend industrial companies to design a small, mobile and low cost machine to be used in treatment of cutaneous leishmaniasis.

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Original Article

Topical corticosteroids: Abuse and Misuse

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ABSTRACT

Background: The Topical Corticosteroids are among the most commonly prescribed medication in an out-patient dermatology setting since they were first introduced in early 1950s.Probably no other group of drugs has had such a profound impact on the specialty as Topical Corticosteroid. They provide rapid symptomatic relief in almost all inflammatory dermatoses, especially in the short term. Multiple pathways including rebound vasodilatation and proinflammatory cytokine release have been proposed as the mechanism for such reactions. **Aim:** To study various adverse effects of topical corticosteroids misuse over face. **Materials and Methods:** 130 patients with a history of topical corticosteroid use on face for minimum 1 month duration were included in this study. **Results:** Majority of patients were between age group of 21 to 30 (65.4%).Female sex preponderance over male sex with 67.8%.Majority of patients were House wives (49%) followed by Employees (23%).Duration of application of TC was 3-6 months (77%) in majority of cases. Most commonly abused TC was Betamethasone Valerate (79.2%). **Conclusion:** Topical Corticosteroid should not be used on the face unless it is under strict dermatological supervision.

Key words: Acneiform Eruptions; Erythema; Steroid dermatitis; Topical corticosteroids

INTRODUCTION

Topical corticosteroids (TCS) are of great value in treating a wide spectrum of dermatological diseases and since the time of its introduction in 1951, a new therapeutic era in dermatology has been emerged [1]. The development of super potent corticosteroid in 1974 added more cutaneous diseases to the list of TCS indications. Meanwhile TCS misuse also appeared as a common problem adding a new complication which has been reported by Variety of investigators [2]. Chronic misuse of TCS on the face produced a clinical condition which was described by various names, like light sensitive seborrheid [2], perioral dermatitis [3], rosacea-like dermatitis [4], steroid induced rosacea-like dermatitis [4], Steroid Rosacea [5], and steroid dermatitis resembling Rosacea [6].

PATIENTS AND METHODS

A hospital based, cross sectional study was conducted in the department of Dermatology, Venereology, and Leprosy, P.E.S. Institute of Medical Sciences and Research, Kuppam. A total of 130 patients with facial dermatoses using TC over face for a minimum period of 1 month duration, reported between AUGUST 2012 and JULY 2014 were enrolled in this study. Details about the usage of TC and their side effects were recorded.

Ethical Requirements for Studies Involving live human subjects or animal: accepted by all authors.

Method of collection of data

Inclusion Criteria

1. A total of 130 cases presenting with facial dermatoses resulting secondary to application of a TC were included in the study.
2. Age group between 12 to 50 years.
3. Both sexes.

Exclusion Criteria

1. Patients not giving consent for the study.
2. Patients with pre-existing co morbidities that can

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resemble or could cause changes similar to topical corticosteroid side effects or cases where the topical application in use cannot be confirmed as a corticosteroid. Eg: Cushing syndrome, polycystic ovary disorder, thyroid disorder.

3. Patients with dermatoses papulosa nigra, melanocytic naevi and xanthelasmata.

A particular attention was given to corticosteroid therapy regarding the type, potency, duration of therapy, purpose, and the source of its use. Patients were thoroughly examined for the type of skin, site, erythema (mild, moderate, severe), xerosis, scaling, telangiectasia, hyper- or hypopigmentation, atrophy, wrinkles, comedones, papules, pustules, nodules, and hirsutism. Additional symptoms and signs of skin diseases were noted. The general physical and systemic examination was done on all patients. Medical photographic documentation of the patients was done using digital camera. Formal consent was obtained from each patient after full explanation of the aims and the nature of the study to them and the study was approved by the Ethical Committee of College of PESIMSR, Dr. NTRUHS.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

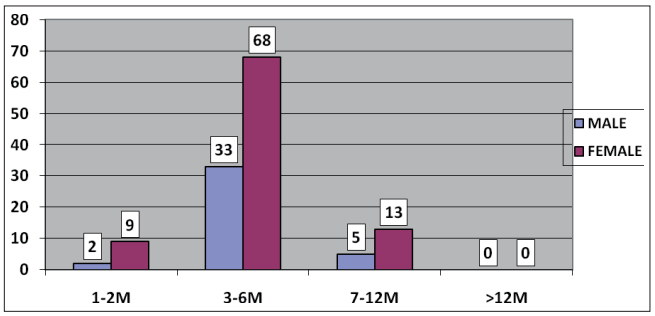
RESULTS

In the study out of 130 cases 85 cases are between age group of 21-30 years with Mean ± SD: 23.92±5.17.The age of youngest patient with TC abuse was 13 years and the age of the oldest patient was 42 years. The most frequently involved age group 21-30 years (65.4%) followed by age group 11-20 years (25.4%) and 31-40 years (7.7%). In the study out of 130 cases 90 were of female sex and 40 were of male sex (Graph. 1). Majority of population belongs to rural areas.

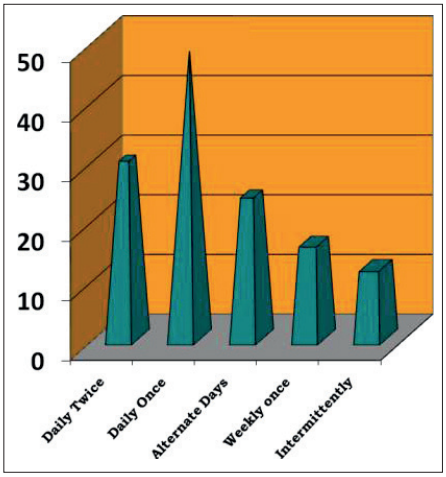
Most of patients are house wives (49.2%) followed by Employee (23.8%), then by student (20.8%) and staff nurse (3.8%). The minimum duration of steroid application over face was 3-6 months (77.7%) followed by 7-12 months (13.8%) and then by 1-2 months (8.5%) (Graph. 1). Majority of cases applied Daily once (37%) followed by Daily twice (23%), then by Alternate days (18.6%) and finally by weekly once (12%) (Graph. 2).

Most commonly used topical corticosteroid was Betamethasone valerate cream (78.5%) followed by Mometasone cream (14.6%), then by Panderm cream (3.86%) and finally by Clobetasol cream (2.31%) (Graph. 3) The most commonly explained reasons were fairness cream (51.54%) followed by as an Acne cream (27.69%) and by Pigment disorders (20.77%). (Graph. 4).

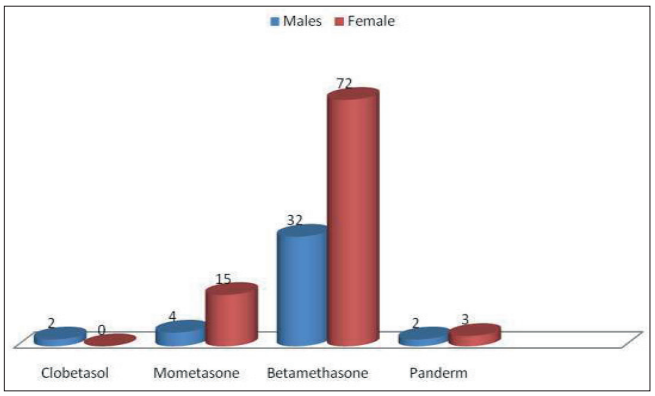
The main source of prescription was Registered Medical Practioners (30%) followed by Friends (23.1%), then by Pharmacist (19.2%), and Self (12.3%). Prescription



Graph 1: Showing duration of Topical Corticosteroids application.



Graph 2: Showing frequency of Topical Corticosteroids application.



Graph 3: Showing type of Topical Corticosteroids used by patients.

by MBBS (11.6%) and Beautician (3.85%) respectively (Graph. 5). Majority of patients presented with chief complaints of Acne exacerbation (62.4%) followed by photosensitivity (55.6%), then by Redness (40.8%) and by pigmentary marks (35.8%) finally by Dryness (18.5%) (Graph. 6).

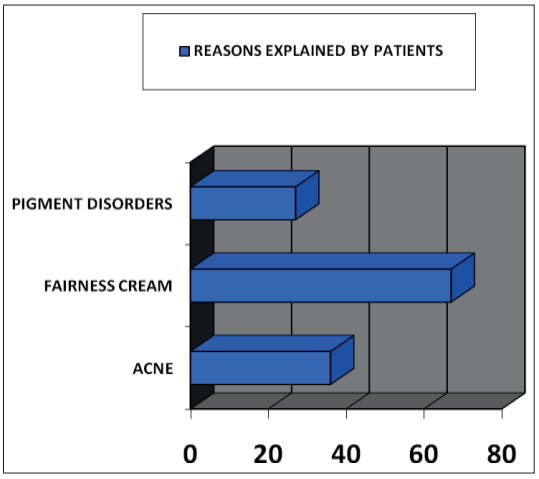
The most common adverse effect was Acneiform eruptions (88.5%) followed by hyper pigmentation (21.5%), then by erythema (18.5%) and finally atrophy (4.6%),Hypo pigmentation (3.8%), Infections (3.1%) each one respectively (Graph. 7).

DISCUSSION

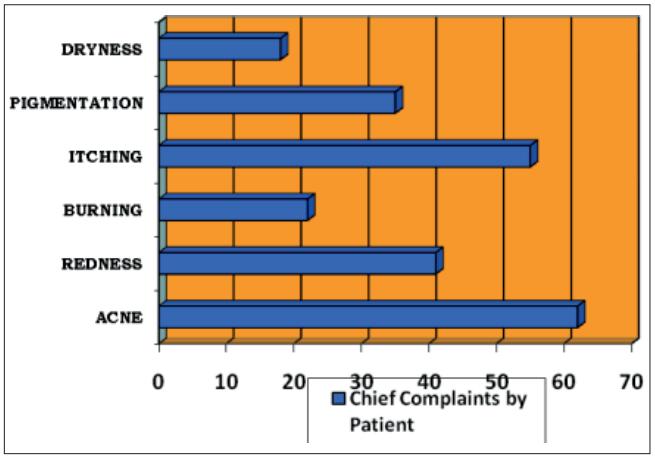
Corticosteroids are not the panacea for all forms of dermatological diseases but it is extremely valuable when their limitations are realized. TCS are the treatment of choice for a variety of cutaneous disorders when it is used on the appropriate site and in proper concentration. However, TCS should not be used on the face except for acute inflammatory conditions provided that it will be not used for more than one month [7,8].

At first the vasoconstrictive and anti-inflammatory effects of the steroids result in what seems to be clearance of the primary dermatitis but persistent use leads to epidermal atrophy, degeneration of dermal structure and collagen deterioration after several months. Continued or overuse of steroids can result in thinning of the skin as well as skin dependency on the steroid [5,9]. Multiple pathways including rebound vasodilatation and proinflammatory cytokine release by chronic intermittent steroid exposure induces various effects.

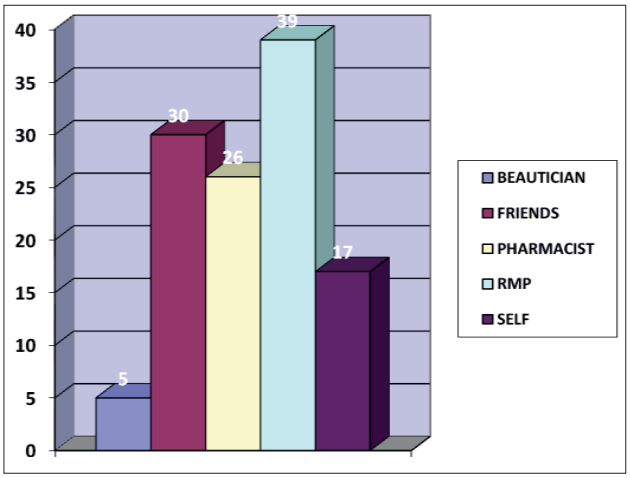
There were few common features in all subjects reported here. They started to use steroid cream as daily cosmetic/fairness cream. Minimum duration required to develop the dermatosis was 5 months. They all had



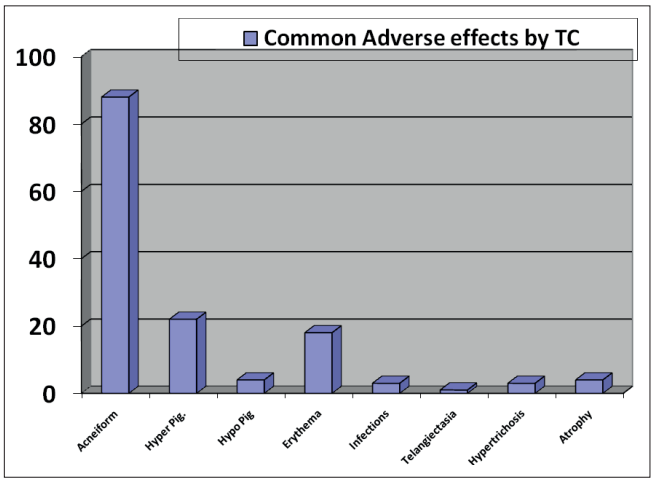
Graph 4: Showing reasons explained by patients.



Graph 6: Showing chief complaints by patients.



Graph 5: Showing source of prescription.



Graph 7: Showing common adverse effects of Topical Corticosteroids.

magical response earlier; later started to develop rashes on stopping.

In the present study, majority of cases were reported between age group of 21-30 years, similar results were seen with Bhat YJ et alstudy [9] and saraswati et al study [10]. Female preponderance showed like Rathi sk [3] and Bhat YJ et al study [9]. In Bhat YJ et al study [9] reported that majority of cases were House wives like the present study.

In the Present study, majority of patients belong to rural areas, because my college located in rural area. Similar results were seen with Bhat YJ et al study [9]. In saraswati et al study [10], involvement of urban population was more.

In a majority of studies reported, duration of application of TCS ranges from 1w – 30 yr. In the present study majority of patients with steroid application over face presented after 3-6 months (77.7%).

In a study by Bhat YJ et al [9], Rathi SK [3], Saraswat et al [10], Ammar F Hameed [11], reported that majority of patients used Betamethasone Valerate. In the present study Betamethasone valerate cream (78.5%) was most commonly used TC.

In the present study, source of prescription was Registered Medical Practioners (30%). These results were consistent with Rathi SK study [3]. saraswati et al study [10] reported that the most common reason explained by the patient for using TC was as a fairness cream. In a report by Bhat YJ et alstudy [9], the most common reason explained by patient was dryness of skin. In the present study the most common reasons for using TC were as a fairness cream (51.54%). Similar results were found in saraswati et al study [10].

In a study, Ammar F Hameed [11] reported that most common adverse effect was burning. In Bhat YJ et al study [9] showed that there were more number of Rosacea cases than acne. In the present study majority of patients presented with chief complaints of acne exacerbation (62.4%), followed by photosensitivity (55.6%), redness (40.8%), pigmentary marks (35.8%) and finally by Dryness (18.5%). Similar results were seen with saraswati et al study [10].

To prevent the harmful effects of corticosteroids, it is important to understand how to use these medications. The use of the finger tip unit is quite helpful. That is

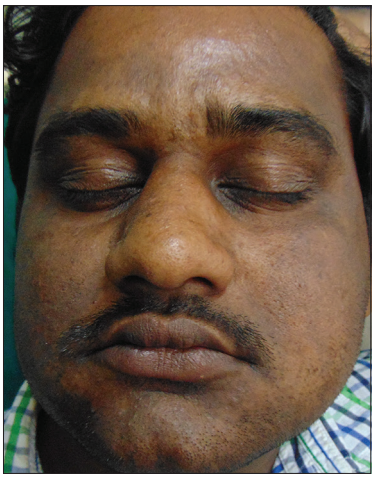


Figure 1: Diffuse hyper pigmentation and hypo pigmentation.

the cream is measured on the index finger between the tip and the first crease on that finger. That quantity of cream should be enough to apply on the size of the body that both hands can cover. Another way is to use these topical agents on a week on, week off basis or three days on and four days off basis to prevent tachyphylaxis.

We advised oral azithromycin 500mg in the form of weekly pulse therapy (3 tabs per week for 4–6 weeks) or oral doxycycline 100mg twice daily for 6-10 weeks, along with topical clindamycin, topical retinoic acid and topical tacrolimus 0.03% ointment once daily showed a good response in around 2–3 months. Emollient, oral vitamin E and C had additional beneficial effect in relieving other symptoms.

CONCLUSION

TCS abuse becoming a great cause concern for their dramatic clinical effects, peer pressure to use them for cosmetic purpose, easy availability of products, inadequate information of their adverse effects, and phenomenon of steroid addiction.

There is always a doubt as to which steroid is safe for face; in fact no steroid is safe for face, and to be prescribed only if specifically indicated for shorter duration and it is very essential to educate patient about side effects and dependency in order to prevent the consequences of abuse. The awareness among doctors and patient is highly essential as magnitude of problem is high.

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CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Original Article

Comparative study of calcipotriol ointment and mometasone furoate ointment in patients of psoriasis vulgaris: A double blind study

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ABSTRACT

Introduction: Psoriasis is a chronic, inflammatory papulosquamous disease clinically characterized by erythematous, sharply demarcated, indurated papules and rounded plaques covered by silvery, micaceous scales. Psoriasis is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, infiltration of mostly T lymphocytes and various endothelial vascular changes in the dermal layer, such as angiogenesis, dilatation and high endothelial venule (HEV) formation. **Material and Methods:** The study was conducted on 70 patients of psoriasis attending the outpatient department. Patients who fulfilled the selection criterion were alternately assigned into two groups, 35 patients in each group. The assessment of effectiveness was done with the help of PASI. Follow up of patients were done after 1st, 2nd, 4th and 6th week of initiation of treatment. **Results:** We observed 70 patients and both the group showed statistically significant reduction in the disease severity. **Conclusion:** The calcipotriol and mometasone furoate ointment were found to be equally effective in clearance of the disease.

Key words: Calcipotriol ointment; Mometasone furoate ointment; Psoriasis

INTRODUCTION

Psoriasis is a chronic, inflammatory papulosquamous disease clinically characterized by erythematous, sharply demarcated, indurated papules and rounded plaques covered by silvery, micaceous scales [1]. Recently there is increase in a number of population-based studies providing a global prevalence estimate of psoriasis. It has been found that the prevalence of psoriasis varies considerably in different parts of the world. Psoriasis affects approximately 3.5% of the world population [2]. Psoriasis vulgaris is identified as the most prevalent autoimmune disease which is caused by an inappropriate activation of the cellular immune system. The genetic basis of psoriasis has been known since many decades. The incidence of psoriasis in siblings has been found to be as high as 68% [3].

Psoriasis is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, infiltration of mostly T lymphocytes and various endothelial vascular changes in the dermal layer, such as angiogenesis, dilatation and high endothelial venule (HEV) formation [4]. The exact role of T-cells in the pathogenesis and development of lesions can be explained in 3 events that are initial activation of T lymphocytes, the migration of T lymphocytes into the skin, and the various roles played by cytokines released from T lymphocytes and other cells [5]. The typical psoriatic plaque is characterized by well demarcated, elevated, erythematous plaque with dry, loosely adherent silvery-white scales which preferentially involves extensors of the body. The various clinical variants of psoriasis are chronic plaque psoriasis, guttate psoriasis, exfoliative psoriasis, pustular psoriasis, psoriasis unguis and regional variants.

Topical therapies remain the mainstay of treatment for mild psoriasis and in combination with other modalities for patients with moderate to severe psoriasis. The main

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groups of topical therapies for psoriasis are emollients, keratolytics, corticosteroids, coal tars, dithranol (anthralin), vitamin D3 analogues (Calcipotriol), tazarotene, tacrolimus and pimecrolimus. Calcipotriol (calcipotriene) is already established to be effective topically in the treatment of psoriasis [6]. It has a high binding affinity to the vitamin D receptor (VDR) for the biologically active form of vitamin D3 (1,25-dihydroxy vitamin D3). VDR have been demonstrated in epidermal keratinocytes, melanocytes, dermal fibroblasts and many other cell types [7]. Calcipotriol reduces epidermal cell proliferation and enhances differentiation in the skin lesion by binding to the VDR located in the nucleus of keratinocytes which is found to be increased in number in psoriatic skin. Its advantage over corticosteroids is that it does not cause atrophy, so can be used for longer period. Recently calcipotriol, a synthetic vitamin D3 analogue, has become one of the most widely used treatments for psoriasis. To assess the effectiveness of calcipotriol compared with the more traditional topical treatments for psoriasis we undertook a study to compare 0.005% calcipotriol and 0.1% mometasone furoate ointment.

MATERIAL AND METHODS

The study was conducted as double blind, randomized comparative trial on 70 patients of psoriasis attending the outpatient department of dermatology at a tertiary care hospital.

Inclusion criteria

1. Patients having mild to moderate psoriasis.
2. Percentage of body surface area affected by psoriasis less than or equal to 20%.

Exclusion criteria

1. Patients suffering from hepatic or renal diseases.
2. Pregnant or lactating women.
3. Allergy to study medication.
4. Psoriatic lesions over face.

Approval from institutional ethical committee was obtained before initiation of the study. Patient fulfilling the entire inclusion and exclusion criterion and those willing to complete the follow up examinations were included in the study. A written consent was taken from all the patients. Then a detailed history was taken and recorded. The examination of psoriatic plaque was done in detail with special focus on erythema, induration and scaling. Auspitz 's sign has been performed in every patient to clinically confirm the diagnosis. Routine blood investigations were advised to confirm any association of underlying organ or system involvement. Patients who fulfilled the selection criterion were alternately assigned into 'Group A' and 'Group B' by one study coordinator who was not interested in the result of this study. Each group includes 35 patients. Name of the drug used in both the group was revealed after completion of study. The study has been carried out for 18 months.

The assessment of effectiveness was done with the help of 'Psoriasis Area Severity Index' (PASI) score which was recorded at the baseline and at each follow up.

Psoriasis Area Severity Index (PASI)

PASI is a commonly used measure in clinical trials for psoriasis treatments and the severity scores appear to be highly subjective. The classical psoriatic plaque is characterized by erythema, indurtion and scaling. This provides a means of assessing the severity of psoriasis. PASI is believed to be the gold standard for assessment of psoriasis [8]. The PASI score is calculated as follows [9].

PASI = 0.2 (EU+SU+IU) AU+0.3 (ET+ST+IT) AT+0.4 (EL+SL+IL) AL
Where;
E = Erythema or redness
I = Induration T = Trunk
S = Scaling L = lower limb
A = Area of involvement
U = Upper limb

Area of extent of lesion is classified on a 7-point scale as
0 – No involvement
1 – Less than 10%
2 – 10-29%
3 – 30-49%
4 – 50-69%
5 – 70-89%
6 – 90-100%

The severities of lesion (erythema, scaling, induration) are classified on a
5-point scale
0 – Complete lack of involvement
1 – Mild involvement
2 – Moderate involvement
3 – Severe involvement
4 – Severest possible involvement

Follow up of patients were done after 1st, 2nd, 4th and 6th week of initiation of treatment (Figs 1 and 2). Assessment of adverse effects was also done at each follow up. PASI score changes within the group were analyzed by non-parametric, Wilcoxon test. The post treatment PASI score changes between two groups were assessed by 'unpaired Student t-test'.

Drugs used in study

Group A: Topical calcipotriol (0.005%) ointment, once daily application in evening.
Group B: Topical mometasone furoate 0.1% ointment, once daily application in evening

Liquid paraffin was also given for topical application in morning to patients of both groups.

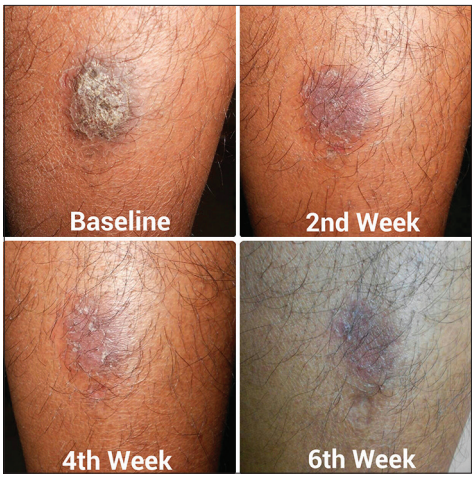

Figure 1: Clinical photograph showing reduction in erythema, induration and scaling of plaque after applying calcipotriol ointment.

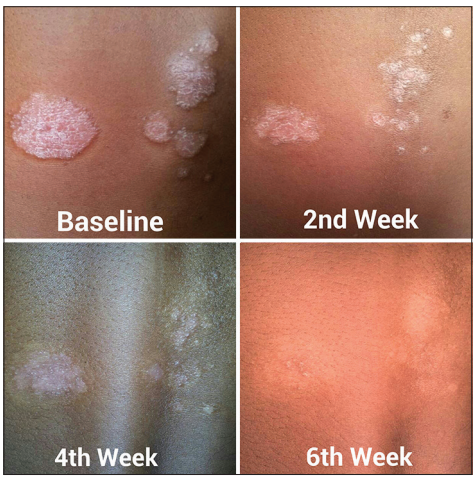

Figure 2: Clinical photograph showing reduction in erythema, induration and scaling of plaque after applying mometasone ointment.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

RESULTS

In our study maximum patients were presented in group A between 31 – 40 years (28.5%) and in group B between 21 – 30 years (25.7%) with mean age of presentation being 36.1 years in group A and 37.2 years in group B (Tabl 1). The overall male to female sex ratio was found to be 9:1. Disease exacerbation due to seasonal variation was observed by 26 patients (37.14%) and 4 patients (5.71%) in winter and summer respectively. In group A patients the mean PASI at baseline was 5.54 and it was reduced after 1st, 2nd, 4th and 6th by 19.4%, 36.9%, 50.5% and 73.1% respectively (Tabl. 2) and in group B patients the mean PASI at baseline was 5.13 and it was reduced after 1st, 2nd, 4th and 6th by 8.5%, 12.3%, 52.8% and 78.6% respectively (Tabl 3). The reduction of mean PASI score on each follow up in both the group were found to be statistically significant as compare to baseline PASI score.

After comparing both the groups the difference in mean PASI score was observed to be 4.05 in group A and 4.03 in group B on 6th follow up. From the above data we observed that there was no statistically significant difference between the reductions in PASI score of both the groups (Tabl 4). More than 75% reduction in PASI score is shown by 54.3 % and 68.6 % of patients in group A and group B respectively (Tabl 5). Adverse effect in the form of irritation and burning were experienced by 2 patients using calcipotriol.

DISCUSSION

Psoriasis is a common, chronic and relapsing inflammatory skin disease. Topical treatment is the mainstay of management for mild to moderate psoriasis and often the initial treatment for severe psoriasis. Despite the availability of several treatments, psoriasis is usually difficult to treat because of its sporadic course, variable response to treatments and adverse effects. Approximately 80% of the patients having psoriasis are treated by the topical therapy [10]. Topical corticosteroids and vitamin D3 analogue are the treatment of choice for mild to moderate psoriasis [11].

Table 1: Age distribution

Age group (years)	Group A		Group B		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
< 20	6	17.14	4	11.43	10	14.29
21 – 30	8	22.86	9.00	25.71	17.00	24.29
31 – 40	10	28.57	8	22.86	18	25.71
41 – 50	5	14.29	8	22.86	13	18.57
51 – 60	0	0	2	5.71	2	2.86
61 – 70	5	14.29	4	11.43	9	12.86
>70	1	2.86	0	0	1	1.43
Total	35	100	35	100	70	100
Mean±SD	36.14±15.93		37.26±14.08		36.7±14.94	
Range	16-72 years		17 – 68 years		16 – 72	

Table 2: Group A comparison of changes in PASI scores (Calcipotriol)

Particulars	Baseline	1st week	% Diff.	2nd week	% Diff.	4th week	% Diff.	6th week	% Diff.
Mean	5.54	4.46	19.40	3.49	36.95	2.74	50.57	1.49	73.17
SD	2.19	2.03		1.85		1.56		1.02	
Z#	-	7.13		5.19		5.16		5.16	
P value		<0.001 (HS)		<0.001 (HS)		<0.001 (HS)		<0.001 (HS)	

#Wilcoxon test (Paired) Z, P<0.001 Highly significant (HS). % - Percentage. Diff. – Difference

Table 3: Group B comparison of changes in PASI scores (Mometasone Furoate)

Particulars	Baseline	1st week	% Diff.	2nd week	% Diff.	4th week	% Diff.	6th week	% Diff.
Mean	5.13	4.69	8.58	4.49	12.37	2.42	52.84	1.1	78.60
SD	2.11	2.06		2.02		1.45		0.96	
Z#		5.22		5.2		5.16		5.16	
P value		<0.001 (HS)		<0.001 (HS)		<0.001 (HS)		<0.001 (HS)	

#Wilcoxon test (Paired) Z, P<0.001 Highly significant (HS). % - Percentage. Diff. – Difference.

Table 4: Inter Group comparison of changes in PASI score

Groups	Particulars	Baseline	6th week	Difference
Group A	Mean	5.54	1.49	4.05
	SD	2.19	1.02	1.33
Group B	Mean	5.13	1.1	4.03
	SD	2.11	0.96	1.46
Unpaired t -Test	t			1.695
	P value	-	-	>0.05NS

Table 5: Treatment response in PASI

Groups	Percentage of patients showing clearance					Total (%)
	100	90-100	75-89	50-74	<50	
Group A	8.6	8.6	37.14	45.7	0	100
Group B	11.4	8.6	48.6	31.4	0	100

Bruce S et al and Queille-Roussel et al found that topical calcipotriol was effective in patients of psoriasis [12,13].

Topical corticosteroids are the oldest, effective and most commonly used treatment modality for mild to moderate psoriasis. Apart from its good effectiveness, topical corticosteroid failed to maintain the effect and showed decreased response, tolerance and tachyphylaxis [14]. They are also known to cause local adverse effects such as striae, hypopigmentation, atrophy, telangiectasis and contact dermatitis. According to the studies conducted by Gulam Kazem Ali Ahmad et al, a medium potent (class 4 and 5, American system classification) topical corticosteroid has been found to be effective in treatment of psoriasis [15]. Our study is consistent with the above studies in showing the effectiveness of mometasone furoate 0.1% (class 4 and 5, American system classification) ointment in treatment of psoriasis.

In our study both the topical agents were found to be effective in clearance of psoriatic lesions, but on comparing the effectiveness of calcipotriol with mometasone furoate ointment, we found at the last follow up of 6th week that there was no significant difference between the effectiveness of the two drugs ($P > 0.05$). Our study is consistent with a comparative study by Gulam Kazem Ali Ahmad et al which revealed that calcipotriol ointment was as effective as medium potent corticosteroid (class 4 and 5, American system classification) ointment [15].

Therefore the result of our study showed, topical calcipotriol can be used in treatment of mild to moderate psoriasis involving less than 20% of the body surface area as an alternative to topical corticosteroid, as it is equally effective and safe.

CONCLUSION

The calcipotriol and mometasone furoate were equally effective in clearance of the disease, Therefore from the current study we conclude that 0.005% calcipotriol ointment can be used in the treatment of psoriasis involving less than 20% of the body surface area as a replacement of the very commonly used topical corticosteroid ointment which are known to be associated with tolerance and many adverse effects.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Original Article

Age-related differences in the incidence and clinicopathological findings of malignant melanoma of the skin

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ABSTRACT

Introduction: In malignant melanoma of the skin, age has been found to be one of the factors associated with different clinical outcome and prognosis of disease. The purpose of our study was to investigate differences in the incidence and clinicopathological findings of cutaneous melanoma in relation to the age of the patients. **Material and methods:** Study group consisted of 116 primary invasive malignant melanomas of the skin from 116 subjects (57 men, 59 women) between 31 - 93 years of age. They were stratified into three separate age groups: group I (≤ 43 years, young age), group II (44 – 60 years, middle age) and group III (≥ 61 years, old age). **Results:** In group I, II and III, we confirmed 22 (19%), 45 (38.8%) and 49 (42.2%) individuals, respectively. As age increased, proportion of males, as well as melanomas located on the head and neck were rising. There was evident decline in the percentage of superficial spreading melanoma and conversely, increase in the percentage of nodular melanoma. Acral lentiginous melanoma and lentigo maligna melanoma was found only in patients over 60 years old. In general, advancing age was associated with lower prevalence of stage pT1 and higher prevalence of stage pT4, higher mean Breslow´s thickness and mitotic rate and with larger proportion of ulcerated lesions. In comparision to younger individuals, patients ≥ 61 years of age exhibited melanocytic nevus remnants in melanomas less commonly. **Conclusion:** We found apparent age-related differences in the incidence and clinicopathological characteristics of malignant melanoma of the skin. In general, unfavourable prognostic variables predominated in the oldest population. Further research is needed to clarify, to what extent are these age-related disparities associated with distinct etiopathogenetic mechanisms and primary tumor biology.

Key words: Malignant melanoma; Age; Prognosis

INTRODUCTION

The incidence of malignant melanoma of the skin has dramatically increased over the last several decades [1-3]. Although some recent data indicate that the rate of such increase began to stabilize, this has been observed predominanly in younger perons [2]. Conversely, the rate of increase in both, incidence and mortality has been significantly higher for age groups older than 60 years [2]. In general, malignant melanoma is one of the most aggressive neoplasms in humans characterized by a relatively poor prognosis. In developed countries, it represents the leading cause of death among malignant skin tumors [3]. However, overall clinical outcome of disease directly depends on several clinical and histopathological parameters [4], which individually determine the choice of the therapeutic strategies and managment of the patients. Among them, age has been found to be one of the clinical factors associated with different incidence, clinical outcome and overall prognosis of disease. Many studies demonstrated [1,2,5-11], that clinical presentation and pathological characteristics in melanoma of the elderly differ from that of their

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younger counterparts. When compared to younger age groups, older individuals are more likely to acquire and to die from melanoma implicating age as a poor prognostic factors [12]. The most striking differences in melanoma incidence and mortality occur in individuals over age 65, although modest differences are notable in those over age 50 [12]. We undertook a retrospective study to investigate the differences in the incidence and clinico-pathological prognostic factors of cutaneous melanoma in relation to the age of the patients.

MATERIAL AND METHODS

Study group consisted of 116 consecutive representative primary invasive malignant melanomas of the skin, that were histologically diagnosed at the Department of Pathology in Faculty Hospital in Zilina (Slovakia) between January 2007 – October 2014. They were obtained from 116 subjects (57 men, 58 women) in the age range between 31 - 93 years. In situ and reccurent melanomas, as well as mucosal and ocular melanomas were excluded from the analysis. The topographic localization of tumors studied was as follows: head and neck (n = 12), trunk (n = 56), upper extremities (n = 32) and lower extremities (n = 16). The lesions were excised in several clinical departments of the hospital (i.e., departments of surgery, dermatovenerology and otorhinolaryngology). Treatment consisted of wide surgical extirpation and a subsequent regional lymph node disection was performed in some patients (n = 13) with suspected regional metastases. All tumors were removed completely with negative surgical margins and objective assessment of all conventional histomorfological parameters was possible. In each case, melanoma characteristics that were analyzed for the purpose of this study included: histologic type, tumor thickness according to Breslow, level of invasion as defined by Clark, pT-stage, ulceration, pre-existing nevus, mitotic rate expressed as the number of mitoses per square millimeter and sentinel lymph node status. All cases were staged according to 7th edition of UICC (Union for International Cancer Control) TNM classification of tumors [13]. Biopsy material was fixed in buffered formalin, embedded in paraffin blocks, stained with hematoxylin and eosin, and the slides were reviewed by pathologists under the light microscope. In addition to standard hematoxylin and eosin staining, we also use special histochemical (Pearls, Fontana-Masson stains) and immunohistochemical (antibodies against melan A, HMB-45, S-100 protein, polyclonal cytokeratins, Ki-67 antigen) methods for better microscopic evaluation of tumor tissue. According to recent paper published by Liljana Mervic [14], patients were cathegorized into three separate age groups: group I (≤ 43 years, young age), group II (44 – 60 years, middle age) and group III (≥ 61 years, old age). After this stratification, we compared clinicopathological data between all given groups. Informations on patients were received from the clinical hospital records, or by consultation with the clinicians.

RESULTS

A summary of the distribution of various clinical and histopathological characteristics of our cohort of patients stratified by age groups is presented in Table 1. Overall, group I, II and III consisted of 22 (19.0%), 45 (38.8%) and 49 (42.2%) individuals, respectively. The mean age of the patients at the time of primary diagnosis was 58.4 years. As age increased (in terms of group I → II → III), there was a mild increase in the prevalence of men and decrease in the prevalence of women. While male/female ratio was 1.2 in the youngest group, it was only 0.9 in patients older than 60 years. In each age group, melanomas occured most frequently on the trunk, especially on the back. However, advancing age was associated with rising percentage of tumors located on the head and neck. Whereas they represented only 4.5% of all melanomas diagnosed in group I, it was more than 3 times (16.3%)

Table 1: A summary of the clinicopathological characteristics of our cohort of melanoma patients stratified by age groups

Clinicopathological parameter	≤43 years	44-60 years	≥61 years
Number of patients	22	45	49
Men	10 (45.5%)	22 (48.9%)	25 (51.1%)
Women	12 (54.5%)	23 (51.1%)	24 (48.9%)
Anatomic localization			
Head and neck	1 (4.5%)	3 (6.6%)	8 (16.3%)
Upper extremities	4 (18.2%)	17 (37.8%)	11 (22.4%)
Lower extremities	5 (22.8%)	4 (8.9%)	7 (14.3%)
Trunk	12 (54.5%)	21 (46.7%)	23 (47.0%)
Breslow´s thickness (mean)	1.6 mm	2.9 mm	3.2 mm
Clark´s level (most frequent)	III	III	IV
Mitotic rate (mean)	3.0	5.2	5.8
Ulceration	4 (18.1%)	12 (26.6%)	16 (32.6%)
Pre-existing nevus	12 (54.5%)	25 (55.6%)	19 (38.7%)
Histologic type			
Superficial spreading melanoma	19 (86.4%)	33 (73.3%)	25 (51.0%)
Nodular melanoma	2 (9.1%)	12 (26.7%)	14 (28.6%)
Lentigo maligna melanoma	0	0	8 (16.3%)
Acral lentiginous melanoma	0	0	2 (4.1%)
Nevoid variant of melanoma	1 (4.5%)	0	0
pT stage			
pT1	13 (59.1%)	26 (57.7%)	23 (46.9%)
pT2	5 (22.7%)	8 (17.8%)	8 (16.35%)
pT3	2 (9.1%)	4 (8.9%)	8 (16.35%)
pT4	2 (9.1%)	7 (15.6%)	10 (20.4%)
Sentinel lymph node metastasis	1 (4.5%)	3 (6.6%)	2 (4.0%)

in group III. Conversely, in the youngest group there was a higher prevalence of melanomas located on the trunk (54.5%), although when compared to both other groups (46.7% and 47%), these differences were not so much striking. In addition, as age increased, there was continuous decline in the percentage of superficial spreading melanoma (86.4% vs 73.3% vs 51%) and increase in the percentage of nodular melanoma (9.1% vs 26.7% vs 28.6%). Acral lentiginous melanoma and lentigo maligna melanoma were found only in patients over 60 years old. Comparative analysis of three given age groups have shown that advancing age was associated with lower prevalence of stage pT1 (59.1% vs 57.7% vs 46.9%) and higher prevalence of stage pT4 (9.1% vs 15.6% vs 20.5%), greater mean tumor thickness (1.6 mm vs 2.9 mm vs 3.2 mm) as well as number of mitoses per 1 mm^2 (3.0 vs 5.2 vs 5.8) and with larger proportion of ulcerated lesions (18.1% vs 26.6% vs 32.6%). The elderly aged 60 and over were less likely to have melanoma histologically associated with a pre-existing melanocytic nevus (38.7%) compared to both younger groups, where this percentage was about the same (54.5% and 55.6%). We did not confirm convincing differences in the incidence of sentinel lymph node metastasis among the study age groups (4.5% vs 6.6% vs 4.0%), although this assessment can be considered only informative, since it is limited due to the small number of persons who underwent regional lymph node extirpation. Of these, the interval between histological verification of primary melanoma and lymph node metastasis varied from 1 to 18 months except for one patient, in whom both, skin lesion and positive lymph node biopsy were made during one surgical procedure.

DISCUSSION

Malignant melanoma of the skin exhibits a variety of clinicopathological differences depending on age, for example in the site distribution, gender prevalence, histomorphological features and prognostic variables derived therefrom. The results of our observations correspond to the literature data reporting that with increasing age, melanomas occur more frequently in men [1,2,5] and their proportion on the head and neck is rising [1,2]. Higher incidence of head and neck melanoma is likely attributable to cumulative photodamage as patients age [1]. While in young individuals a melanoma genesis is associated with intensive intermittent solar exposure and sunburns, in older people melanomas develop more commonly on the skin permanently exposed to sunlight throughout life [7]. Consequently, melanomas are more likely to arise on the trunk at a younger age, and on the head and neck in the elderly. From the practical point of view, as the percentage of older persons in the world's population continues to grow, physicians performing melanoma screening should devote heightened attention to heavily sun-exposed body sites [1]. As for histological types, older patients are characterized by relatively higher percentage of lentigo maligna melanoma, nodular melanoma and acral lentiginous melanoma [2,7,11]. Our results are consistent with these reported data, as the highest percentage of nodular melanoma was present in patients over 60 years old and both, acral lentiginous melanoma and lentigo maligna melanoma were found only in this age cathegory. Melanoma in the elderly less likely arise from a pre-existing melanocytic nevus [1,15,16], but it is closely linked with their predominant histological types. Superficial spreading melanoma (which occur most commonly in younger persons and on the trunk) develops from previous melanocytic nevus most frequently [15,16]. On the contrary, lentigo maligna melanoma (which occur predominantly in the elderly and on the chronically sun-exposed body sites) has the lowest probability to be in continuity with associated nevus remnants [15,16]. Lentigo maligna melanoma possesses clinical characteristics and epidemiologic patterns that are distinct from other melanomas. As mentioned above, it usually develop later in life and has the strongest relationship with a chronic ultraviolet radiation among all types. These observations could suggest that lentigo maligna melanoma arises along a causal pathway driven by accumulated sun exposure as distinct from arising in association with a melanocytic nevus [15]. The vast majority of studies have shown, as we did, as age increased, percentage of thicker melanomas was significantly rising [1,2,5-11]. This is probably due to delayed diagnosis of disease, feature more typical for the elderly males [7], as well as apparent rising predponderance of nodular melanoma [2,10,17]. The significance of different melanoma subtypes is controversial in this regard, since the thickness of melanoma shows progressive diminution in nodular vs superficial spreading vs lentigo maligna melanoma [4]. However, it may reflect reproducible differences in the biology. Thus, nodular melanoma, which manifests a vertical growth phase *de novo* would naturally be expected to have the greatest thickness, however, also to contain a clone of neoplastic cells more capable of metastatic progression [4]. One

study indeed found [18] that nodular melanoma, along with older age and male gender are associated with rapid and more aggressive tumor growth. Advancing age is also associated with greater percentage of tumor ulceration [2,5,8,9,11], tumor regression [5] and pronounced mitotic activity [1] – factors that reflect more aggressive biological behaviour of melanoma and adversely affect both, recurrence and mortality rate.

The issue of whether age alone directly correlates with clinical course and worse survival has been debated over the past several decades [12]. As most histopathological melanoma features worsen with increasing age, not surprisingly it parallels poorer prognosis. Therefore it has long been questionable whether age is really an independent significant prognosticator. However, the results of several multivariate studies have supported this assumption [2,6,8,9], since prognostic significance of age has been demonstrated after adjusting for all known prognostic variables. For example, Austin, et al [8] observed significant disease-free survival differences in the older population, with only 55% of the elderly population being disease free at 5 years compared with 65% for the younger population. Regression analysis showed age was an independent survival predictor. Lasithiotakis, et al [2] found, melanoma patients older than 65 years had lower 10-year disease-specific survival than younger ones and this difference was more pronounced in women than in men. Males had lower 10-year disease-specific survival than females but this difference did not reach statistical significance in individuals older than 65 years. In multivariate analysis, age was independent prognostic indicator. Similar results have also been reported by Balch, et al [6] and Caraco, et al [9]. This may suggest that the role of age in the natural course of melanoma might not be entirely explained by differences in the proportions of the known clinicopathologic variables of disease.

Unfavorable prognosis in older population may be explained by several reasons, such as diminished immune response with increased age, changes in host immune biology, decreased ability to repair DNA in sun-damaged melanocytes [12]. Older people don't pay such attention to the pathological changes arising on their skin and they seek medical care in more advanced stage of disease [2,7,12]. Furthermore, worlwide educational and preventive programs for melanoma have generally targeted younger age groups [1,2]. The elderly have often (due to comorbidity) limited choice of the best therapeutic modality performation [2,12].

Cutaneous malignant melanoma has a clinical pecularity, which has not yet been completely elucidated and probably suggest different age-specific tumor biology. While increasing age is associated with worse prognosis, it is accompanied by significant decrease in the incidence of sentinel lymph node (SLN) metastasis. This inverse relationship (higher mortality rate and lower incidence of SLN metastasis in older people vs lower mortality rate and higher incidence of SLN metastasis in younger people) has been confirmed by many [1,2,5,19] but not all authors [9]. In the most recent robust study Balch et al [1,9] demonstrated, that the highest incidence of SLN metastasis (25.8%) was in melanoma patients younger than 20 years and the lowest (15.5%) among patients ≥ 80 years of age in spite of the fact, older persons had tumor features associated with more adverse histomorphology. While 5-year mortality was only 10% in individuals under 20 years of age, it reached 20% for those 20–40 years of age, 38% for those over 70 years of age and 45% for those age 80 years and older. These data confirm a phenotypic diversity of primary cutaneous melanomas, that should be taken into account in clinical practice. In addition, biological basis of this interesting phenomenon may be promising field for further research. It is quite possible, that skin melanomas in younger and older people have distinct genetic and molecular profile, different preferential routes of metastasis, as well as different host response to metastatisizing melanoma cells [19]. Indeed, relatively recently published study [20] has really demonstrated distinct expression of several genes (regulating for example cycle-cell mechanisms, inflammation, epithelial-mesenchymal transition) between the youngest and oldest patients with skin melanoma. Futhermore, there exist three main patterns of metastatic melanoma progression, which differ between men and women [14], a fact that may also be regarded age-related, as women are more commonly affected at a younger and men in older age.

As mentioned above, different types of primary melanoma with distinct prognosis are distributed unequally across age groups. A wide morphological diversity of malignant melanomas (and melanocytic lesions as general) is particularly observed among children and adolescents, in whom disease exhibited more favourable clinical outcome. One explanation may be, that very young people have more commonly diagnosed atypical spitzoid melanocytic tumors and melanocytic neoplasms of unknown malignant potential, both are known to have a better prognosis in comparision to "usual" cutaneous melanomas in spite of the fact, they are accompanied by regional lymph

node metastasis more frequently [21,22]. Therefore, some authors [19] discuss about a possible inclusion of the patient´s age into the melanoma staging, as is already applied for example in follicular and papillary carcinoma of thyroid gland [13]. It is quite likely that cutaneous melanomas arising in the youngest and the oldest population have distinct etiopathogenesis and biological behaviour in comparision to "middle" age and hence, their clinical management and treatment should be performed differently.

CONCLUSION

We found apparent age-related differences in the incidence and clinicopathological characteristics of malignant melanoma of the skin. Since unfavourable prognostic variables generally predominated in the oldest group, the elderly comprise an important high-risk group among melanoma patients. We are of the opinion, further research is needed to clarify, to what extent are these age-related disparities associated with distinct etiopathogenetic mechanisms and primary tumor biology and how to translate the survival advantage of younger individuals into a survival benefit for all patients with cutaneous melanoma.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Original Article

Anti-thyroglobulin Antibody and Vitiligo: A Controlled Study

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ABSTRACT

Introduction: Vitiligo is an acquired skin disorder characterized by depigmented maculae resulting from a reduction of the number and function of melanocytes. The etiopathogenesis of the disease is still unclear, but there is evidence that autoimmunity and endocrine disfunction may be involved. **Objective:** The aim of this study was to evaluate serum levels of anti-thyroglobulin antibody (anti-Tg) in vitiligo patients and control subjects, and also to assess the difference between the localized and generalized forms of the disease. **Methods:** In this prospective study we investigated serum level of anti-Tg in 33 patients with vitiligo and 33 healthy controls. We also examined a possible association between serum levels of anti-Tg and disease severity. **Results:** Comparison of median values of anti-Tg has showed that serum concentrations of anti-Tg are significantly higher ($p<0.05$) in serum samples of vitiligo patients in relation to control group. Statistically significant difference was also found in values of anti-Tg between patients with generalized and patients with localized vitiligo ($p<0.05$). **Conclusion:** This study shows a significant association between vitiligo and thyroid autoimmunity, and that tests to detect anti-Tg are relevant in patients with vitiligo.

Key words: Vitiligo; thyroid autoimmunity; anti-thyroglobulin antibody

INTRODUCTION

Vitiligo is a chronic skin disorder characterized by progressive loss of functional melanocytes, which results in depigmentated macules in skin, hair and mucous membrane. It affects approximately 1% of the general population, with the disease beginning before the age of 20 in 50% of cases [1]. The disease is classified according to its extent and distribution, and can be subdivided into generalised or localised. In both types, the melanocytes are destroyed, resulting in loss of pigment from circumscribed areas of the skin. Although several theories have been proposed to explain the loss of melanocytes in vitiligo, the etiopathogenesis of the disease is still unclear. The clinical association with autoimmune disorders and organ specific antibodies indirectly support the idea of an autoimmune pathogenesis of the disease. In addition, many studies have indicated a role for both cellular and humoral immunity in the pathogenesis of vitiligo [2,3]. At the site of depigmentation, T cell infiltrates are invariably seen in patients with active vitiligo, along with a high frequency of cytotoxic T lymphocytes specific for melanocytic antigens, suggesting a direct melanocyte specific T cell attack [4]. Furthermore, many patients with vitiligo have serum auto antibodies directed against melanocytes. How antibodies to pigment cells arise, in vitiligo patients, has not yet been elucidated. They might result from a genetic predisposition to immune dysregulation at T or B cell levels. Involvement of the immune system in the pathogenesis is evidenced by the effectiveness of immunomodulatory agents, such as, corticosteroids and calcineurin inhibitors [5].

In 1956, anti-thyroglobulin antibody (anti-Tg) was first demonstrated as an auto antibody in the serum of patients with Hashimoto's thyroiditis [6], and this finding first established the concept of organ-specific autoimmune disease. It has been known for some time

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that anti-Tg shows direct cytotoxic and cell destruction activity and maintain the thyroid autoimmune process over time, promoting the presentation of anti-Tg to T-cells by B-cells with antigen-presenting function [7]. Anti-Tg also promotes the proliferation of CD4-positive B- and T-lymphocytes in response to thyroglobulin [8]. These effects seem to be directly correlated with autoantibody concentration, and open up a new scenario regarding the role of B-cells with antigen-presenting function, in autoimmune thyroid disease, and new therapeutic possibilities for autoimmune diseases.

In the past, several authors described an association of vitiligo with autoimmune disorders and the presence of different tissue auto antibodies. A review of the literature showed large differences in the results. Therefore, the aim of our study was to evaluate serum levels of anti-Tg in patients with vitiligo and healthy subjects, and also to assess a possible association between anti-Tg and clinical type of the disease.

METHODS

The study is a clinical cross-sectional study carried out among patients with vitiligo in the Department of dermatology at the Sarajevo University Clinical Center. The study included 33 patients with vitiligo, 20 female and 13 male, median age 34.67 (±14.74) years. Of them, there were 14 (42.4%) patients with generalized vitiligo (GV) and 19 (57.6%) patients with localized form of disease (LV). A detailed history and examination were undertaken in all study subjects, including patients' age, age at onset, duration of disease, and the severity of disease. The diagnosis of vitiligo was made on clinical grounds. Skin biopsy was performed in selected cases. Patients with depigmenting disorders other than vitiligo were excluded. The control group consisted of 33 volunteers, 19 female and 14 male, median age 40.33 (±14.78) years. Blood samples were taken and a physical examination was performed. All subjects gave their informed consent in accordance with the requirements of the institutional Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki.

Serum levels of anti-Tg (threshold value: 115 IU/ml) were measured by use of electrochemiluminiscence immunoassay (ECLIA) accorsing to standard protocols (COBAS, Roche Diagnostics GmbH, Germany).

Statistics

Analysis was carried out by calculating 95% confidence interval (95%CI) for median values of anti-Tg (IU/ml). The distribution of laboratory values anti-Tg were compared between groups using Mann-Whitney test. Values with $P<0.05$ were accepted as statistically significant. We used the point biserial correlation coefficient (r_{pb}) for analysis of the relationship between dichotomous variable (vitiligo and control) and continuous variable (anti-Tg). Statistical significance was set at $P<0.05$.

Statistical analyses were performed using MedCalc for Windows, version 11.4.1.0 (MedCalc Software, Mariakerke, Belgium).

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the study.

All subjects gave their informed consent and ethical clearance was obtained from local ethical committee.

RESULTS

We performed a cross-sectional study in 33 consecutive patients with vitiligo and 33 sex- matched controls. The mean age of onset (SD) was 37.74 (12.45) years. The duration of vitiligo ranged from 1 to 252 months, the mean duration (SD) was 55.85 (66.24). Fourteen (42.4%) patients had generalized, and nineteen (57.6%) patients had localized vitiligo. The most commonly involved site was the face in 15 (45.5%), followed by upper limbs in 10 (30.3%) and lower limbs in 8 (24.2%) patients.

In patients with vitiligo anti-Tg antibody titers were ranging from 10.5 to 1021 IU/mL, with the highest values observed in the GV patients. In control group anti-Tg antibody titers were ranging from 5.1 to 129 IU/mL.

Mann-Whitney test found statistically significant difference in anti-Tg (IU/ml) between Vitiligo group (VG) (Md=31.000, n=33, 95%CI=15.441-92.382) and Control group (CG) (Md=16.300, n=33, 95%CI=12.941-35.263), z=2.334, P=0.0196 (Table 1, Fig. 1).

Table 1: Serum levels of anti-Tg in patients and controls

	Vitiligo group (n=33)		Control group (n=33)		Z statistic	P for Mann-Whitney test
	Median	95% CI	Median	95% CI		
anti-Tg (IU/ml)	31.000	15.441-92.382	16.300	12.941-35.263	2.334	0.0196

Table 2: Results of laboratory analysis and differences between groups with generalized and localized vitiligo

	Generalized vitiligo group (n=14)		Localized vitiligo group (n=19)		Z statistic	P for Mann-Whitney test
	Median	95% CI	Median	95% CI		
anti-Tg (IU/ml)	198.050	51.549-787.699	15.500	12.978-39.918	3.023	0.0025

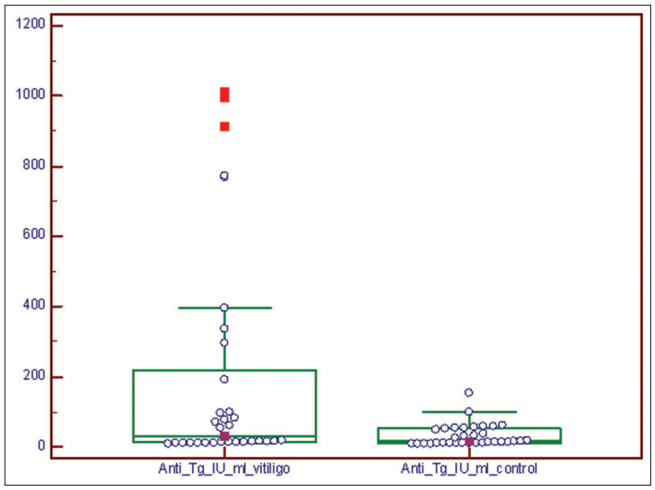

Figure 1: Serum levels of anti- Tg (IU/ml).

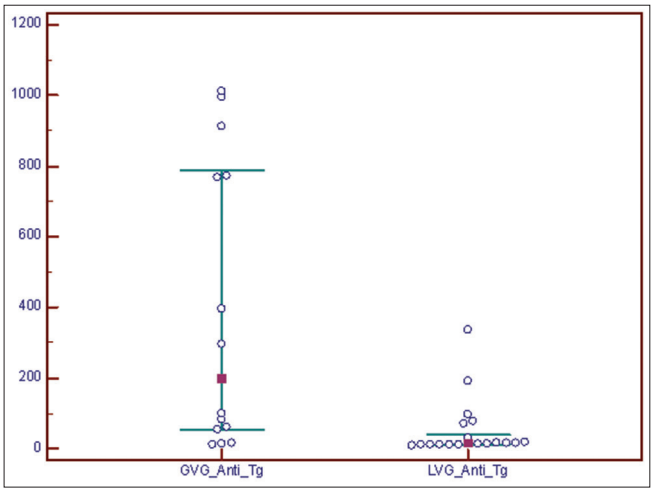

Figure 2: Differences of values anti-Tg between groups with generalized and localized vitiligo.

Test point biserial coefficient of correlation showed that more values of anti-Tg correlated moderately r_{pb}=0.290 (P=0.018) with vitiligo.

Mann-Whitney test found statistically significant difference in anti-Tg (IU/ml) between Generalized vitiligo group (GVG) (Md=198.050, n=14, 95%CI=51.549-787.699) and Localized vitiligo group (LVG) (Md=15.500, n=19, 95%CI=12.978-39.918), z=3.023, P=0.0025 (Table 2, Fig. 2).

DISCUSSION

Known for thousands of years because of its visually evident phenotype, vitiligo is the most common pigmentary disorder [9]. Despite its long history, our knowledge is actually limited. Several hypothesis have been proposed to explain the pathogenesis of vitiligo and indeed it is likely that more than one mechanism is responsible for the clinical manifestations of the disease [10]. Autoimmunity is one hypothesis forwarded to explain vitiligo aetiology.

Vitiligo has been reported in association with numerous autoimmune disorders and the presence of different tissue antibodies. One of the main associations is the one marked with thyroid abnormalities. Both clinical and subclinical thyroid diseases have been mentioned to be more common in patients with vitiligo, as compared with healthy subjects. It was already in 1941, when Robert suggested that vitiligo might be connected with an increased activity of the thyroid gland [11]. He noted a distinct rise of the basal metabolism in 10 out of 20 vitiligo patients tested. Several authors reported a significantly increased prevalence of autoimmune thyroid disease in vitiligo patients, while the rate of positivity of thyroid auto antibodies varied from 2.2% [12] to 82% [13]. In addition, there is also a study reporting a significantly increased prevalence of vitiligo in patients with autoimmune thyroid disease compared to patients with non autoimmune thyroid disease [14,15]. The risk for patients with vitiligo to develop thyroid diseases is almost twice as high, when compared to patients without vitiligo, and the risk of elevated thyroid antibodies with vitiligo is more than five-fold higher in comparison with patients without vitiligo [16]. It is possible that the occurrence of these diseases in the same patient is the result of

the basic autoimmune disturbance involving the melanocytes, and the thyroid glands in a patient who is genetically predisposed to these disease. Both diseases shows alteration of T-cell population and this can be explained with common genetic background of their autoimmunity. Spritz demonstrated inherited susceptibility to generalized vitiligo involves a number of specific genes, many of which are shared with other autoimmune diseases that are epidemiologically associated with vitiligo, including autoimmune thyroid diseases [17,18].

In accordance to previous studies, we also demonstrated that anti-thyroglobulin antibody was significantly increased in vitiligo patients in comparison to healthy subjects. The patients with generalized vitiligo have higher occurrences of both thyroid disease and thyroid antibodies, compared with localized vitiligo. This is in accordance with the assumption that the susceptibility for autoimmune disease concerns generalized vitiligo more than localized vitiligo [19]. In our study, statistically significant difference was also found in values of anti-Tg between patients with generalized and patients with localized vitiligo.

The nature of the relationship between vitiligo and thyroid autoimmunity is presently unknown. Possible explanations for the relationship of these autoimmune diseases include: (1) immunomodulatory effects of antithyroid antibodies, (2) molecular mimicry between thyroid and disease-specific epitopes, and (3) genetic linc between thyroid autoimmunity and the susceptibility to autoimmune disease [20]. It is a multidisciplinary problem requiring cooperation of specialist in different fields of medicine. Both dermatologist and endocrinologists have to inquire their patients about the family history of autoimmune diseases and to look for associated autoimmune disorders.

CONCLUSION

Vitiligo often precedes thyroid dysfunction by many years. Therefore, the presence of elevated thyroid antibodies may serve as useful clinical tool in euthyroid subjects with vitiligo to identify patients at risk for thyroid disease. The increased frequency of autoimmune diseases, in patients with vitiligo, suggests that all these conditions share a common etiologic factor.

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Our Dermatology Online

Original Article

Efficacy of excimer light therapy for treatment of localized, progressive vitiligo

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ABSTRACT

Introduction: Vitiligo is an acquired, circumscribed, depigmented macules due to loss of functional melanocytes. Excimer light cause immunosuppression as well as stimulation of follicular melanocytes. **Materials and methods:** After taking consent, the dose of the therapy was arbitrarily started at 100 mj/cm^2, given twice a week, with incremental dose of 100 j/cm^2 every sitting. If erythema (or blister, if any) persists for more than 2 days, the dose was skipped until erythema (or blister) subsided. Then, the previous safe dose was continued. A total of 16 sittings was given. Photographs were taken pretreatment, after 2 months and after 4 months and were assessed by two independent doctors who were not involved in the study. **Results:** Among 25 patients, 16 patients (64%) achieved good results and 3 patients (12%) achieved excellent result. **Conclusion:** Excimer light therapy is a good option for treatment of localized vitiligo. However, those lesions on the lips and acral areas responded very poorly.

Key words: Vitiligo; Excimer light therapy; Keratinocytes; Melanocytes

INTRODUCTION

Vitiligo is an acquired, circumscribed, depigmented macules due to loss of functional melanocytes [1]. It has a great psychosocial impact on the patients. The exact etiopathogenesis is unclear. It seems to be multifactorial, i.e., genetic, endogenous and exogenous factors [1-3]. There are two types of vitiligo, viz. Absolute which has no DOPA – positive melanocytes and Relative type which has decreased DOPA-positive melanocytes. Keratinocyte-derived cytokines like decreased stem cell factor (SCF), TNF-alpha and IL-1 may play role in the pathogenesis [3-10]. There are few hypothesis regarding pathogenesis. Autoimmune hypothesis in which complement fixing antibodies against melanocytes are pathogensic. Neurogenic hypothesis states that a compounds released from the peripheral nerve ending have toxic effects on melanogenesis. The Self-destructive theory suggests that melanocytes are destroyed themselves due to defect in natural defence mechanism that removes toxic materials. Vitiligo may be localised, which may be focal or unilateral/segmental: Generalized, like vitiligo vulgaris, acrofacial vitiligo or mixed or Univarsalis where complete/almost complete depigmentation. Excimer light emits UV light of 308 nm wavelength, causing immunosuppression by T cell apoptosis. The apoptosis mechanism may be caused by the damage of the epidermal and dermal cells which are susceptible to UV light exposure. It causes DNA damage and formation of pyrimidine dimer. In addition to T cell apoptosis, it also triggers changes in cytokine production, local immunosuppression, stimulation of melanocyte-stimulating hormone (MSH), increases migration, proliferation of melanocytes and melanogenesis. The current therapies include Corticosteroids, Calcineurin inhibitors, UV Therapies and surgical procedures like mm grafting. UV Light stimulates activation and migration of melanocytes which are lying dormant in the hair follicles [1-14].

MATERIALS AND METHODS

The aim of the study is to know the efficacy of excimer light therapy foot treatment of vitiligo. The study was done at RNT Medical College, Udaipur, Rajasthan. Ethical clearance and informed consent were taken prior

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to the study. Patients having localized patches, who had not taken any treatment within 8 weeks, were included in the study. Widespread lesions, patients taking any treatment within 8 weeks, pregnant and lactating and patients having history of photosensitivity were excluded from the study. Only emollient was allowed to apply in the treated areas during the study. The dose of the therapy was arbitrarily started at 100 mj/cm^2, given twice a week, with incremental dose of 100 j/cm^2 every sitting. If erythema (or blister, if any) persists for more than 2 days, the dose was skipped until erythema (or blister) subsided. Then, the previous safe dose was continued. A total of 16 sittings was given. Photographs were taken pretreatment, after 2months and after 4 months, and were assessed by two independent doctors who were not involved in the study. Less than 50% improvement after treatment was considered as failure to treatment, 50-75% as good response, and >75% as excellent response.

RESULTS

A total of 25 cases enrolled in the study, aged between 12 – 40 years. 15 patients were female and 10 patients were male (Table 1). The photos showing the progress of treatment were made for each patient (Figs 1 – 3); a control site showing on the Figures 4 and 5.

Table 1: A total data of all patients

Sl.no	Age	Sex	Duration of the disease	Site/ sites	Improvement after treatment
1	18	F	1 year	Feet	60%
2	21	F	6 months	Hands	40%
3	23	F	8 months	Arms	80%
4	21	F	2 years	Forearms	70%
5	34	F	10 months	Cheeks	60%
6	30	F	3 years	Back	80%
7	40	F	4 years	Back	60%
8	25	F	2 years	Feet	80%
9	34	F	2 years	Arms	60%
10	32	F	4 years	Neck	60%
11	20	F	6 months	Back	60%
12	19	M	4 months	Neck	70%
13	12	M	3 months	Feet	60%
14	15	M	11 months	Forearms	70%
15	24	M	12 months	Arms	60%
16	27	M	2 years	Face	60%
17	31	M	2 years	Lips	<10%
18	33	M	5 years	Fingers	<20%
19	23	M	3 years	Lips	<10%
20	21	M	2 months	Fingers	<20%
21	26	F	1 year	Forearms	30%
22	25	F	4 months	Arms	55%
23	29	F	2 months	Leg	60%
24	22	F	6 months	Leg	60%
25	23	M	8 months	Leg	55%
<50% improvement					6
50-75% improvement					16
>75% improvement					3

Figure 1: Before treatment

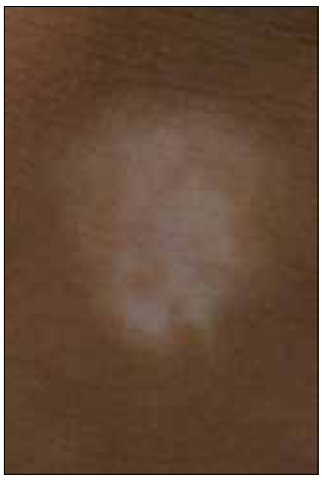

Figure 2: After 1 months of starting therapy

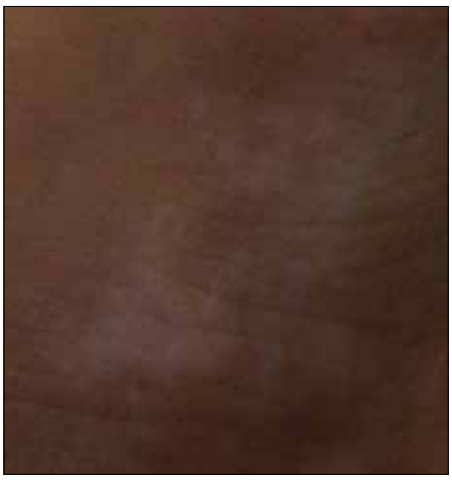

Figure 3: After 2 months of treatment

Figure 4: Control site (before treatment)

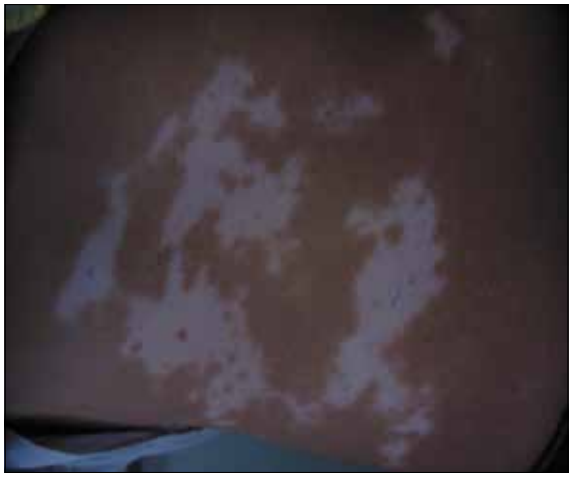

Figure 5: Control site after 2 months

DISCUSSION

An excimer laser (sometimes more correctly called an exciplex laser) is a form of ultraviolet laser. The wavelength of an excimer laser depends on the molecules used and is usually in the ultraviolet spectrum at wavelengths [3-9]. The depth of penetration depends upon wavelength of laser and tissue type. It does not cause thermal destruction on interaction with human tissue, a photochemical mechanism is responsible for decomposition and for explosion of the organic material, termed ablative photodecomposition. Excimer lasers and light are pulsed wave lasers, they deliver a high energy in a short time, thus rapidly breaking chemical bonds. The pulse width of these lasers is so short that the temperature of surrounding material does not change but remains intact [6-13]. It can be delivered through a fiber optic cable which makes it possible to selectively target different lesions on the body surface. The use of a monochromatic wavelength of 308 nm gives photobiological effects superior to those provided by NB-UVB. The main targets for UV-B is DNA contained in epidermal cells (keratinocytes, melanocytes) and to a lesser extent, in dermal cells (fibroblasts). Inflammatory reactions could also be involved [3-15].

According to Al-Otaibi SR, et al (2009), Thirty-four patients (14 males and 20 females) with localized treated using a 308-nm excimer laser twice weekly for 13 weeks with a dose started with 50 to 100 mJ/cm2 (according to site) and increased by 50 mJ/cm2 in every session until erythema appeared for 25 sessions, or until 100% repigmentation, whichever was achieved first showed. Lesions on the face responded better than elsewhere on the body. The least responsive areas were the hands and feet. The average number of treatment sessions prior to repigmentation was 11. Untreated control patches remained unchanged. In higher skin phototypes the response was more favorable. There was no significant correlation between the age of the patients and their response to treatment [16].

Study conducted by Wang HW, et al (2009) on 170 patients with stable vitiligo by using the 308 nm excimer laser showed that rates of "remarkably improved" and "cured" were 67.97% and 32.03% in faces, 54.55% and 27.27% in necks, 63.26% and 26.53% in trunks, 38.84% and 15.70% in limbs, and 0 and 0 in hands and feet. The areas of faces had a better response than those of necks, trunks, or limbs ($P < 0.01$) and the areas of trunks or limbs had better response than that of hands and feet ($P < 0.01$) [17].

Another study by Xiu-Ying Zhang, et al (2010) [18] on thirty-six patients with 44 vitiligo patches were treated using a 308 nm excimer laser, which was performed twice a week, for a total of 30 treatments showed after 30 treatments, 27/44 patches (61.4%) achieved more than 75% repigmentation, 4/44 lesions (9.1%) showed 51–75% repigmentation, 10/44 (22.7%) showed 26–50% repigmentation and 3/44 (6.8%) showed 1–25% repigmentation [18].

In our study, almost all patients developed repigmentation, but only 16 patients (64%) achieved good results and only 3 patients (12%) achieved excellent result. Those lesions on the lips and acral areas responded very poorly as expected from most of the literature. Repigmentation was started in the 2nd month in most of the patients. The difference in response in the different groups like age, sex and durations were not statistically significant as the p value was >0.005 for

both parameters. It was usually given for stable, localized vitiligo. But in our study, it was given for localized, progressive vitiliginous patches too where it not only stopped the progression of the lesion, it also helped in repigmentation. Regarding the safety, except transient erythema which was lasted for 3-4 days, no other serious side effect was encountered during the study period. There was no single patient who developed recurrence during the 6 months follow up period.

CONCLUSION

Excimer light therapy is an efficacious and safe option for treating localized vitiligo. It not only helped in repigmentation, it also stopped progression of the localized disease.

CONSENT

Ethical Requirements for Studies Involving live human subjects or animal: accepted by author. The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Brief Report

Cutaneous tuberculosis in Niger: a 9-year retrospective study

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ABSTRACT

Introduction: Cutaneous tuberculosis is a skin infection due to the *Mycobacterium tuberculosis* and rarely due to *Mycobacterium bovis or Mycobacterium africanum*. The disease is difficult to diagnose, given the fact that the skin is seldom a location for tuberculosis. The aim of this study is to determine the epidemiological, clinical and therapeutic profile of the disease in Niger. **Materials and Methods**: This is a retrospective study over a period of 9 years in the Department of Dermatology and Venereology at the National Hospital of Niamey. The study included all cases of cutaneous tuberculosis that were clinically diagnosed and confirmed or not by some conventional complementary examinations. **Results:** Over a period of nine years, 49 cases of cutaneous tuberculosis were diagnosed, which represents 0.34% of the total 14376 dermatological consultations in the dermatological unit. Patients of both sexes were affected, but the majority were male with 69% or a sex ratio M/F of 2.26. The patients ranged in age from 6 to over 60 years. The mean age was 34.67 years. Patients between 31 and 40 years were the most affected at 34.69%. A personal or family history of tuberculosis was noted in 8.16% of the cases. Scrofuloderma is the most frequent form of the disease (93.87% of the cases). The average course of the disease before consultation was 30.28 months. The tuberculin skin test was positive in 83.67% of the cases. The TB smear test was positive in only 6% of the cases. The hyperleukocytosis, which was mostly lymphocytic, was noted in 21.62% of the cases. Radiological evaluation was normal in 91.83% of the cases. All patients responded well in 100% of the cases with a treatment period ranging from 6 to 9 months. No clinical and/or biological treatment-related side effects were observed. **Conclusion:** Cutaneous tuberculosis is still a common infection in third world countries where it affects both sexes. The scrofuloderma is the most observed form in our study. A TB test-based treatment is often a good solution in the face of an array of clinical and epidemiological evidence. Systematic vaccination after birth would drastically reduce all forms of tuberculosis.

Key words: Cutaneous tuberculosis; therapeutic response; Niger

INTRODUCTION

Cutaneous tuberculosis, like any non-pulmonary form of the disease, is most often due to the *Mycobacterium tuberculosis* and rarely due to *Mycobacterium bovis or Mycobacterium africanum* [1]. The disease is difficult to diagnose because of its rarity and clinical polymorphism. The diagnosis relies on a body of epidemiological, clinical, para-clinical evidence or just on test evaluation. Its treatment is based on TB antibiotics, which in most cases gives excellent results [2-6]. The aim of this study is to determine the epidemiological, clinical and therapeutic profile of the disease in Niger.

MATERIALS AND METHODS

This is a retrospective study carried over a period of 9 years in the Dermatology and Venereology Unit at the National Hospital of Niamey. The study included

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cases of cutaneous tuberculosis and their handling for the period between January 2004 and December 2012. Data collection was carried out using a survey form that specified epidemiological, clinical, para-clinical and therapeutic information.

Consultation records at Dermatology and Venereology Unit from 2004 to 2012 were used as source of information. For this study, we considered all cases of cutaneous tuberculosis that were treated with standard therapy regimes involving 2 months of quadruple therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol) following by futher 4 months of izoniazid associated to rifampicin. All data were entered in and processed with EXCEL 2007.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

RESULTS

Cutaneous tuberculosis occurred in 49 cases, out of a total of 14376 dermatological consultations over 9 years (or 0.34% of the cases). The average annual cases was 5.44. The patients were 34 men (69%) and 15 women (31%) or a sex ratio M/F of 2.26. The subjects ranged in age from 6 to over 60 years. The mean age was 34.67 years. The age group between 31 and 40 years was most represented (34.69% of the cases). Four patients (8.16% of the cases) showed a personal or family history of tuberculosis. Weight loss was the most frequent clinical sign (32.65% of the cases), followed by fever (26.53%) and anorexia (22.44%). Scrofuloderma (Fig. 1) was the most common manifestation of the disease (93.87% of the cases), followed by tuberculosis verrucosa cutis (4.08%) and tuberculous gumma (2.04%).

The average course of the disease before consultation was 30.28 months and ranged from 2 to 156 months. The major folds (inguinal and axillary) were the most common sites (30.61% of the cases). There were other important affected areas such as the neck, the trunk and the pelvic limbs (Figs 2A and 2B) (each at 12.24% of the cases). In 55.10% of the cases, the disease was restricted to one area only, and to two areas in 24.48% of the cases. Attacks in more than three area represented 20.42% of the cases. The tuberculin skin test was performed on all patients and was positive in 83.67% of the cases. A diameter of induration measuring 16 to 24 mm was observed in 41.46% of the cases, with a mean value of 15.41 mm. The smear test was positive in 6% of the cases. Lymphocytic hyperleukocytosis was noted in only 21.62% of the cases followed untyped anemia in 13.51% of the cases. The accelerated rate of sedimentation was significant only in 10.81% of the cases. Chest radiographs were performed on 37 patients and were normal in 33 of the them (91.83%). However, 4 patients (8.16%) showed pathological radiographs (such as geodes, osteoporosis and shrinking of the space between vertebral bones). Most of histopathology results showed granulomatous dermatitis. So, the diagnosis of CTB was based on classic combination of clinical, epidemiologic laboratory features and responses to anti-tuberculosis therapy.

Among the 39 patients, 37 underwent a regular TB treatment, first during 2 months in a daily quadruple therapy (isoniazid 3 to 5 mg/Kg/day, rifampicin 10 mg/Kg/day, pyrazinamid 20 to 30 mg/Kg/day; and ethambutol 15 to 20 mg/Kg/day) and then during 4 months in a daily bitherapy (isoniazid 3 to 5mg/Kg/day, rifampicin 10 mg/Kg/day). For the whole

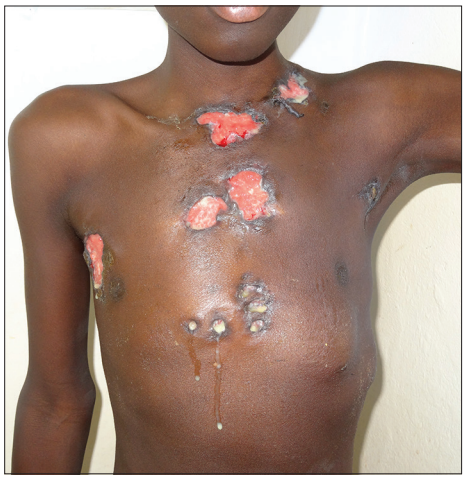

Figure 1: Scrofuloderma before treatment.

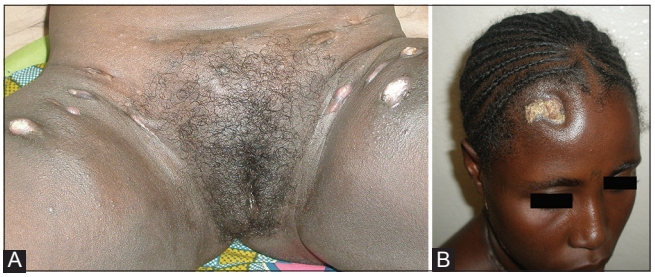

Figure 2: Multiple localization. A: inguinal, B: cephalic (before treatment).

patients, we adjusted the doses. All 37 patients were cured at the end of the treatment like in those images (Figs 3, 4A, 4B and 5).

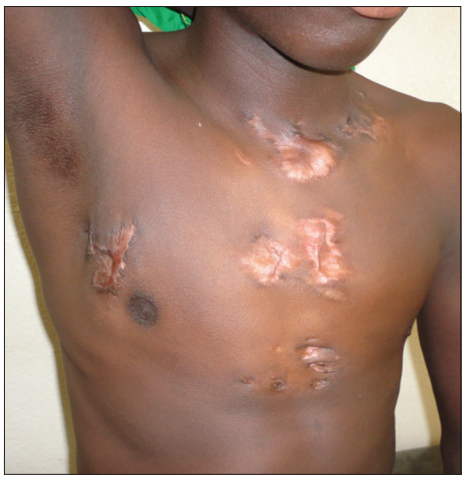

Figure 3: Scrofuloderma, after treatment.

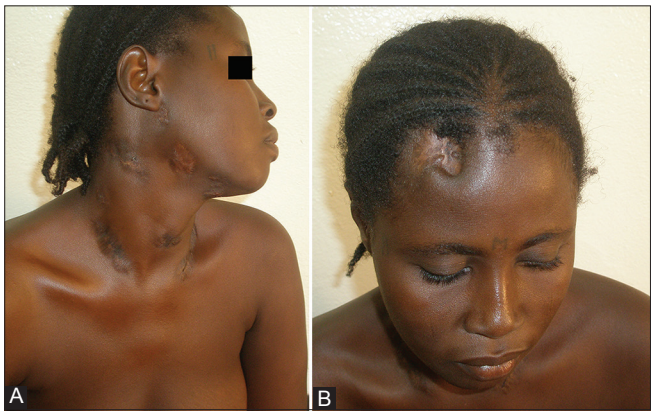

Figure 4: A Multiple localization, neck after treatment; B Multiple localization, head after treatment

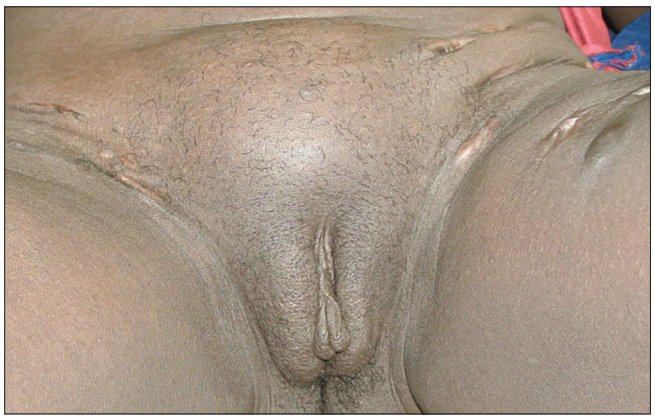

Figure 5: Lesions in inguinal after treatment.

DISCUSSION

In our study, cutaneous tuberculosis accounted for 0.34% of all consultations in dermatology with an annual incidence of 5.44 cases. The annual number of cases reported in other studies varies from less than 1 to 8.6 cases [4,6]. Our study showed that the disease affected young subjects with a male predominance, as is noticed in other studies [7-10]; although other studies found a feminine predominance [5,6,11].

In our study, the scrofuloderma was the most common cutaneous form accounting for 93.87% of the cases. Some publications have also reported the prevalence of this form [6,8,10]. In our study, tuberculosis verrucosa cutis and the tuberculosis of the gum were less important, at 4.08% and 2.04% of the cases, respectively. This is not congruent with other studies, where tuberculosis verrucosa has a frequency of 19.59% [12] and the tuberculous gumma frequency of 46.6% [13]. The average course of the disease before the consultation was 30.28 months in our study. In some studies [10,11], this period ranged from 16 to 38.4 months, confirming the chronic aspect of the disease. Location in the large folds (30.61% of the cases) was predominant in our study; while in other studies the most frequent the cervical area and the lower limbs [5,11] were most affected. Overall, we founded that the disease affects many more skin areas than what is usually reported in other studies [6,11]. In our study the tuberculin skin test was positive in 83.67% of the cases, the smear test was positive in 6% of the cases. The chest radiograph was normal in 91.83% of the cases and most of histopathology results showed granulomatous dermatitis. This points to the heterogeneous nature of the para-clinical aspects. The same heterogeneity is reported in other studies [13,14]. All of the 37 patients in our study were totally cured. This result is also reported in other studies [5,9,11,15]. This confirms the effectiveness of conventional TB therapy protocols. We noted no clinical or laboratory side effects related to the TB treatment.

CONCLUSION

Cutaneous tuberculosis, although relatively rare, is still a concern in third world countries. Scrofuloderma and other cutaneous forms can be handled with a standard TB therapy. While a test-based TB treatment is often a good solution in the face of an array of clinical and epidemiological evidence, systematic vaccination at birth is the best way to combat all forms of tuberculosis.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

Written informed consent was obtained from the patient for publication of this article and any accompanying images.

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Our Dermatology Online

Brief Report

Cutaneous manifestations in patients attending the hematology clinic at King Fahd Hospital of the University during a 13 week-period

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ABSTRACT

Background: Cutaneous disorders are common in patients with hematological diseases especially anemia. Dermatologists usually contribute to the management of these patients in parallel with other medical specialties. **Aim:** To report common dermatological problems in patients attending the hematology clinic at a secondary care hospital. **Materials and methods:** The study was conducted at the hematology clinic of King Fahd Hospital of the University during a thirteen week period starting 17th of November, 2013 till 31st of January, 2014. All patients were fully examined and a consultative opinion was given to the attending hematologist. Data sheet was filled and analyzed by SPSS (Statistical Package for the Social Sciences) software version 17.0. **Results:** 138 patients were seen during the period of 13 weeks. There were 27 males and 111 females. Hemoglobin level was less than 10 gm/dl in 40.6% of patients. The most common reported cutaneous features were diffuse alopecia, hair thinning, pallor, pruritus, fragile skin, easy brusability, dry mouth and gum bleeding in descending frequency. **Conclusion:** Hematology patients suffered from variable dermatological disorders which suggest the importance of the initial dermatology consultation for those patients as part of their management plan.

Key words: Anemia; Alopecia; Dermatitis; Pallor; Pruritus

INTRODUCTION

Dermatologists play an important role in providing consultative service to other medical specialties. Previous studies have shown that the discipline of Medicine make the most requests for inpatient dermatologic services [1-4]. While most requests for dermatologic consultations are for common skin conditions, challenging scenarios and diagnostic dilemmas are frequently encountered. Skin problems are common in patients with hematological disorders and dermatologist usually add to the management plan of those patients.

OBJECTIVE

To characterize the profile of dermatological issues frequently encountered in patients attending the hematology outpatient clinic at King Fahd Hospital of the University during three months period.

MATERIALS AND METHODS

This prospective cross sectional study was conducted at the hematology outpatient clinic of King Fahd of the University Hospital in Alkhobar, Saudi Arabia during a 13-week period starting 17th of November, 2013 till

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31st of January, 2014. The Hematology Department in this hospital accepts referrals from other departments and outside hospitals in the Eastern Province also. All patients were fully examined by a consultant dermatologist with assisting interns trained by the dermatologist. Data sheet was filled for each patient with documentation of age, gender, associated conditions and all observed cutaneous lesions. Data was entered in the computer and analyzed by SPSS (Statistical Package for the Social Sciences) software Version 17.0.

RESULTS

A total of 138 patients were examined during the study period. There were more females (n = 111; 80.4%) than males (n = 27; 19.6%) and the mean age was 45 years (range: 13-66 years). Hemoglobin level was less than 10 gm/dl in 40.6% of patients and less than 9 gm/dl in 21.7%. Causes of anemia in a descending frequency included Iron deficiency anemia 73 (53%), sickle cell anemia 37 (26.8%), thalassemia 15 (10.9%) and less than 10 cases with G6PD (Glucose-6-phosphate dehydrogenase), thrombocytopenia, vitamin B12 defeciency and leukemia. A total of 67 dermatologic conditions were diagnosed Table 1. The frequency of these dermatologic conditions in descending pattern included: alopecia 92 (66.7%), pallor 71 (51.4%), thinning of the hair 54 (20.3%), skin dryness 49 (35.5%), pruritis 33 (23.9%), increased skin fragility 28 (20.3%), dry mouth 21 (15.2%), gum bleeding 18 (13%), dermatitis 17 (12.3%), jaundice 17 (12.3%) and fragile ridged nails. Different types of dermatitis were represented, ranging from contact, asteatotic, seborrhoeic and nummular eczema Figure 1.

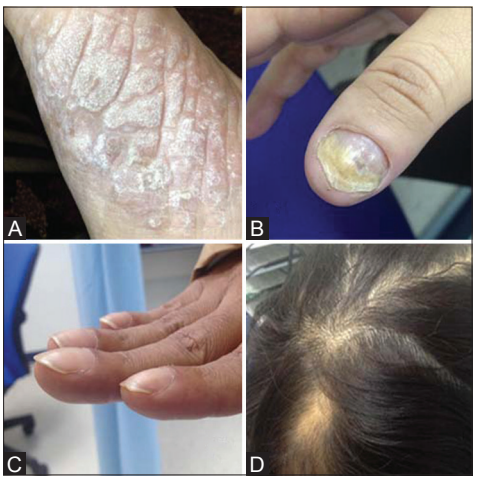

Figure 1: Variable skin, nail and hair changes in our patients. A. Dermatitis and severe dryness. B. Brittle nail with super imposed fungal infection. C. Nail Clubbing. D. Diffuse alopecia

None of the patients had a skin biopsy because a clinical diagnosis was deemed sufficient. There was other associated medical conditions in some patients including hypertension, diabetes mellitus, hepatitis c, liver cirrhosis, gastritis, dyslipidemia, hypothyroidism, congenital adrenal hyperplasia, acne vulgaris, discoid lupus eruthematosus and psoriasis.

DISCUSSION

Cutaneous problems are common in patients with anemia. Unfortunately no similar study was previously conducted in Saudi Arabia to compare it. However, the study reveals the importance of

Table 1: Percentage of some of the reported cutaneous conditions found our patients

Dermatological conditions	Percentage
Dryness	35.5
Pruritis	23.9
Increased skin fragility	20.3
Dry mouth	15.2
Dermatitis	12.3
Gum bleeding	13
Edema	7.4
Psoriasis	4.4
Actinic keratosis	3.7
Gingival hypertrophy	3.7
Angular stomatitis	2.2
Post-transfusion purpura	2.2
Glossitis	1.5
Pitryasis alba	1.5
Varicose vein	1.5
Milia	1.5
Leg ulcer	0.7
Livedo reticularis	0.7
Prurigo nodularis	0.7
Telangiectasia	0.7
Acrocyanosis	0.7
Keratosis pilaris	0.7
Skin discoloration	
Pallor	51.4
Jaundice	12.3
Hyperpigmentation	7.4
Blue sclera	3.7
Hemosiderin deposition	0.7
Hair changes	
Alopecia	66.7
Thin, dry hair	20.3
Dandruff	1.5
Hirsutism	1.5
Nail changes	
Brittle nails	0.7
Leukonychia	3.0
Koilonychia	2.2
Clubbing	1.5
Onycholysis	0.7
Ingrowing nails	0.7
Pitting	0.7

internist, hematologist and dermatologist in the management of patients with anemia. In a random review of patients admitted to a Hematology-Oncology unit, Pearson et al found mucocutaneous disorders in 88% of cases seen. The most common findings in their study were alopecia, mucositis, palm and sole erythema [5]. In another similar study done by Hy Koh in Singapore [6], 692 patients were referred for primary dermatological issues during six months period. This is implies that non-dermatologists face difficulties diagnosing common dermatoses [1,4,7-10]. Besides, a dermatologic consultation resulted in changes in diagnosis and management in 60% to 77% of the cases [1,8,10], which highlights the importance of dermatologic education of the consulting physicians regardless of his specialty [11]. Our findings in this study highlights the importance of the involvement of the dermatologist in the management of hematology patients through initial consultation as part of their general management plan.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Ethical Requirements for Studies Involving live human subjects or animal: accepted by all authors.

Written informed consent was obtained from the patient for publication of this article.

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Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Brief Report

Pyogenic granuloma treated with continuous wave CO2 laser followed by ultrapulsed CO2 laser ablation

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ABSTRACT

Pyogenic granuloma is a benign polypoidal or exophytic vascular lesion. It can occur at any age. The hypothetic etiologies include trauma, viral or hormonal factors. A total of 16 patients were enrolled in the study after taking consent. A total of 4 females and 12 males. All of them had single lesions which tend to bleed especially on touching. All of them were satisfied with the treatment. Regarding the immediate side effect, 6 patients developed transient bleeding, which was stopped after 15 minutes of pressing the bleeding areas. 1 patient reported recurrence after 3 months, which may be due to incomplete removal of the lesion. No other side effect was seen in all the patients. The combined continuous-wave/pulsed CO2 laser is our treatment of choice for pyogenic granuloma as it provides less bleeding than the other modalities.

Keywords: Pyogenic granuloma; continuous-wave; ultrapulsed CO2 laser

INTRODUCTION

Pyogenic granuloma is a benign polypoidal or exophytic vascular lesion. It can occur at any age. In children, there is slight male predominance. In adult, female dominance is due to pregnancy related lesions [1,2]. There is no racial or familial predisposition. The exact etiopathogenesis is not clear. It may be due to NO synthase dependent mechanism which contributes to angiogenesis [2-4]. The hypothetic etiologies include trauma, viral or hormonal factors [1-5]. It usually presents as a solitary, well-circumscribed, dome-shaped, 1-10mm or more, sessile or pedunculated, bright or dull red, smooth nodule with tendency to bleed. Histopathology reveals a lobular pattern separated by fibrous septa. Each lobule consists of capillaries and venules lined by plump endothelial cells, embedded in a gelatinous stroma [3-7]. The overlying epidermis may embrace the lesion. The current treatment includes shave removal, surgical excision, curettage, chemical or electrical cauterization, cryotherapy, CO_2 laser ablation and pulsed dye laser [6-8].

MATERIAL AND METHODS

Patients who were diagnosed to have pyoderma ganrenosum are enrolled in the study (Fig. 1). Informed consent was taken from all the patients. A total of 16 patients were enrolled in the study. Ethical clearance from the college was taken as per norm.

Investigations like haemogram, ESR, Liver function test, renal function test, urine r/m and BT/CT/PTTK were done to exclude comorbidities which can cause complications and for post treatment purpose. Photographs were taken prior to the treatment and just after the treatment. The treatment area was cleaned with soap water, followed by betadine (spirit was not used as it is inflammable). The area was given local anaesthesia 2% (lignocaine 1:20000, ring block) and wait for 5-10 minutes. Then, continuous wave 3 mj/cm^2 was used for ablation of the bulk at the peduncle. When the bulk was reduced, Ultrapulsed 1-3 mj/cm^2 (depends on the lesions) was given to maintain ablation as well as for haemostasis. In case of bleeding (although not common after CO_2 laser, the patients were asked to

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press the bleeding areas for 15 -20 minutes and the bleeding stops. Dressing with Betadine was done everyday and antibiotic cream was applied till healing occurs. Oral antibiotic was also given for 7 days along with nonsteroidal anti inflammatory for few days to suppress trauma induced inflammation. The patients were followed up for 6 months.

RESULTS

A total of 16 patients were enrolled in the study after taking consent. A total of 4 females and 12 males. All of them had single lesions which tend to bleed especially on touching. All of them were satisfied with the treatment (Fig. 2). Regarding the immediate side effect, 6 patients developed transient bleeding, which was stopped after 15 minutes of pressing the bleeding areas. 1 patient reported recurrence after 3 months, which may be due to incomplete removal of the lesion. No other side effect was seen in all the patients.

DISCUSSION

It is a xenon chloride (XeCl) laser that delivers concentrated, but painless, high-dose radiation directly to target lesions without exposing surrounding healthy tissue. It emits a wavelength of 308nm and shares the physical properties of lasers, Monochromatic and coherent beam of light, Selective treatment of the target, The ability to deliver high fluencies are the main principle. The articulated arm also makes it easier to reach areas that are usually difficult to treat, such as folds and mucosa. The use of a monochromatic wavelength of 308 nm gives photobiological effects superior to those provided by NB-UVB. The main targets for UV-B is DNA contained in epidermal cells (keratinocytes, melanocytes) and, to a lesser extent, in dermal cells (fibroblasts). Inflammatory reactions could also be involved. The decrease in T-lymphocyte proliferation caused by inducing cellular apoptosis resulting from DNA lesions is likely to be one of the most important mechanisms of action of UV-B phototherapy. 308 nm is the most efficient wavelength for inducing DNA lesions on lymphocytes. The dose needed to induce apoptosis in 50% of T lymphocytes is 95 mJ/cm2 with the 308-nm excimer laser vs. 320 mJ/cm2 with NB-UVB. Similar levels of depletion of T lymphocytes due to apoptosis after treatment with 308nm monochromatic excimer laser have been reported in psoriasis lesions. The main disadvantages are limited size of spots means that large surfaces (more than 20% of total surface body area) cannot be treated. Purchase and maintenance costs of devices quite expensive. In this study, limited size of spots means that large surfaces (more than 20% of total surface body area) cannot be treated. Purchase and maintenance costs of devices quite expensive.

Study conducted by Lindenmüller IH on CO2 laser-assisted treatment of a giant pyogenic granuloma of the gingiva of a 34-year-old woman in the 39th week of pregnancy presented for surgical treatment with a mass on the lingual mandibular gingival [7]. She had been surgically treated alio loco in the 37th week, but this failed. The patient was reassured and an individual oral hygiene programme was initiated in our department. The tumour was about 20 mm in diameter. A CO_2 laser-assisted surgical excision was performed 4 weeks after delivery. The lesion was analysed histopathologically using a von Willebrand Factor immunoreactivity staining. The highly vascularized tissue with a dense inflammatory infiltrate was in accordance with

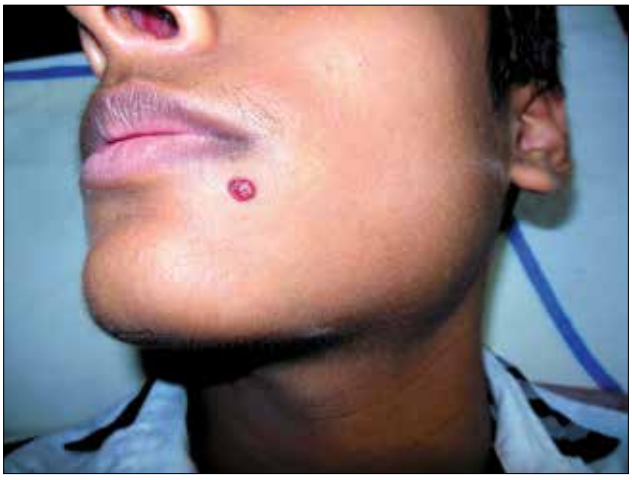

Figure 1: Lesion pre treatment.

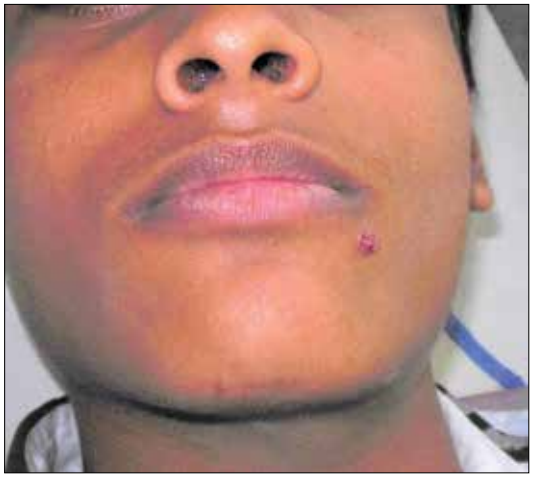

Figure 2: Immediately after ablation.

the diagnosis of a PG. The initial wound healing was uneventful. A 12-month follow-up revealed no recurrence of the mass and healthy periodontal tissues. This report describes an oral complication during pregnancy for which surgical excision of a PG after delivery seemed the best treatment. It is possible that gender-specific periodontal disease risk factors contributed to the development of the lesion. This is another reason why pregnant women should be encouraged to be assessed by oral health professionals before late pregnancy.

Roulin C, et al studied on the combined continuous-wave/pulsed carbon dioxide (CO2) laser comprising 1 treatment session with 6-week and 6-month follow-up examinations and evaluations [8]. The laser was first used in continuous mode (power, 15 W) and then in pulsed mode (pulse length, 0.6-0.9 milliseconds; energy fluence, 500 mJ/pulse). Pyogenic granuloma was removed completely in 1 treatment session in 98 patients without recurrence. In 88 cases there were no visible scars; in 10 cases slight textural changes of the skin were observed. Hypertrophic scars or keloids did not occur. Sixty-three patients were very satisfied with the result of the treatment, 37 were satisfied (ie, 100% patient satisfaction) and none indicated that they were not satisfied. No permanent hypopigmentation, hyperpigmentation, or erythema was observed.

In this study, most of the lesions were removed as described. There is no serious side effects including excessive bleeding or scar formation. Patients were satisfied. Small but cosmetically more acceptable scar than the nodules (pretreated) were observed in 50% of the patients, although the patient did not bother as the larger and more troublesome due to bleeding was removed.

CONCLUSION

The combined continuous-wave/pulsed CO2 laser is our treatment of choice for pyogenic granuloma as it provides less bleeding than the other modalities.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article

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Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Brief Report

Comparative study of efficacy of 30% Salicylic acid peel VsLong-pulsed 1064 nm Nd:YAG laser for treatment of Keratosis Pilaris

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ABSTRACT

Introduction: Keratosis pilaris(KP) is a disorder of keratinization of hair follicles characterized by keratin plugs in the hair follicles with perifollicular erythema.It may be inherited with X-Linked Dominant, or may be sporadic. **Aim of the study:** to compare the efficacy of 30% Salicylic acid and Long pulsed 1064nm Nd:YAG laser for treatment of keratosis pilaris. **Materials and methods:** Out of 20 patients, 10 patients were given 30% Salicylic acid peel (after washing their face) every 15 days for 2 months. Another 15 patients were given the 1064 nm Nd:YAG Long pulse, Spot size:10 mm, Pulse width: 30 ms every 4-6 weeks for 4 sitting. **Results:** Among salicylic acid treated group, only 2 out of 10 showed improvement between 50-75%, and were slightly satisfied; none showed >75% improvement, and 8 out of 10 failed to show >50% improvement and were considered as failure of the therapy. Among the Nd:YAG treated group, 3 out of 10 showed 50-75% improvement and were slightly satisfied;none showed > 75% improvement, 7 out 10 failed to show successful results i.e. >50% improvement. **Conclusion:** Both of the treatments are not much effective and do not give consistent and satisfactory results for treatment of keratosis pilaris.

Keywords: Keratosis pilaris, Salicylic acid, Nd:YAG laser

INTRODUCTION

Keratosis pilaris (KP) is a disorder of keratinization of hair follicles characterized by keratin plugs in the hair follicles with perifollicular erythema.It may be inherited as X-Linked Dominant, or may be sporadic also. Familial type is often associated with icthysosis (mutation in filaggrin gene), or atopic dermatitis [1-3]. It may be due to translocation or deletion of chromosome 18. It is thought to be due to hyperkeratinization of hair follicles, which block the path for hairgrowth, thereby trapping the hair inside the follicles, which further leads to inflammation in the perifollicular areas. So, the histology shows the follicular orifice, distended by horny plug, which may be associated with mild inflammatory changes or inflammatory infiltrates in the dermis [1-3]. The usual sites affected are upper arms, thighs and buttocks, but it may involve face, trunk, or may be generalized also.The onset is usually childhood. It may be improved after puberty [1-3].There might also be seasonal variation with winter aggravation due to dryness of skin [1-3]. Variants of keratosis pilaris include Keratosis pilaris rubra, Keratosis pilaris atrophicans faciei, Ulerythema ophryogenes – involvement of the outer eyebrow, Atrophoderma vermiculata, Keratosis follicularis spinulosa decalvans and Lichen spinulosus (keratosis spinulosa [1-3]). The current treatment includes Retinoids, Salicylic acid, and Laser in the form of Pulsed dye, IPL (intense pulse light) or Nd:YAG [4-9].

MATERIALS AND METHODS

The aim of the study is to compare the efficacy of 30% Salicylic acid and Long pulsed Nd:YAG laser for treatment of keratosis pilaris. The study was conducted at RNT Medical college and MB General Hospital, Udaipur, Rajasthan, between january 2012 to October

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2014 (including the follow up period).The study was conducted under the approval from the ethics committee. 20 patients with keratosis pilaris were enrolled in the study in which 10 patients were given 30% Salicylic acid peel and 10 patients were given Nd:YAG laser therapy. The inclusion criteria includes patients with KP, who had given consent for the therapy and the study; age between 15-30 years of age, as aging process starts at the age of 30 years, which may affect the treatment response, which will further cause bias during comparison; who had lesions in the arms, so that it will be more accurate to compare the effects in the same sites, as different sites may give different response which will again cause bias in the study. The exclusion criteria includes those patients who did not give consent; who had history of photosensitivity; age <15 years and > 30 years; those who had lesions at the sites other than arms. Those patients with Salicylic acid treatment group were given 30% Salicylic acid peel (after washing their face) every 15 days for 2 months. Those patients under Nd:YAG laser treatment group were given the 1064 nm Nd:YAG Long pulse, Spot size:10 mm, Pulse width: 30 ms every 4-6 weeks for 4 sittings. Their eyes were protected with goggles during the laser treatment; and were advised to use sunscreen lotion to protect themselves from sunlight. Assessment: Photographs were taken prior to treatment (Figs. 1 and 3), and 2 months of follow up (i.e. 2 months after the last treatment) (Figs. 2 and 4) , and were compared by 2 independent observers who were not involved in the study. Subjective Assessment Grading of improvement was done as follows: < 25% - poor, 25-<50%- fair, 50-<75%- good, >75%- very good. Degree of satisfaction at the end of the study was graded as: < 25% - Unsatisfied, 25-<50%- Slightly satisfied, 50-<75%- Satisfied, >75%- Very satisfied. < 50 % improvement was considered as failure of the therapy.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

Informed Consent: the patient's informed consent was obtained. Prior to the study, every patient gave written consent to the examination.

RESULTS

20 patients were enrolled in the study, with 10 patients in each group. All of them were females. Age segregation was not done as the patients were randomly selected for each group. Regarding the subjective assessment results, among Salicylic acid treated group, only 2 out of 10 showed improvement between 50-75%, and were slightly satisfied; none showed >75% improvement, and 8 out of 10 failed to show >50% improvement and were considered as failure of the therapy. Among the Nd:YAG treated group, 3 out of 10 showed 50-75% improvement and were slightly satisfied,;none showed > 75% improvement, 7 out 10 failed to show successful results i.e. >50% improvement. There is no statistically significance between the results of the two groups.

DISCUSSION

Keratosis pilaris is the keratinization disorder of follicular epithelium in which the hair is trapped in the follicle due to hyperkeratinization of follicular epithelium [1-3]. Salicylic acid is a beta-Hydroxy acid, which is lipid soluble and can penetrate and reach the hair follicles. It has keratolytic property and removes the surface keratin from upper parts by exfoliating the keratin layer by layer, thereby removing the hyperkeratotic keratin. It also has antiinflammatory property by inhibiting COX enzymes, thereby decreasing production of the pro-inflammatory prostaglandins and leukotrienes [4]. Long pulse 1064nm Nd:YAG laser emits light waves, which target the chromophores in the skin, which are mainly Melanin in the hair and hair follicles. So, it selectively target the pigmented hair with the follicles, destroying them by the mechanism of photothermolysis as it generated heat at the target sites. It is better suited for fair skin as the darker skin has more melanin due to which more side effects can be seen with the laser therapy [5-9].

In this study, among Salicylic acid treated group, only 2 out of 10 showed improvement between 50-75%, and were slightly satisfied; none showed >75% improvement, and 8 out of 10 failed to show >50% improvement and were considered as failure of the therapy. Among the Nd:YAG treated group, 3 out of 10 showed 50-75% improvement and were slightly satisfied,;none showed > 75% improvement, 7 out 10 failed to show successful results i.e. >50% improvement. There is no statistically significance between the results of the two groups.

A pilot study was conducted by Saelim and his allies (Saelim et al, 2013) on Long-pulsed 1064-nm Nd:YAG laser for keratosis pilaris on Eighteen patients with untreated KP on the upper outer arms. One arm was

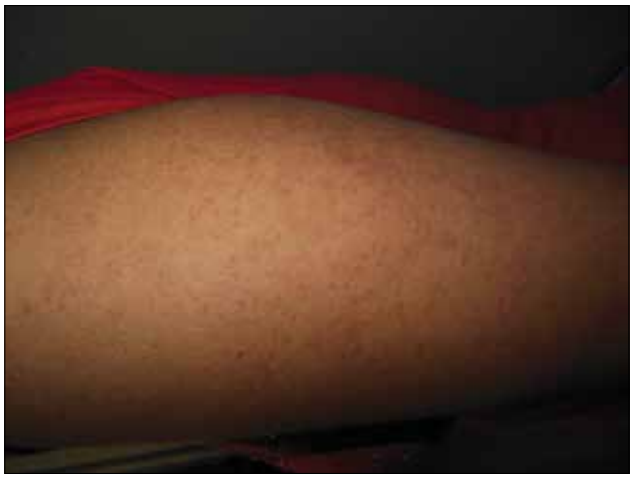

Figure 1: Keratosis Pilaris prior to Salicylic acid peeling

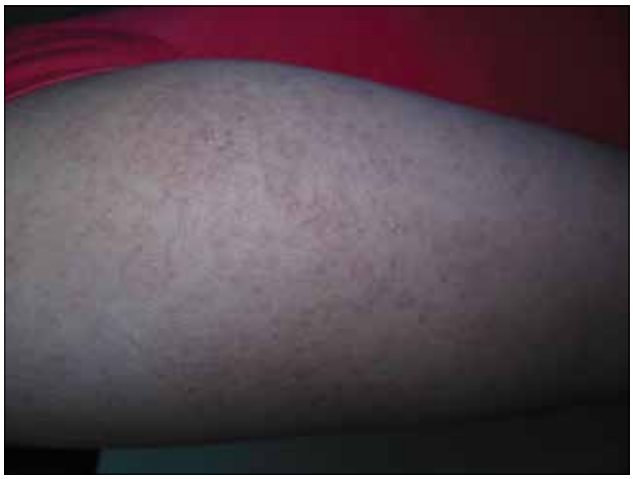

Figure 2: Keratosis Pilaris 2months after 4th sitting of salicylic acid peeling

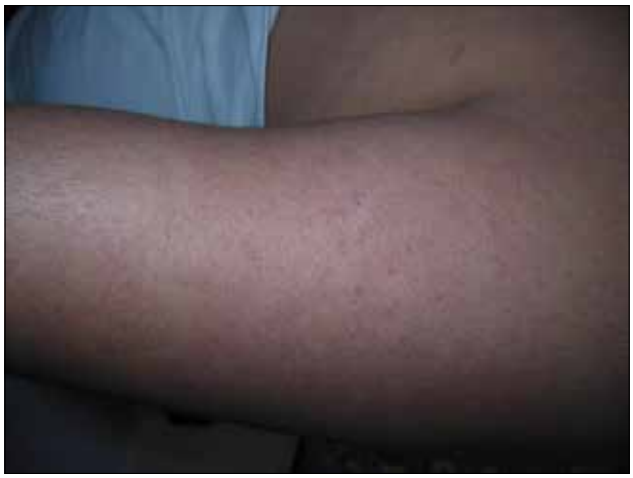

Figure 3: Keratosis Pilaris prior to treatment with Long pulsed 1064 nm Nd:YAG Laser

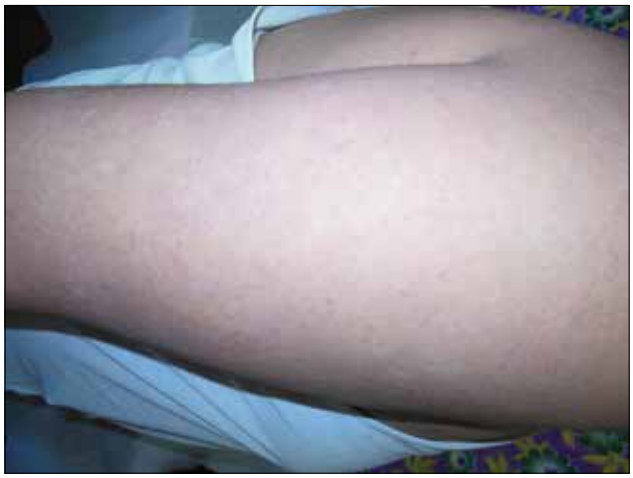

Figure 4: Keratosis Pilaris 2 months after last treatment of Long pulsed 1064 nm Nd:YAG laser

treated with long-pulsed 1064-nm Nd:YAG laser at 30 msec pulse width and fluence of 34 J/cm^2, while the contralateral arm served as control. Patients received three consecutive treatments at 4-week intervals. Three blinded dermatologists assessed digital photographs using a quartile grading system to separately rate global improvement, erythema and the number of keratotic papules. Seventeen patients completed the study. There were statistically significant improvements in global assessment, erythema and the number of keratotic papules at 4 weeks after the last treatment ($p < 0.05$). All patients also stated that their lesions improved and were satisfied with the laser treatment [7].

Another study was conducted by Kim S(Kim S 2011) on Treatment of pigmented keratosis pilaris in Asian patients with a novel Q-switched Nd:YAG laser. Ten patients with pigmented keratosis pilaris underwent five weekly treatments using a Q-switched Nd:YAG at 1064 nm with a 6-mm spot size and a fluence of 5.9 J/cm^2. Photographic documentation was obtained at baseline and 2 months after the final treatment. Clinical improvement was achieved in all 10 patients with minimal adverse effects [8].

Another pilot study was done by Juhee Park, et al [9] to evaluate the effectiveness of the Q-switched 1064-nm Nd:YAG laser for the treatment of KP. Total of 12 patients with KP were treated with a Q-switched 1064-nm Nd:YAG laser. Ten sessions of laser treatment were delivered once every two weeks. The entire lesions were treated with the following laser settings: 4.0~5.0 J/cm^2, 4-mm spot size, and three passes. Two dermatologists' clinical evaluations and patients' satisfaction were assessed between before treatment (baseline) and at 1 month after the last treatment. Eleven of the twelve patients showed more than grade 2 (>25%) improvement in texture and dyspigmentation

in KP lesions, respectively. A half of the patients (50%) showed more than 50% improvement in the skin texture. Regarding dyspigmentation, five patients (41.7%) showed more than 50% improvement. Eleven out of twelve participants were satisfied (>25% of the Patients' self assessment) with the procedure. No significant adverse effect was observed [9].

In this study, only 20% of salicylic acid treated group and only 30% of Long pulsed Nd:YAG treated group showed significant improvement (>50% improvement) with mild satisfaction.

CONCLUSION

In contrast to the theoretical mechanism of actions of Salicylic acid and Long pulsed Nd:YAG laser for treatment of keratosis pilaris, both of the treatments are not much effective and do not give consistent and satisfactory results for treatment of keratosis pilaris. Both treatments did not give signifcant difference in their efficacy.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article. A copy of all documents available for review by the Editor-in-Chief of this journal.

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Our Dermatology Online

Case Report

Epithelial predominant synovial sarcoma presenting as chronic non-healing ulcer of foot: A rare presentation

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ABSTRACT

Synovial sarcoma is a morphologically and cytogenetically distinct aggressive neoplasm which presents as a deep seated painful mass in the lower extremities of young adult males. We report a rare case of synovial sarcoma presenting as a non-healing ulcer over the foot in a 29 year old male, which was misdiagnosed initially as a malignant skin adnexal tumour.

Key words: Synovial sarcoma; Epithelioid variant; Non-healing ulcer

INTRODUCTION

Synovial sarcoma is defined as a mesenchymal spindle cell tumour which displays variable epithelial differentiation including glandular formation and has a specific chromosomal translocation [1]. It is an aggressive and rare neoplasm which is histologically classified into two subtypes: monophasic and biphasic. Epithelial predominant synovial sarcoma can mimic epithelial neoplasms and is frequently misdiagnosed.

CASE REPORT

A 23 year old male patient presented to his GP with history of non-healing ulcer over the lateral aspect of the right foot for 1 month. A clinical diagnosis of Madura foot was made and a biopsy was performed, which was reported as malignant adnexal tumour at the local diagnostic centre. He was referred to our hospital for further management.

At presentation in our surgery OPD, a 4x5cm chronic non-healing ulcer was noted along the lateral and plantar aspects of the right foot having irregular margins covered with granulation tissue. An enlarged right inguinal lymph node (1x1cm) was also noted. Magnetic Resonance Imaging (MRI) was was performed, which revealed an ill-defined heterogeneous lesion along the lateral and plantar aspects of the right foot measuring approximately 5.3x4.2cm, infiltrating the subcutaneous fat, skeletal muscles and skin with surface ulceration.

FNA of the inguinal node showed reactive hyperplasia of lymphoid tissue.

A wide excision was performed followed by split skin grafting. The excised specimen was subjected to histopathological examination which revealed a poorly circumscribed multifocal tumour composed of varying sized nodules of epithelial cells forming cleft-like and tubular spaces lined by cuboidal to low-columnar cells with nuclear pleomorphism, nests and sheets focally merging with a cellular spindle cell component with occasional mitosis. Immunohistochemically, the epithelial cells showed strong reactivity for cytokeratin and weak to moderate CD99, while the spindle cell component showed strong CD99 positivity. A diagnosis of epithelial predominant biphasic synovial sarcoma was made (Figs 1 and 2).

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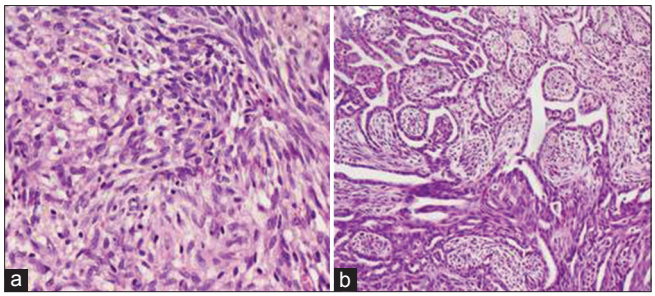

Fig 1: Shows a biphasic tumor: A) shows spindle shaped tumor cells and B) epithelioid component with clefts and trabecular spaces lined by cuboidal cells. H&E, 200X

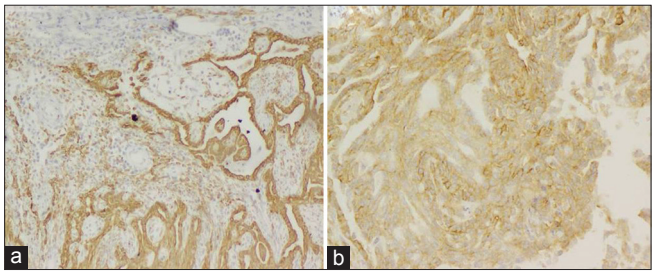

Fig 2: IHC showing A) Cytokeratin positivity among the epithelioid component and B) showing CD99 positivity among the epithelioid and spindle cell component. IHC, 200X

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure

The patient received radiotherapy over 6 weeks (total 60 Gy). Chemotherapy was started but he developed significant side-effects after the first cycle of chemotherapy with Etoposide, refused further treatment and got discharged against medical advice. Despite repeated attempts, skin grafting was unsuccessful and the patient returned two months later with a large non-healing ulcer having slough and purulent discharge. In view of the progressive nature of the disease and the deteriorating clinical condition he underwent a below-ankle amputation (Fig. 3). The subsequent postoperative period was uneventful and the patient was discharged with advice to follow up regularly.

DISCUSSION

Synovial sarcoma is a rare malignant soft tissue neoplasm typically seen in the extremities of adolescents and young adults in the age group of 15-40 years, with a predilection for knee and ankle [2]. There is a slight male preponderance with male to female ratio being 1.2:1 [3]. The term synovial sarcoma is a misnomer since it does not arise from the synovium, although at microscopy it does resemble developing synovial

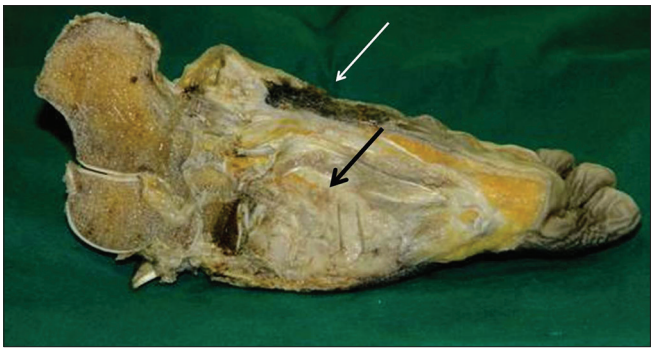

Fig 3: Cut section of Amputated foot showing surface ulcer (white arrow) and an underlying irregular grey white tumor (black arrow).

tissue. According to some authors, it is believed to arise from multipotent stem cells with the potential to differentiate into epithelial or mesenchymal structures [4].

It typically presents as a painful deep seated swelling or mass gradually increasing in size, unlike most other soft tissue sarcomas which are painless. Ours is a rare case which presented as a non-healing ulcerated lesion with very few similar cases having been reported in literature. One similar case was reported by Zhang at al, as a non-healing ulcer on the buttocks in a young female [5].

Microscopically, synovial sarcomas are composed of a varying proportion of well-defined epithelial cell components and fibrosarcoma-like spindle cell components, depending on which, they can be subclassified into four types:

a) Biphasic with predominance of epithelial/spindle cell component
b) Monophasic spindle cell/fibrous
c) Monophasic epithelial and
d) Poorly differentiated round cell type

A synovial sarcoma with predominance of epithelial cells and minimal spindle cell component makes it difficult to differentiate from other lesions displaying similar morphologic appearance, such as a malignant skin adnexal tumour, thus posing a diagnostic difficulty as happened in our case. The differential diagnosis includes metastatic and malignant adnexal carcinoma, malignant melanoma, malignant epithelioid schwannoma and epithelioid sarcoma [6]. Hence, small tissue biopsies showing predominantly epithelial cells with glandular formation should be viewed cautiously.

The epithelial component in our case was strongly positive for cytokeratin while the spindle component

was positive for CD99 confirming our diagnosis. Thus immunohistochemistry and cytogenetic studies have proved to be excellent tools in the diagnosis. Synovial sarcomas are uniformly positive for Cytokeratin, CD99, EMA, vimentin, desmoplakin, Leu-7, S-100 protein and negative for CD34, desmin, smooth muscle actin and vascular tumour markers [4].

Recent molecular studies have shown that a majority of synovial sarcomas are associated with a specific balanced chromosomal translocation (X;18) (p11.2 q11.2) which is not associated with other sarcomas [7]. The molecular and cytogenetic studies can supplement the morphological and immunohistochemical diagnosis.

Prognosis of synovial sarcoma generally considered poor. However some studies show that not all synovial sarcomas are associated with a bad prognosis [6]. Some indicators of adverse prognosis are male gender, truncal location, tumour size more than 5cm, higher tumour grade, aneuploidy and neovascular invasion. On the contrary, young age at onset, Her-2 expression, complete tumour resection with free margins and response to chemotherapy have been defined as good prognostic indicators [4].

The preferred choice of treatment is surgery with emphasis on adequate margins. Chemotherapy and radiotherapy may be beneficial, particularly in high risk patients. According to a study by Siegel et al patients who received chemotherapy following surgery have shown better survival rates compared to those who did not. The role of radiotherapy has been controversial. According to studies by Ocku et al lack of radiotherapy is also one factor associated with poor outcome, especially in high risk patients [6].

CONCLUSION

We have reported a case of epithelial predominant biphasic synovial sarcoma presenting as a non-healing ulcer of the foot with rapid progression, that was initially misdiagnosed as a malignant skin adnexal tumour. This stresses on the point that not only is a high degree of clinical suspicion essential in evaluating young male patients presenting with non-healing ulcer of the foot, as also the role of immunohistochemistry in differentiating epithelial predominant synovial sarcoma from its mimics.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Case Report

Adventitious discovery of elastofibroma dorsi on skin biopsy

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ABSTRACT

Elastofibroma dorsi is a rare soft tissue pseudotumor, slow-growing, sitting in 99% of cases at the subscapular region and occurring in the elderly active people. Its pathogenesis is unclear. It is often asymptomatic. However, the diagnosis can be made on the typical topography of the mass and its characteristic appearance on CT and MRI. Thus, in the literature, most of the reported cases were radiologically discovered. An incidental histological discovery, like in our case is rare. We report the case of a 63 year-old man who had multiple nodular lesions, well circumscribed, firm, sometimes inflammatory, measuring between 3 and 5 cm, and located on the thighs and the paravertebral and scapular regions. The chest x-ray showed a right basal opacity suggesting a malignant processus. These nodules were biopsied in search of cutaneous metastasis of a probable pulmonary neoplasia. At histological examination, the diagnosis of elastofibroma was retained. Despite its rarity, the dorsal elastofibroma deserves to be known, thus avoiding excessive surgery. We propose to study its clinical, radiological and pathological features and its therapeutic modalities.

Key words: elastofibroma; dorsal; histology

INTRODUCTION

Elastofibroma (elastofibroma dorsi) is a relatively rare and slowly growing pseudotumor of the soft tissue. It is usually located at the inferior subscapular region, between the lower pole of the scapula and the chest wall. Other localizations are possible but remain rare. It is more frequent in old individuals with a predilection for women. Generally, elastofibromas are unilateral and asymptomatic. Multiple forms are rare. In most reported cases, this lesion was incidentally discovered by radiological examination. In our case, it was an incidental histological discovery.

CASE REPORT

A 63 year-old man consulted for fever, weight loss and impaired general condition. On physical examination, there were multiple nodular lesions, well circumscribed, firm, sometimes inflammatory, measuring between 3 and 5 cm and located on thighs, paravertebral and periscapular regions. The chest x-ray showed a right basal opacity suggesting a malignant processus. These nodules were biopsied in search of cutaneous metastasis of a probable pulmonary neoplasia. The periscapular nodules were biopsed, they corresponded to a very limited, non-encapsulated lesion, showing numerous eosinophilic elastic fibers which were fragmented, often globulous and scattered (Figs 1 - 3). The collagen fibers were thick. Rare fibroblasts and mononuclear inflammatory elements were found. The diagnosis of elastofibroma was retained.

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

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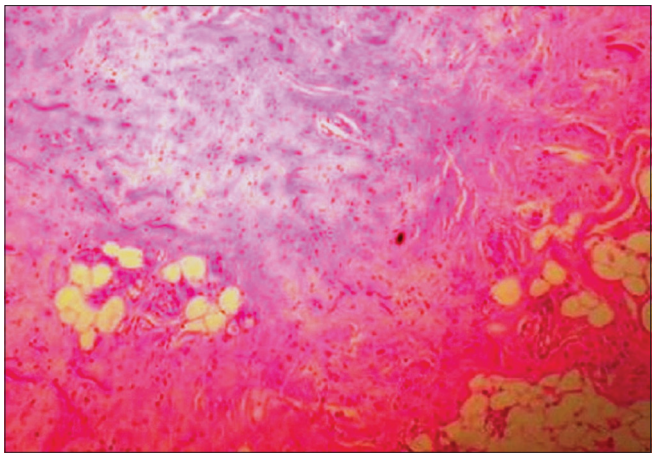

Figure 1: Fragmented and globulous elastic fibers within a hyalinized connective tissu. (HEx10)

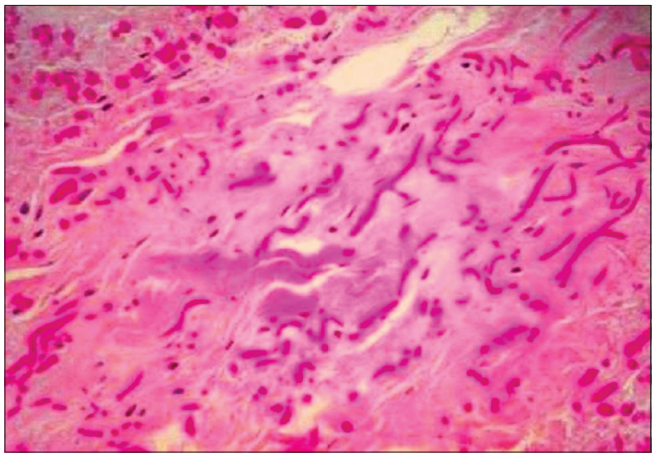

Figure 2: Fragmented, globulous and scattered elastic fibers intermixed with thick collagen fibers within a halinized stroma. (HE ×40)

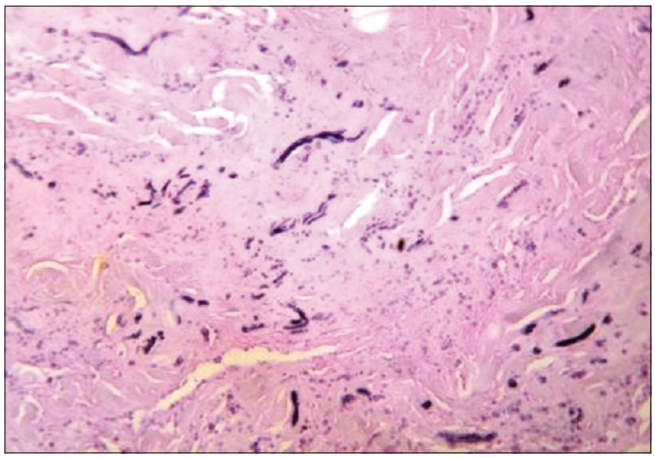

Figure 3: Orcein stain showing numerous fragmented and globular elasticfibers.

DISCUSSION

Elastofibroma dorsi was first described by Jarvi and Saxen in 1961 [1]. This uncommon benign and mesenchymal connective tissue lesion usually occurs in elderly people but it has been described in children under 6 years of age [2]. Women are more affected with a sex ratio M/F over 1 / 13 [3]. In our case, the patient was a man. The mean age at onset is 70 years.Elastofibroma's site of predilection is the subscapular region (99%), deep to serratus anterior, often attached to the periosteum of the ribs. Rarely, it is found in other locations such as extremities, head, abdominal and thoracic cavities, spinal canal and even cornea [3]. This lesion is often unilateral but it can be bilateral in 10 at 66% of cases occuring in the subscapular region [4]. Multiple elastofibromas were rarely described; Satoko Shimuzu, et al.. reported 17 distinct elastofibromas in a single patient [5]. The pathogenesis of this lesion is unclear although it is thought that mechanical microtrauma by heavy manual labor causes the friction of the scapula against the ribs and so causes this fibro-reactive lesion and this would explain the right- sided predominance. Genetic factors may also be involved. In fact, 32% of reported cases had a family history of elastofibroma. Actually, there is evidence of cytogenetic and molecular genetic changes in elastofibroma. Aberrations of the short arm of chromosome 1 and translocation involving chromosome 8 and 12 have been described [6].

Clinically, elastofibroma is often asymptomatic like in our case. However, patients can present with swelling, discomfort, snapping, clicking or clunking of the scapula and occasionally moderate pain. Subclinical elastofibromas have been found at autopsy. On physical examination, it presents as a well circumscribed and non adherent to the overlying skin mass. Otherwise, the diagnosis of elastofibroma can be made by both, histological or radiological examination.

Ultrasound examination, in the typical location of the elastofibroma, shows an abnormal mass of tissue with an alternating pattern of hyperechogenic and hypoechogenic lines that are roughly parallel to the chest wall. Computed tomography usually shows a heterogeneous soft tissue mass with poorly defined margins. MRI is the technique of choice and it reveals characteristic findings. Elastofibromas appear as poorly circumscribed soft tissue lesions with alternating areas of fibrous and fatty tissues. On T1-weighted and T2-weighted sequences, fibrous tissue produces low-intensity signals identical to that produced by muscular tissue, while the fatty tissue is seen as a high-intensity signal on T1- weighted sequences and as an intermediate signal on T2- weighted sequences.

The need of biopsy is controversial. Hayes, et al. [7] recommended it to confirm the diagnosis. Massengell

and al thought that biopsy is not necessary for diagnosis if clinical findings were typical and the MRI pattern was characteristic [8]. As cases of coexisting sarcoma and elastofibroma were reported, Alberghini, et al.. suggested a possible link between the two pathologic states so they consider that histological evaluation is essential [9]. In the recent literature, authors reserved histological confirmation to difficult and atypical cases.

Elastofibroma have typical macroscopic and histological aspects.

Macroscopically, it is ill-defined, gray white, rough-textured, measuring 5 to 10 cm. Sectioning reveals cystic degeneration and fat islets [10,11].

Histologically, elastofibromas present as non-encapsulated lesions which blend with the surrounding fat and connective tissue. The diagnosis is based on the presence of the altered elastic fibers embedded in a collagenous matrix, riddled with various amounts of fat cells. These elastic fibers are often fragmented into discs or globules and larger than regular ones. The fibers, which account for almost 50% of the tissue, stain black with the Verhoeff elastic stain. Some fibers are branched while others show a serrated edge.

Elastofibroma is stained positively with vimentine and CD34 but not with SMA, desmin, p53 and S100 [12]. These features indicate the fibroblastic nature of this tumor-like lesion.

The differential diagnosis is made with the other soft tissue tumors of the scapular region like lipomas, desmoid tumors, neurofibroma, cicatricial fibroma and sarcomas. Unlike elastofibromas, these tumors usually show strong enhancement after gadolinium injection.

Several treatment options have been discussed. It depends on whether or not there are symptoms. In fact, asymptomatic patients are simply observed while severely symptomatic people should have marginal excision which decreases recurrence risk. In some studies, radiotherapy can give good results [13]. Kransdorf, et al.. reported a rate of recurrence of 7% and attributed it to incomplete resection [14]. No malignant transformation has been mentioned [15].

CONCLUSION

In conclusion, elastofibroma dorsi is an under diagnosed lesion which should be considered in the differential diagnosis of the soft tissue tumors of the scapular region. Its diagnosis is easy when the clinical presentation and the radiological characteristics are typical. Recently, authors recommend biopsies only for atypical cases. In our knowledge, this is the first case of elastofibroma whose diagnosis was made incidentally on histological examination.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article and any accompanying images.

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Our Dermatology Online

Case Report

Soft tissue chondroma: a rare tumor presenting as a cutaneous nodule

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ABSTRACT

Soft tissue chondroma (STC), also known as extraskeletal chondroma or chondroma of soft parts is a benign cartilaginous tumor which arise de novo from soft tissue. Also, it is an extremely rare entity predominantly involving extremities, especially fingers. A 26 year old male presented with 3 year history of swelling in left index finger. On local examination a hard 2 × 2 cm swelling was seen over the volar aspect of left 2nd proximal phalanx. Swelling was mobile on contraction of tendons. X-ray showed a soft tissue shadow on volar aspect of left second proximal phalanx. Histopathology showed a well encapsulated, hypo cellular nodule composed of benign chondrocytes surrounded by hyaline chondroid matrix. Nuclear pleomorphism, mitosis or necrosis was not seen. Based on radiological and histopathological findings a diagnosis of STC was made. STC should be considered in patients with slow growing, soft tissue masses.

Key Words: Chondroma; Soft tissue; Extraskeletal

INTRODUCTION

STC, also known as extraskeletal chondroma or chondroma of soft parts and is a benign cartilaginous tumor. It commonly affects soft tissues of hands and feet [1]. Fingers are most commonly involved followed by hands, toes, feet and trunk. It can also be seen in dura, larynx, pharynx, oral cavity, skin, parotid gland and fallopian tube [2].

CASE REPORT

A 26 year old male presented with 3 year history of cutaneous swelling left index finger. No significant past history or history of trauma was present. On local examination a hard 2 × 2 cm swelling seen over the volar aspect of left 2nd proximal phalanx. Swelling was mobile on contraction of tendons. X-ray showed a soft tissue shadow on volar aspect of left second proximal phalanx. The underlying bone was free (Fig. 1). Grossly, the excised specimen consisted of a single nodular tissue bit with dimensions of 1.5 × 1.5 × 1 cm. Cut section was glistening white. Microscopically, a well encapsulated hypocellular nodule was seen composed of benign chondrocytes surrounded by hyaline chondroid matrix. Nuclear pleomorphism, mitosis or necrosis was not seen (Fig. 2). A diagnosis of soft tissue chondroma was made based on clinical, radiological and histopathological findings. The patient has been on regular follow-up (4 months) with no evidence of local recurrence.

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Chondroma is a benign cartilaginous tumor. When it arises in the medullary cavity, it known as enchondroma, which is an extremely common bone tumor. When it arises from soft tissue without attachment to underlying bone, it is known as Soft tissue chondrom [3,4].

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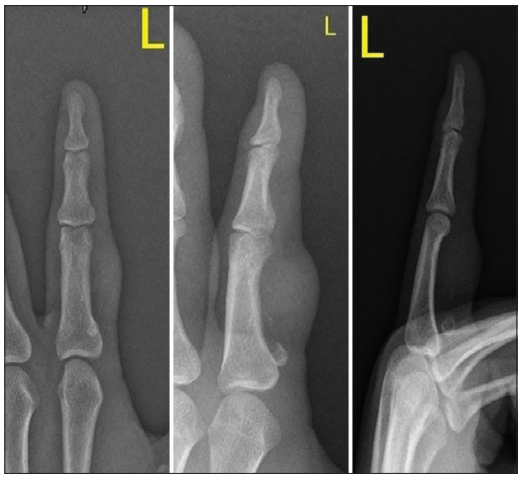

Figure 1: Soft tissue swelling in the volar aspect of left phalanx. No evidence of calcification or involvement of underlying bone.

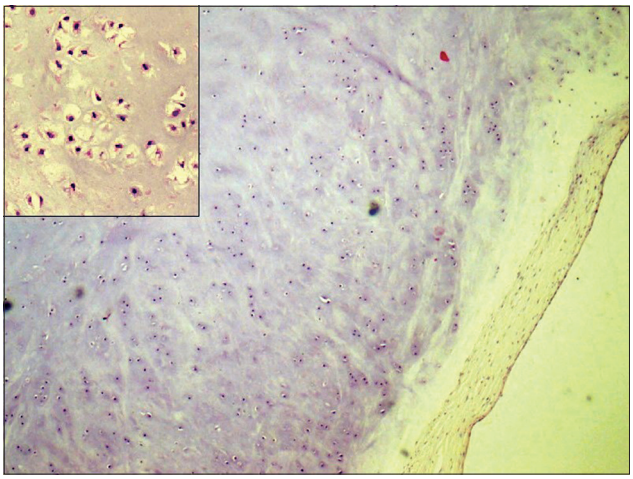

Figure 2: A well encapsulated hypocellular nodule showing chondrocytes surrounded by abundant hyaline chondroid matrix. H&E x40. Inset: Focal cellular areas seen.

STC was first described by Baumuller in 1883 and since then around 200 cases had been reported in the world literature [5]. They commonly arise as painless slow growing swelling in the extremities especially hands and feet. It frequently affects adults of 30-60 years of age and rarely occurs in children [6]. The nodule can be associated with pain or cause nail deformity, depending upon the localization [5]. Radiologically, the tumor is well demarcated and does not involve bone. Ring-like, curvilinear calcification can be seen. Rarely, calcification may be absent contributing to missing the diagnosis of chondroma [7]. The present case did not show evidence of calcification.

Grossly STCs are well circumscribed round to oval masses rarely exceeding 3 cm in greatest diameter. Sometimes it may be friable with cystic changes. Histologically, well circumscribed tumor with lobules of mature chondrocytes or chondroblasts surrounded by hyaline matrix is seen. Less commonly focal fibrosis (fibrochondroma), ossification (osteochondroma) or myxoid change (myxochondroma) can be seen [8,9]. Malignant transformation has not been reported in the literature. Immunohistochemically, the tumour cells are positive for vimentin, S100 and negative for epithelial and myoepithelial markers [10].

Clonal chromosomal abnormalities have been detected in some extraskeletal chondromas including monosomy 6, trisomy 5 and rearrangements of chromosome 11 [11,12]. The histological differential diagnosis includes calcifying aponeurotic fibroma, tumoral calcinosis, periosteal or juxtacortical chondroma, synovial chondromatosis, extraskeletal myxoid chondrosarcoma and chondroid syringoma [13]. Calcifying aponeurotic fibroma occurs in young patients and predominantly involves hands. Microscopically short bar like foci of cartilaginous metaplasia surrounded by infiltrating fascicles of fibromatosis-like plump fibroblasts is characteristic. Tumoral calcinosis mimics heavily calcified chondroma but lacks cartilage and shows histocytic reaction in response to the calcified material. Synovial chondromatosis differs from extraskeletal chondroma by its occurrence in large joints. It is characterized by formation of numerous metaplastic cartilaginous or osteocartilaginous nodules of varying sizes attached to the synovial membrane of the joint, tendon sheath or extra-articular bursa. Microscopically cartilaginous masses just beneath the thin lining of the synovial membrane are seen [14]. Extraskeletal myxoid chondrosarcoma can mimic myxoid variant of STC. However, chondroma is smaller, well defined and less cellular with cells being better differentiated. Chondroid syringoma will show eccrine ducts and glands surrounded by myxoid matrix with cartilaginous differentiation.

CONCLUSION

STC is an extremely rare, slow growing, benign cartilaginous tumor which commonly arises from soft tissue of hands and feet. Complete surgical excision is adequate treatment. Recurrence is uncommon and malignant transformation is rare. STC should be considered in patients with slow growing, soft tissue masses.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written

informed consent was obtained from the patient for publication of this article and any accompanying images.

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Our Dermatology Online

Case Report

Mimic of cellulitis: Primary cutaneous B cell lymphoma – Leg type

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ABSTRACT

Primary cutaneous B-cell lymphoma, leg type, is an uncommon and aggressive subtype of Primary cutaneous B cell lymphoma that is recently updated by the World Health Organization–European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas. We present a case of an 80-year-old woman who presented with redness and swelling mimicking cellulitis of her right leg, along with few skin colored nodules. Skin biopsy revealed pathology consistent with this entity. The patient was treated with systemic chemotherapy, but expired while on treatment secondary to sepsis.

Key words: Primary cutaneous B cell lymphoma; leg type; cellulitis

INTRODUCTION

Primary cutaneous B-cell lymphoma-LT (PCBCL-LT) belongs to a distinct group of B-cell lymphoproliferative disorders defined by its presentation in the skin, without evidence of extra cutaneous spread at the time of diagnosis [1]. It is a rare form of Primary cutaneous B cell lymphoma (PCBCL) that has an inferior prognosis when compared to other subtypes of PCBCL and requires treatment with aggressive chemotherapy.

CASE REPORT

An 80 year old female presented with complaints of pain and swelling of her right leg along with mild fever since 5 days. On clinical examination, the skin over her left leg appeared red and inflamed and was tender on palpation with local rise of temperature. Doppler study revealed no evidence of deep vein thrombosis. She gave history of similar complaints in the past that responded to antibiotics. Patient was treated with antibiotics, with partial response. The pain and swelling subsided but the redness persisted with thickening of skin, along with the presence of pea sized nodules (Figs 1 and 2). Hence a biopsy was taken with a clinical differential diagnosis of Pseudo Kaposi's sarcoma, Pretibial myxedema and Cutaneous lymphoma.

Histopathological examination revealed diffuse infiltration of the dermis by medium to large sized atypical monotonous appearing non cleaved lymphoid cells, that stained positive with CD20, CD 79a, Bcl2 and negative with CD 10 on immunohistochemistry (Fig. 3) suggesting a diagnosis of Primary cutaneous large cell lymphoma (PBLBCL) - leg type. Patient was started with systemic chemotherapy with rituximab, but developed sepsis secondary to severe neutropenia during the first cycle of chemotherapy and expired.

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure

DISCUSSION

The incidence of Cutaneous lymphoma is reported to be 0.5 to 1 per 100,000 [1]. While Most of the nodal lymphomas are B cell type, PBCBL account for only

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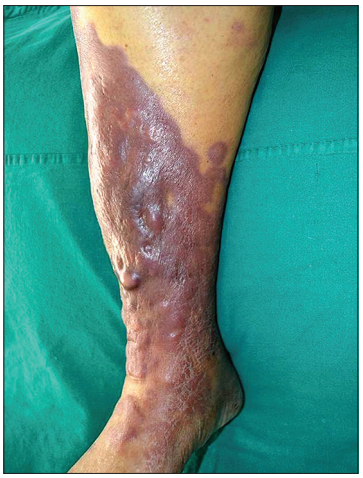

Figure 1: Clinical picture showing swelling and redness of left lower leg with thickening and skin nodules

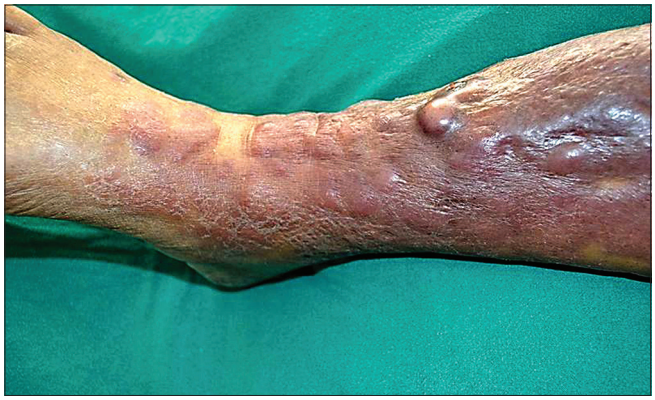

Figure 2: Close up picture showing pea sized skin colored nodule measuring 1cm across

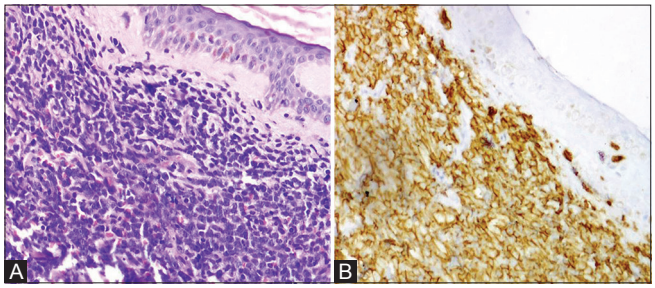

Figure 3: (A) shows diffuse infiltration of dermis by medium to large sized non-cleaved lymphoid cells, H&E, 200X. (B) shows CD 20 positivity on Immunohistochemistry

20-25% of Cutaneous lymphomas. The new 2008 World Health Organization – European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas classifies PCBCLs into three types: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicular center lymphoma (PCFCL) and PCLBCL,LT [2].

PCLBCL, LT represents approximately 20% of all PCBCLs and 4% of all cutaneous lymphomas. This condition preferentially affects elderly women who usually present with rapidly growing red or bluish-red cutaneous nodules or tumors on one or both lower legs [3]. About 10% to 15% of these patients are noted to present with lesions outside of the lower extremities. Cutaneous lymphoma presenting as cellulitis has rarely been described in literature [4].

PCLBCL, LT is more aggressive and has a worse outcome when compared with other subtypes of PCBCLs (PCMZL and PCFCL). They frequently disseminate to lymph nodes and visceral organs [5].

A diagnosis of PCLBCL, LT is made based on Clinical, histologic, immunohistochemical and molecular studies [3]. Pathology reveals diffuse non-epidermotropic infiltrates made up of a monotonous population of large non-cleaved B cells that is seen extending into the subcutaneous tissue. There is absence of reactive or inflammatory cells in the background. The neoplastic cells express B-cell markers (CD12, CD20, CD22, CD79a) and also often express surface immunoglobulin. They are strongly positive for bcl-2, but the translocation t (14:18) characteristic of PCFCL is not a feature of PCLBL-LT [6]. Bcl-6, MUM-1 and FOXP1 are usually positively expressed, while CD10 and CD138 are negative. Fluorescent in situ hybridization studies reveal breakpoints in at least one loci involving *IGH*, *MYC*, *BCL6* or *MALT1* genes in majority of cases similar to its systemic counterpart.

While watch-and-wait strategies are often employed with the other subtypes PCBCL, aggressive systemic therapy with combination chemotherapy with or radiation therapy remains the recommended approach for PCLBCL, LT. Alternative therapy with systemic single-agent rituximab may be appropriate in elderly patients unable to tolerate multi agent chemotherapy; however, long-term data are lacking [7].

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

A tricky man issue: Angiokeratomas of scroti

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ABSTRACT

Angiokeratoma is a benign cutaneous lesion of capillaries, resulting in small marks of red to blue colour spots and characterized by hyperkeratosis. They often unnoticed, may become crusty and bleed if accidentally scratched or damaged.

We presented our cases because of its apprehension, health anxiety created to patients by complaint it as malignancy of scrotum and sexually transmitted diseases. Most of patients seek medical advice to rule out sexually transmitted diseases and malignancy. The cases well highlights these unusual complaints of Angiokeratoma and only two reports of multiple Angiokeratomas available in an Indian Dermatology literature.

Key words: Angiokeratoma; Electrocauterisation; Histopathology; Laser; Scrotal Bleeding; Vascular malformation

INTRODUCTION

Angiokeratoma of the Scroti is often a benign and asymptomatic condition [1]. It is a vascular dermatosis characterised by dilated vessels of the superficial dermis associated with epidermal hyperplasia. Angiokeratomas are characterized by ectasia of the superficial dermal vessels and hyperkeratosis of the overlying epidermis.

The term 'Angiokeratoma' is derived from three Greek words meaning vessels, horn and tumour respectively, although it is not a tumour in its true sense. In 1896, John Addison Fordyce [2] reported the first case of atypical Angiokeratoma of scrotum followed by Imperial and Helwig [3] in 1967.

We presented our cases because of its apprehension, health anxiety created to patients by complaint it as malignancy of scrotum and sexually transmitted diseases. Most of patients seek medical advice to rule out sexually transmitted diseases and malignancy. The cases well highlights these unusual complaints of Angiokeratoma and only two reports of multiple Angiokeratomas available in Indian literature. The clinical and histological features of this cases are described here.

CASE REPORT

Case 1

A 26 year old male patient reported to our department with a one month history of multiple bleeding spots over the scrotum after sexual intercourse. He was openly worried about the possibility of a sexually transmitted infection and denied any urethral discharge, dysuria or sexual dysfunction (Fig. 1).

Case 2

A 31 years male patient working as daily labourer came with chief complaints of severe itching over scrotum since 6 months (Fig. 2).

Case 3

A 17 years boy was presented with complaints of red spots over scrotum since 6 months (Fig. 3).

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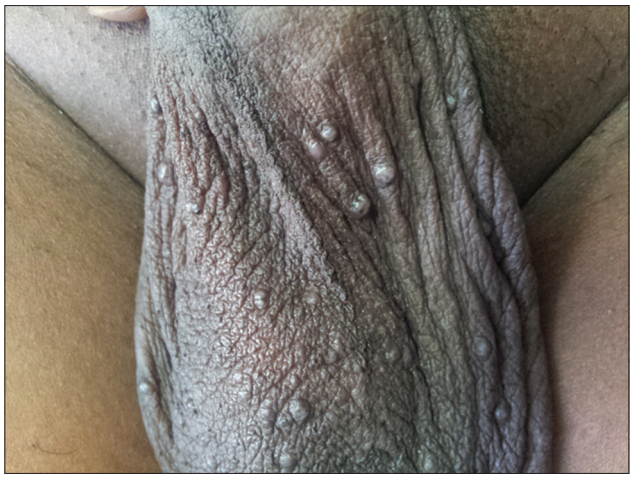

Figure 1: Show multiple dark colour papules, dome shaped papules, 2-6 mm size

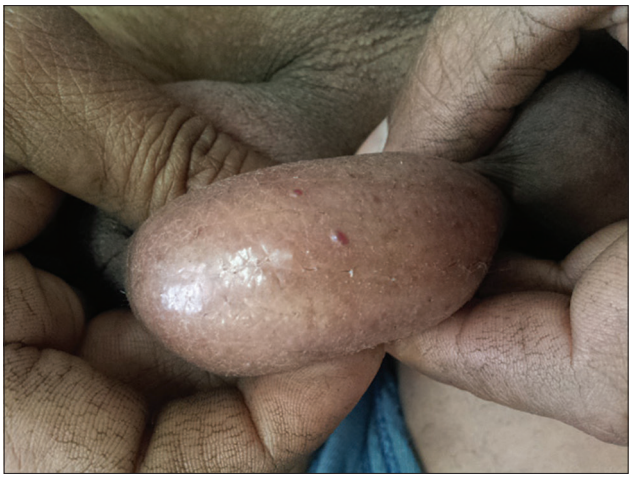

Figure 3: Show multiple dark red papules over scrotum

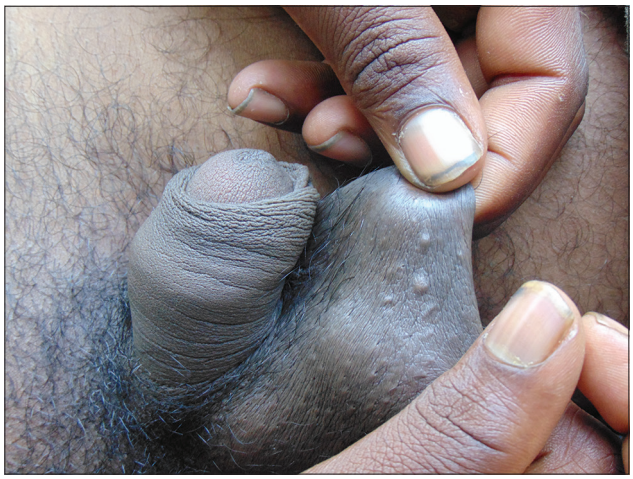

Figure 2: Show multiple skin coloured papules of size 3-5 mm over scrotum

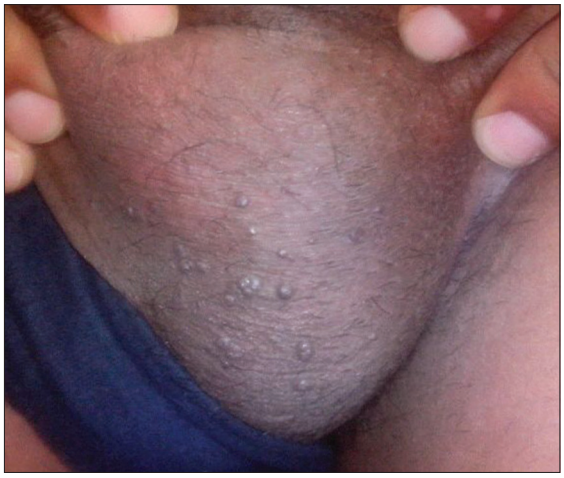

Figure 4: Show multiple pearly dome shaped papules over scrotum.

Case 4

A 28 years old male complaints of black spots over scrotum since one year (Fig. 4).

They had no prior medical history and were not taking any regular medication. No history of similar skin lesion in family members. They had no history of systemic complaints. The physical examinations were within normal limits. Palpation ruled out varicocele, epididymal mass or inguinal hernia.

On cutaneous examination, there were multiple purple to black colour, diffusely distributed, dome shaped papules over scrotum, size of 2-6 mm, few lesions show scaling. Hair, nail and oral mucosa were not involved.

Laboratory investigations revealed normal Complete blood counts, ESR, Liver function tests and Kidney function tests. Screening for HIV, Hepatitis B, and Hepatitis C were Negative. VDRL was Non reactive. Radiography of the chest and vertebral column, as well as abdominal sonography was normal. USG abdomen, pelvis and scrotum were done to rule out any vascular anomaly.

Histopathological examination from one of the papules on skin under haematoxylin and eosin staining (H & E) showed mild hyperkeratosis with hyper plastic epidermis and elongated rete ridges encircling large, numerous, dilated, congested capillaries filled with RBC's in an expanded papillary dermis (Figs 5 and 6). On the basis of clinical features and histopathology, the patient was diagnosed as Angiokeratoma of Fordyce.

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure

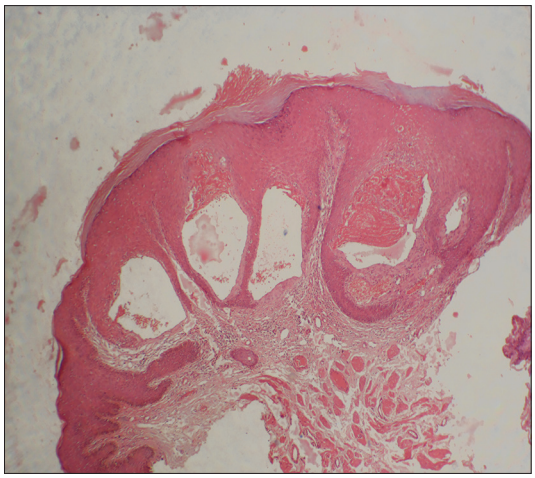

Figure 5: (H&E stain) shows Hyper plastic epidermis, Hyperkeratosis, dilated vessels in dermis

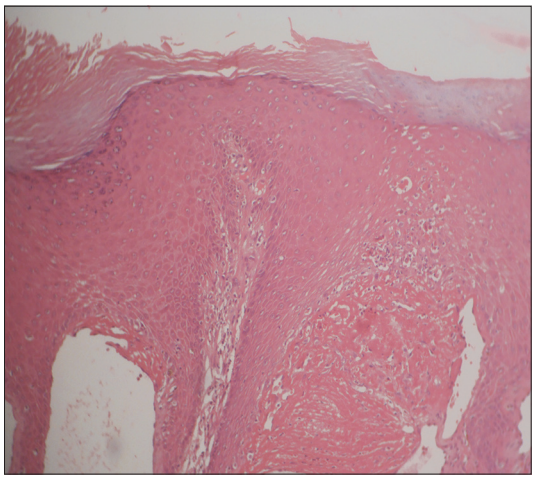

Figure 6: (H&E stain, ×200) shows Hyperkeratosis, elongated rete ridges around blood vessels and capillaries with RBC's

DISCUSSION

Angiokeratomas are well-circumscribed vascular lesions consisting of superficial vascular ectasia and hyperkeratosis. Angiokeratomas result from ectatic dilation of pre-existing vessels in the papillary dermis.

Five variants of angiokeratomas have been recognized:

- Angiokeratoma of the scrotum or vulva (Fordyce type);
- Solitary or multiple papular angiokeratoma;
- Mibelli angiokeratoma;
- Angiokeratoma circumscriptum;
- Angiokeratoma corporis diffusum;

The onset is usually in the second or third decade mostly after the age of 40 years. The prevalence is reported to increase with age, from 0.6% in 16-year-old males to 17% in those older than 70 years. No familial inheritance.

The etiology is unknown. Local venous hypertension might play a causative role and it is more common in patients with coexisting varicocele, hydrocele, inguinal hernia, benign prostatic hypertrophy, or haemorrhoid [4]. Some authors described it as a degenerative disorder [5]. Some experts thought to result from injury or trauma to or chronic irritation of the wall of a venule in the papillary dermis.

Angiokeratoma of Fordyce is the most common type of Angiokeratoma, commonly seen over the scrotum, can also be seen on the vulv, labia majora, clitori and thighs. Occasionally over the penile shaft and glanspenis [6]. Vulvar lesions may be associated with vulvar varicosities, haemorrhoids, oral contraceptive pills or increased venous pressure during pregnancy.

Fordyce angiokeratoma classically presents as multiple dark red, dome-shaped papules of 2 to 6 mm in diameter, with a discrete keratotic surface. Keratotic part may be involuntarily scratched off to produce considerable bleeding. Lesions of recent onset are red, soft, and compressible, whereas older lesions are dark blue to purple, firm, and non compressible. Solitary lesions may confuse with melanoma due to their black colour.

Angiokeratoma of the scrotum can lead to diffuse redness of the scrotum [7]. Angiokeratoma show steaks or bands of papules due to linear distribution, rough scaling on the surface and blood blisters are also experienced sometimes. The lesions can cause the patient health anxiety and embarrassment.

In Differential diagnosis Cherry Hemangioma, Granuloma pyogenicum, Malignant Melanoma, Melanocytic Naevi, Petechial angioma, Genital warts and Angiokeratoma Corporis Diffusum (Fabry Syndrome).

Histopathogy of Angiokeratomas shows mild hyperkeratosis and elongated rete ridges encircling large, numerous, dilated vessels filled with thrombi in the papillary dermis. There are many communicating lacunae in the sub papillary layer are lined with endothelium and connected underneath by dilated veins.

Our cases show mild hyperkeratosis with hyper plastic epidermis and elongated rete ridges encircling large, numerous, dilated, congested capillaries filled with RBC's in an expanded papillary dermis. So Diagnosis is confirmed.

Most of Angiokeratomas are benign and treatment is generally unnecessary. The Primary therapy is Reassurance. If treatment needed local destructive methods like electrodessication, cryotherapy, lasers therapy like Pulsed dye laser [8] and Erbium: YAG [9] lasers and excision may be considered for symptomatic lesions or for cosmoses. Our patients undergone for Electrodessication and advised follows up after three months for recurrence and cosmetic problems.

CONCLUSION

Angiokeratomas are hyperkeratotic vascular cutaneous lesions which may be localized or diffuse. The major morbidity comes from bleeding, anxiety and sometimes over-treatment due to misdiagnosis. Usually, they do not require treatment. Reassurance is the prime therapy. If treatment is needed, laser, electrocoagulation, excision, or cryotherapy may be used.

In conclusion, there have been only a few reports about Angiokeratoma of Scroti in the dermatologic literature. Pahwa P, et al. reported a case of Punctate vascular papules on the tongue and scrotum [10]. Ghosh SK, et al. reported a case of Acute scrotal bleeding [11]. Masuria BL, et al. also described an Angiokeratoma of Fordyce on unusual site [12]. Pande, et al. reported a case of Unilateral Angiokeratoma of fordyce [13], to the best of our knowledge, we are reporting four cases of multiple Angiokeratomas of scrotum. So we suggest that the title name Fortuitous stain – A Tricky man issue: Angiokeratomas of Scroti.

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2. Dr Krishna H.L, Principal, PES Medical College, Kuppam.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

Dermatomyositis related to the relapse of cervical cancer

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ABSTRACT

Dermatomyositis (DM) is a rare syndrome which belongs to the group of idiopathic inflammatory myopathies (IIM). The diagnosis of DM in adults is an indication for diagnostic evaluation towards malignancy. The exacerbation of clinical symptoms or laboratory markers of DM may indicate the relapse of neoplasm, therefore close follow-up visits of patients are obligatory. We present the case of a woman with a two-month history of progressive muscle weakness, dysphagia and oedemo-erythematous skin lesions limited to the face and trunk. The patient was diagnosed with DM associated with the relapse of cervical cancer.

Key words: cervical cancer, dermatomyositis, paraneoplastic syndrome

INTRODUCTION

Dermatomyositis (DM) is a rare syndrome which belongs to the group of idiopathic inflammatory myopathies (IIM). Clinical manifestation includes progressive muscle weakness and characteristic skin lesions. The association between DM and malignancy has been confirmed by many reports [1-3].

We present the case of a woman diagnosed with DM associated with the relapse of cervical cancer and review the current literature on DM as a paraneoplastic syndrome - characteristic clinical symptoms, that may indicate the coexistence of malignant process.

CASE REPORT

A sixty-seven-year-old woman was admitted to the Dermatological Department in Medical University of Gdańsk in June 2013 for the evaluation of a symmetrical eyelid oedema, confluent oedematous-erythematous skin lesions of lilac colour localized on the forehead, neckline and neck as well as erythomatous skin lesions and scaling in the area of hand nail folds were observed (Fig. 1). The skin lesions were accompanied by progressive muscle weakness and swallowing difficulties. Furthermore, there was a severe oedema of left lower leg and single, indolent lymph nodes were palpable in the right groin region.

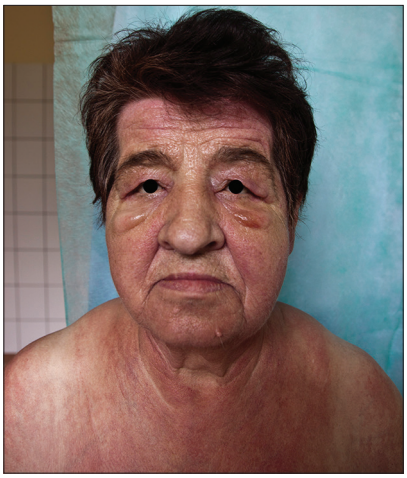

Figure 1: A sixty-seven-year-old female patient with dermatomyositis. Erythematous lesions of lilac colour located symmetrically in the area of eyes accompanied by exudation in the lower eyelids. Erythematous lesions of lilac colour in the skin of forehead and neckline

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The first skin lesions had appeared symmetrically in the area of eyelids in May 2013 and presented as oedema and erythematous lilac-coloured eruptions. The skin lesions were asymptomatic. Similar lesions had appeared shortly after on the skin of the neck and decolletage. During the two-weeks period prior to the hospitalization the patient had started to complain because of progressive muscle weakness manifested by difficulties in performing simple activities, such as combing hair, getting out of bed or climbing stairs. At the same time, symptoms of dysphagia had appeared.

The patient was treated with surgery and radiotherapy combined with chemotherapy due to cervical cancer in the G3 stage at the time of diagnosis in 2006. There were also a history of deep vein thrombosis of left lower limb in 2012 and depression, treated since 2013 with orally administered escitalopram at the dose of 5 mg per day. The patient was regularly controlled by Mental Health Outpatients' Clinic.

The laboratory investigations revealed elevated levels of creatine kinase (CPK) – 1262 U/l, aspartate transaminase (AST) - 108 U/L and lactate dehydrogenase (LDH) - 521 U/L. The peripheral blood smear showed an increased monocytosis, lymphopenia, hyperkalaemia, accelerated erythrocyte sedimentation rate (ESR) - 35 mm/h, high level of D-dimer - 3580,45 mg/l and fibrinogen – 3,78 g/l. Cardiac markers (CK-MB mass, Troponin I) and tumor markers (alpha-fetoprotein, Ca 125, Ca 15.3, Ca 19.9, carcinoembryonic antigen) were within normal limits. The urinalysis did not reveal any pathology. Antinuclear antibodies test on Hep2 cell substrate (ANA-Hep2) was at titer 1:2560 and immunoblot analysis led to detection of anti-Ro-52 antibodies. The myogenic dysfunction was recorded in electromyography (EMG) of quadriceps muscle. Echocardiography did not reveal any significant pathology, whereas the chest radiograph showed an intensified interstitial lung drawing. Lower limbs venous Doppler ultrasound imaging revealed features of superficial vein thrombosis. Due to the patient's history of malignancy, the diagnostic tests concerning the detection of neoplastic disease were performed. The gynecological examination and transvaginal ultrasound imaging did not show any significant pathology. Based on presented clinical features and diagnostic tests performed so far DM was diagnosed. Due to progressive muscle weakness and deterioration of patient's general condition, methylprednisolone pulse therapy was introduced. A single pulse of intravenously administered methylprednisolone at the total dose of 3000 mg resulted in a slight improvement in muscle strength and reduction of dysphagia symptoms. The maintenance therapy included orally administered prednisone at the initial dose of 40 mg per day, whereas the anticoagulant therapy was based on subcutaneously administered dalteparin sodium at the daily dose of 15 000 international units. Along with the treatment we continued diagnostics of neoplastic disease. A contrast-enhanced computed tomography (CT) of abdomen and pelvis showed multiple small lymph nodes along the abdominal aorta, iliac vessels and in the right groin region (Fig. 2). Histopathological examination of the lymph node biopsy (right inguinal region) had revealed metastases of squamous cell carcinoma. In the Regional Oncology Centre in Gdansk a palliative chemotherapy with 5 -fluorouracil and cisplatin was introduced, however after the second cycle of therapy, a deterioration in muscle strength, exacerbation of skin lesions and dysphagia symptoms recurred. The control laboratory tests results of muscle enzymes were normal. After oncological consultation, the palliative chemotherapy (5-fluorouracil, cisplatin) and prednisone were completed by orally administered methotrexate at the dose of 15 mg per week. The improvement in muscle strength, reduction of dysphagia symptoms and resolution of skin lesions were noted.

DISCUSSION

The association of DM with malignant tumors was described nearly 100 years ago by two investigators independently – Kankeleit and Stertz.

DM is considered to be an autoimmune disease. The mechanism of its association with malignancy remains unclear [3]. According to some authors, mediators produced by tumor cells may play role in the initiation

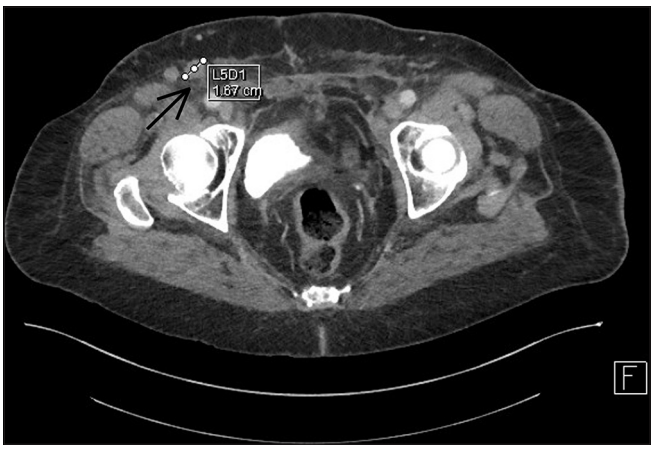

Figure 2: Patient's CT scan of pelvis. Pathological lymph nodes in the right groin region (arrow)

of abnormal immune response against cells of striated muscle and skin [2].

The incidence of cancer in the population of adult patients with DM is estimated at 13-42% [2]. Neoplastic process may precede, appear at the same time or after the onset of DM [4]. The greatest risk of malignancy occurs in a period of first 3 years after diagnosis of DM [5]. The clinical course of the disease correlates with the course of malignant process, however it is difficult to determine whether the resolution of DM symptoms results from tumor remission after oncological treatment or due to immunosuppressive effect of chemotherapy itself [6].

Distribution of tumor incidence associated with DM does not differ from the incidence in the general population, with the exception for ovarian cancer. For this reason, some researchers recommend annual screening towards ovarian cancer in women with diagnosis of DM in the first five years after the diagnosis [7]. In a study population of 618 patients with DM from Sweden, Denmark and Finland, in 198 cases a neoplastic process was diagnosed. A higher incidence of malignant neoplasms of the ovary, lung, stomach, colon and rectum, pancreas and non-Hodgkin's lymphomas was observed in the group of patients with DM compared to the population without DM [8].

The diagnostic criteria of DM introduced by Bohan *et al*. in 1975 have been still actual and include typical for DM skin lesions and three out of four of the following symptoms: symmetrical proximal muscle weakness, abnormal EMG test indicating primary changes in muscle tissue, increased serum levels of muscle enzymes, inflammatory infiltration, degeneration or regeneration and atrophy surrounding muscle bundles in histopathological examination. Pathognomonic for DM skin eruptions include - heliotrope rash, manifested by erythematous-oedematous lesions of lilac colour located symmetrically in the eyelids and Gottron's papules, characterized by the presence of violet papules and plaques over the metacarpophalangeal and interphalangeal hand joints. Similar oedematous-erythematous lilac coloured skin lesions may be also present in the skin of cheeks, knees, elbows, hands, nail folds and the neck, decolletage and shoulders (the shawl sign). In the later stages of the disease skin thickening in the palms of hands (mechanic's hands) as well as linear telangiectasia and splinter hemorrhages in the areas of nails may be observed. The pressure within the nail folds may provoke tenderness (Keining's sign). Skin lesions may either precede or occur at the same time of muscle weakness [9]. In the presented case, the physical examination revealed specific for DM heliotrope rash and less typical erythematous-oedematous lilac coloured eruptions in the skin of forehead, cheeks, neck and neckline.

Progressive muscle weakness is manifested by difficulties in performing daily activities such as getting up from chair, climbing stairs, combing or lifting objects. Fine motor disorders usually occur in an advanced stage of the disease and their severity depend on the initial strength of distal muscles. In the course of DM the involvement of internal organs, including esophagus, respiratory system and heart may appear. DM associated with malignant process may have more fulminant course which can quickly lead to patient's disability or even death.

Clinical observations indicate that in the population of patients with DM, malignancy occur more frequently in males, in the late age of onset, in patients with dysphagia or necrotic skin changes, while in patients with DM presenting arthritis and/or interstitial changes in lungs, naoplasia is rarely found [10].

The histological examination of a biopsy taken from an involved striated muscle reveals characteristic perivascular and perimysial lymphocytic infiltration, which secondarily leads to the perifascicular atrophy [11]. In the presented case the muscle biopsy was not necessary, because the number of required diagnostic criteria fulfilled the diagnosis of DM.

The laboratory findings in patients with DM include numerous non-specific abnormalities, like accelerated erythrocyte sedimentation rate, increased leukocytosis with lymphopenia and eosinophilia. The most characteristic for DM laboratory abnormalities are increased serum levels of enzymes indicative for muscle damage, such as creatine phosphokinase (CPK), which concentration may exceed tens of times the reference value. Moreover, its level correlates with the activity of the disease, however in some cases it may be normal. High serum levels of alanine transaminase (ALT), aldolase and lactate dehydrogenase (LDH) as well as increased level of creatinine in 24-hour urine collection especially at the initial stages of the disease may be also observed. In the presented case, the laboratory assessments performed in the initial stage of the disease showed a significant increase of serum levels of enzymes indicating skeletal muscle damage (CPK, LDH, AST).

Immunological tests reveal positive antinuclear antibodies (ANA) in approximately 50% of adult patients with DM and in 20% of cases the antibodies specific for inflammatory myopathies (MSA) can be found [12,13]. Anti-Mi-2 antibodies are characteristic for DM. Interesting results of a multi-center study by Azuma *et al*. showed that patients with DM associated with malignancy present rather low serum levels of muscle enzymes and the lack of MSA antibodies [14]. Recent independent studies proved that the presence of antibodies against lately described protein with a mass of 155 kDa, may be a negative prognostic marker, which means that in patients with positive above-mentioned antibodies the risk of cancer associated with myopathy is low [15,16]. In our case high titer of ANA was showed. Immunoblot analysis revealed the presence of antibodies against the antigen Ro-52 (anti- Ro52). The antibodies against the antigen Mi -2 (anti -Mi -2) were not detected. The results of immunological tests in the presented case are consistent with the observations by Menéndez *et al*., who showed a higher incidence of malignancy in patients with DM presenting an isolated presence of anti- Ro52 antibodies, without a diagnosis of autoimmune disease [17].

Treatment of DM associated with malignancy includes primarily the therapy of neoplastic process (oncological, surgical). Immunosuppressive therapy used in autoimmune DM is supportive in malignancy associated DM and aims at the improvement of clinical symptoms that result from the involvement of internal organs, striated muscle tissue and skin.

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Our Dermatology Online

Case Report

Generalized keratosis pilaris rubra

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ABSTRACT

Generalized Keratosis Pilaris Rubra is a rare dermatosis that is related to Keratosis Pilaris group of disorders. We are reporting a case of Generalized Keratosis Pilaris Rubra in a young Arabic male whom treatment options failed to improve his condition.

Key words: keratosis pilaris; generalized keratosis pilaris; keratosis pilaris atrophicans

INTRODUCTION

Keratosis pilaris (KP) is a cutaneous disorder of unknown etiology. It presents as symmetric, keratotic follicular papules on the extremities and the cheeks [1]. Rarely, it can be generalized. It usually develops in early childhood, with remission by adulthood.

There are three distinct variants of KP that have been identified: keratosis pilaris atrophicans, erythromelanosis follicularis faciei et colli and keratosis pilaris rubra (KPR). KPR is characterized by significant widespread erythema and persistence after the onset of puberty.

CASE REPORT

18-year-old Arabic male presented to the outpatient clinic in the dermatology department at King Fahd Hospital of the University with a 2-year history of mildly pruritic facial erythema. The intensity of the erythema waxed and waned but never completely resolved. After few months, the facial erythema became persistent irrespective of the season. Besides, there was generalized skin eruption involving the trunk and upper and lower extremities. There was no history of photosensitivity. Past medical and family history was unremarkable. Physical examination revealed facial erythema affecting mainly the cheeks and ears (Fig. 1). Follicular hyperkeratotic papules with a rough, sandpaper quality and variable erythema on the chest, back, upper limbs and lower limbs (Fig. 2). His complete blood count, liver function and renal function tests were normal. Antinuclear antibodies, anti double stranded DNA, anti Ro and anti Jo were negative. A punch biopsy specimen from the posterior aspect of the left shoulder showed follicular infundibular plugging with slight perifollicular lymphocytic inflammatory infiltrate consistent with KP (Fig. 3).

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

The patient was treated with different therapeutics including topical steroid of moderate potency for 3 months, topical etretinoin for 4 months, oral isotretinoin 20 mg daily for six months and acitretin 25 mg daily for 3 months but with no significant improvement. Two sessions of Pulse dye laser was done for the facial lesions but with slight improvement which was discontinued upon the patient request. So we discontinued all medications and kept the patient on regular follow up plan every 12 weeks.

DISCUSSION

Keratosis pilaris (KP) is a common benign condition that can be seen in association with several disorders,

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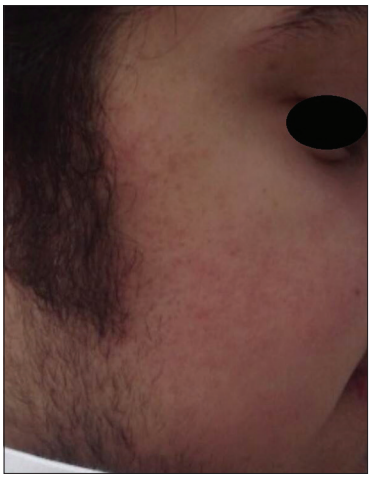

Figure 1: Erythematous patches involving the right cheek.

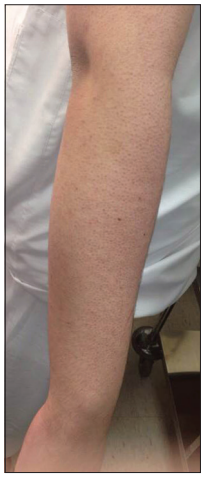

Figure 2: Note the erythematous patches with follicular prominence on the arm.

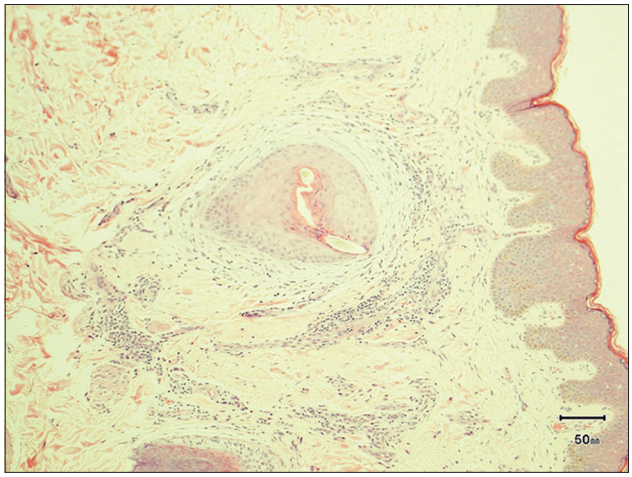

Figure 3: Section showing follicular plug with surrounding dermal perivascular lymphocytic infiltrate. Note also mild acanthosis. H&E, X100.

including ichthyosis vulgaris [2], cardiofaciocutaneous syndrome [3], metabolic disturbances (e.g. malnutrition and hypovitaminosis A), Noonan syndrome, Down syndrome, diabetes mellitus, and obesity [1,4].While Generalized Keratosis Pilaris (GKP) is a rare cutaneous disorder which presents with generalized mildly pruritic symmetric follicular-based papules affecting the face and extremities. Voss [5] studied a large number of patients with KP. He differentiated two forms, keratosis follicularis alba and keratosis follicularis rubra. The rubra form occurred in 25% of the patients with age range of 20 to 40 years and female to male ratio of 2:1. X-linked dominant inheritance of the rubra form was suggested. In Marqueling et al case series [1], 27 cases of KP rubra were reviewed, 63% were males and the maximum age of presentation was 17 years starting mainly during childhood. Pruritus was the main complaint. Our patient is considered the 28th case of generalized KPR reported in the medical literature. The pathogenesis of KPR is not well understood but since the erythema fluctuates and in some patients it is presents without significant keratotic papules. This raises the question of whether flushing via autonomic dysregulation may have a role in the clinical manifestations. Features that differentiate erythromelanosis follicularis faciei et colli from KPR include: erythromelanosis follicularis faciei et colli typically develops in the second decade [6], it lacks the involvement of the torso and there is hyperpigmentation. Treatment for KPR commonly include emollients, keratolytic agents, topical corticosteroids and topical retinoids, but they are of limited efficacy. Pulse Dye Laser and Potassium titanyl phosphate laser were reported to be effective as single case reports [1,7].

In summary, we describe generalized Keratosis pilaris rubra which is a rare entity of KP. Further reports of similar condition will help elucidate its pathogenesis in the future.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article

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Our Dermatology Online

Case Report

Kyrle disease: report of a Tunisian case

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ABSTRACT

Kyrle disease is an uncommon perforating dermatosis which is commonly associated with systemic disorders such as diabete mellitus and renal failure. A 60-year-old man, with no past medical history, consulted for purpuric, infiltrated and crusted lesions of extremities, buttocks and scalp. A punch biopsy showed a hyperkeratotic horny plug invaginating the epidermis. The diagnosis of Kyrle disease was retained. The clinicopathological features of this disease and its therapeutic problems are discussed.

Key words: Kyrle disease; histology; diagnosis

INTRODUCTION

Kyrle disease (KD) was first described in 1916 by Kyrle under the name of hyperkeratosis follicularis and parafollicularis in cutem penetrans [1]. As he described, this is a disorder characterized by the formation multiple hyperkeratotic follicular and parafollicular papular lesions with a central keratotic plug. It is considered as a variant of primary perforating dermatoses which share the same pathophysiology: a transepidermal elimination of dermal substances [2]. The prognosis depends essentially on the association with some systemic disorders such as diabetes mellitus, renal failure, liver disease, congestive cardiac failure hyperlipidemia, etc [2].

CASE REPORT

A 60-year-old man, consulted for papulo-nodular lesions mainly located on the extremities. He had no medical past history particularly of renal failure or diabetes millitus, On examination, there were multiple erythematous, purpuric, infiltrated and crusted papulo-nodular lesions with central keratotic plug located on the forearm, legs (Fig. 1), buttocks and scalp. A punch biopsy of an active lesion was performed. It showed a hyperplastic and hyperkeratotic epidermis with a central invagination. This invagination was filled by a hyperkeratotic horny plug and extended to the superficial dermis (Fig. 2). At this point, the lesion was stressed by a fibrino-leukocytic material. The papillary dermis was loose, edematous, inflammatory and congestive (Fig. 3). The diagnosis of KD was retained. The patient was treated by topical steroids with good evolution.

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Primary perforating disorders include Kyrle disease (KD) elastosis perforans serpiginosa, perforating folliculitis and reactive perforating collagenosis [1]. KD is a rare disorder of keratinization particularly observed in the setting of chronic renal failure and occurs in 10% of hemodialysed patients [2]. It affects both men and women throughout life, with a mean age of 30 years at onset [1]. However, cases in children have been reported [3]. KD seems to affect more frequently African Americans. The incidence of diabetes mellitus

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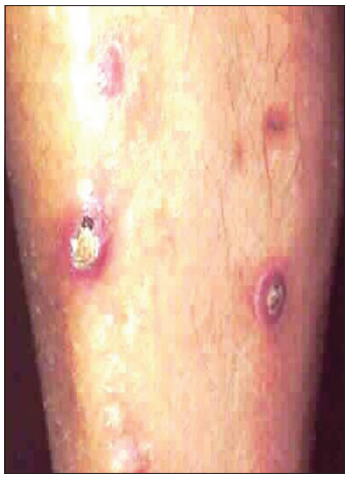

Figure 1: Erythematous, purpuric, infiltrated and crusted papulo-nodular lesions of the leg.

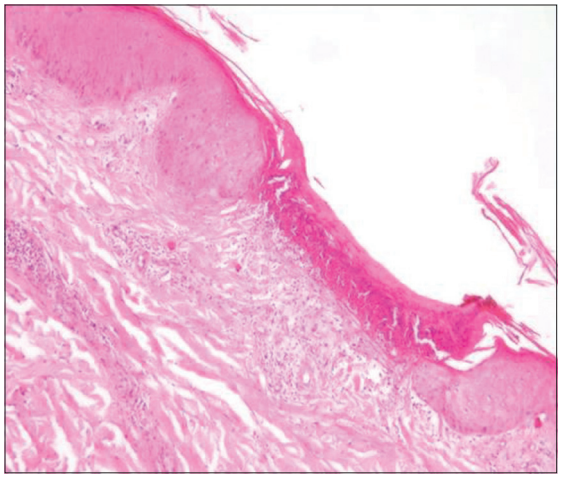

Figure 2: A partially parakeratotic plug fills an epidermal depression (HEx200).

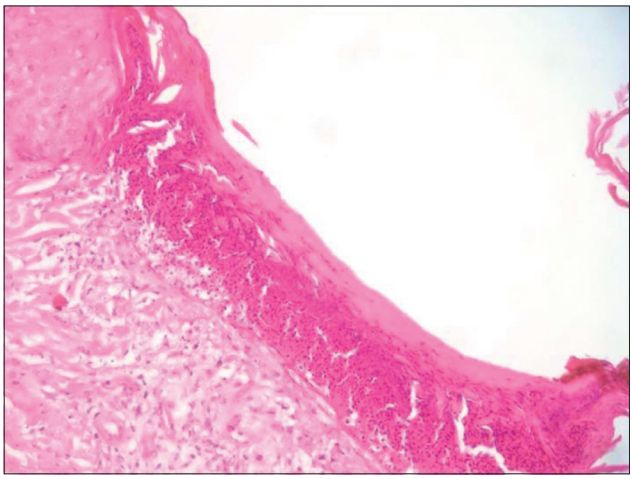

Figure 3: A keratotic plug stressed by a fibrino leukocytic material overlying the papillary dermis which is loose, edematous, and inflammatory (HEx400).

and renal failure is high in this population. Perforating dermatoses are quite rare. Thus, their pathogenesis is still misunderstood [4]. Some cases seem to be idiopathic inherited, but in other cases, KD occurs as cutaneous manifestation of a systemic disorder (diabetes mellitus, hepatic abnormalities, congestive heart failure, renal disease). The role of infectious agents, probably anaerobic bacteria, was suggested by some authors [4, 5]. Clinically, KD is characterized by silvery or red-brown papules or nodules centered by keratin plug or crusts. Some lesions appear to be follicular. They are not typically painful but may be very pruritic. Koebner's phenomenon is exceptional. The lower extremities are mostly affected. Lesions may also develop in the arms and in the head and neck region. Keratotic lesions of conjunctiva and cornea were described in a single case report.

Histologically, Constantine and Carter suggested the presence of some criteria to diagnose KD: keratotic plug filling an epithelial invagination, parakeratosis in parts of the plug, basophilic cellular debris which does not stain with elastin stains and parakeratotic keratinised cells in at least one area deep to the plug. The clinical and histological differential diagnosis can be difficult between KD and perforating folliculitis because they are quite similar. The elastosis perforans serpiginosa should also be evocated [1].

Rapid improvement of lesions is often seen once the underlying disease is treated. Treatments that have been used to treat and reduce lesions include Isotretinoin, high dose vitamin A, Tretinoin cream, emollients and oral antihistamines.

CONCLUSION

The evolution of KD is unpredictable. The absence of a therapeutic consensus is due to the little number of reported cases. Therefore more cases are needed to understand the underlying pathogenesis and to improve the management.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

Addison's Disease: A rare case report

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ABSTRACT

A female patient presented with progressive weakness, asthenia and generalized hyperpigmentation. The characteristic hyperpimentation pointed towards possibility of Addison's disease which was proved by markedly decreased plasma cortisol levels, hyponatremia and hyperkalemia. This could be one of the very few cases of Addison's Disease reported.

Keywords: Characteristic hyperpigmentation, Addison's disease.

INTRODUCTION

Addison's disease (AD) is a rare primary adrenocortical deficiency mostly caused by autoimmune idiopathic atrophy or tuberculous infiltration of the adrenal gland [1]. The other causes are surgical removal, hemorrhage, metastatic invasion and fungal infection of the gland. Weakness, characteristic pigmentation of skin and mucous membrane, weight loss, anorexia and hypotension are the most common features of AD [2]. Primary adrenal insufficiency can be a life threatening disorder particularly in stressful situation, since cortisol secretion cannot be increased on demand at all. The prevalence of primary AD has been reported to be 39 to 60 per million population. Secondary adrenal insufficiency is relatively more common due to increasing therapeutic use of exogenous steroids, but this characteristically lacks pigmentary changes of AD.

CASE REPORT

A 50 years old female patient presented with progressive weakness, fatigability, anorexia and hyperpigmentation of skin since last one year. The pigmentation first started and was more on exposed parts like face, back of the hands, elbows and then it involved some covered parts, oral mucous membrane and nails as well. There was no history of tuberculosis or any other systemic major illness in past. There was no history of any drug therapy preceding these complaints. For her general complaints she was taking treatment from physician and was hospitalized twice for profound hypotension, shock and weakness. Her blood pressure was 90/60 mmHg. All other vital parameters were within normal limits. On dermatological examination she had bluish- black hyperpigmentation of face, more on malar and forehead area, along with hyperpigmentation of the hands, forearms and palms (Figs 1 and 2). The palmar creases and nail bed also showed hyperpigmentation. Tongue and buccal mucosa also showed patchy hyperpigmentation (Fig. 3) The characteristic hyperpigmentation striked a possibility of AD which was confirmed by lowered 8 A.M. plasma cortisol level of 35.48ng/ml (normal 60-285ng/ml), hyponatremia with serum sodium level of 120 meq/litre (normal 135-155 meq/litre), hyperkalemia with serum potassium level of 5.5 meq/litre (normal 3.5-5.2 meq/litre). Other investigations like complete blood count, RBC indices were within normal limits. Peripheral smear and vitamin B12 levels were not done. An ultrasonography was done which revealed partly atrophied adrenal glands. Tuberculosis was ruled out clinically as well as immunologically. Patient was not willing for admission for the treatment with injectable hydrocortisone so, patient was started with tablet prednisolone 5 mg in morning 7 A.M. and 2.5 mg in evening with an advice to take more salts and fruits. The patient in first week started feeling better with significant improvement in general complaints and pigmentation.

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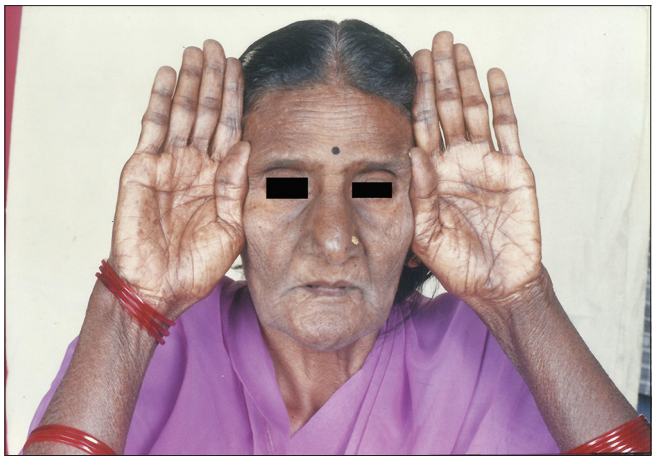

Figure 1: Bluish- black hyperpigmentation of face, more on malar and forehead area.

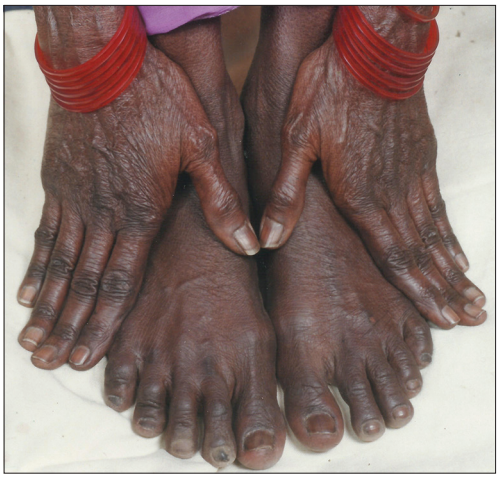

Figure 2: Hyperpigmentation of the hands, forearms and palms.

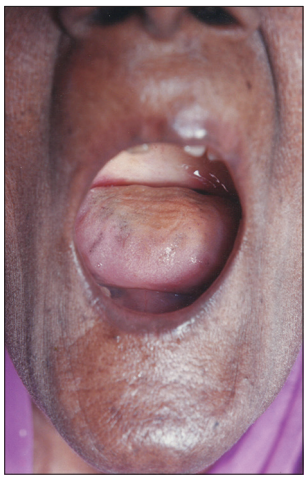

Figure 3: Patchy hyperpigmenation over buccal mucosa and tongue.

DISCUSSION

AD was first described by Thomas Addison in 1855 [3]. In AD, plasma Adrenocorticotropic hormone (ACTH), Melanocyte Stimulating Hormone (MSH) and associated peptides are elevated because loss of the cortisol- hypothalamic-pitutary feedback relationship resulting in characteristic hyperpigmentation which is seen in more than 90% of patients. However, the disease can manifests without any skin changes at all or skin pigmentation may be the only presenting feature in an individual with AD [4,5]. In the secondary adrenal insufficiency which is more common and is generally seen following prolonged administration of excess glucocorticoids, ACTH and MSH level are low or normal and hence no such pigmentary changes are present. Thus, pigmentary changes are one of the differentiating features between primary and secondary adrenal insuffiency. The hyperpigmentation is one of the most striking and commonest feature of AD [1]. It is because of compensatory over secretion of MSH from pituitary in response to poor adrenal secretions. This pigmentation is initially more on sun exposed parts, scars, folds, palmar creases and mucous membranes but may become generalized. The pigmentation may take a form of dark-tan in light colored individuals to bluish-black pigmentation in dark colored patients. 8 AM serum cortisol levels and/or ACTH stimulation either by 8 hour infusion or injecting synthetic ACTH are the definitive mode of investigations. Besides glucocorticoids there is also deficiency of mineralococticoid and aldosterone in some patients which results in sodium depletion, hyperkalemia, hypotension and sometimes acidosis. Some patients may have associated severe gastrointestinal complaints. Drug of choice in AD is hydrocortisone. But management also consists of a physiological replacement of steroid in the form of equivalent doses of prednisolone 7.5 mg, which may be subdivided into 5 mg in morning and 2.5 mg in evening. If available fludrocortisone, a mineralocorticoid may be added to this regimen, besides this patient may be educated regarding the nature of the disease, risk and care to be taken during situations like infections

This could be one of the very few cases of AD reported.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Case Report

Acral pityriasis versicolor - A rare clinical presentation

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ABSTRACT

Pityriasis versicolor is a superficial fungal infection of the skin caused by the yeast of the genus Malassezia and presents as hypo or hyper pigmented scaly macules. The most commonly affected sites include upper trunk, upper arms, neck and the abdomen. Lesions confined to the acral parts like hands and feet have rarely been reported. In this article the author reports a 40 year old male who presented with multiple hypo pigmented scaly macules confined to the acral parts (hands and wrist). The acral variant of pityriasis versicolor is considered to be a very rare clinical entity which prompted the author to report this case.

Key words: Acral; Malassezia; Pityriasis versicolor

INTRODUCTION

It was Eichstedt in 1846 who first noted the disease which is currently called as pityriasis versicolor (formerly tinea versicolor) [1]. Pityriasis versicolor is caused by various species of the genus Malassezia like M. Sympodialis, M. Furfur, M. Globosa, etc. Clinically patients present with hypopigmented or hyperpigmented macules which may be asymptomatic or with mild irritation. The sites of predilection include the upper trunk, upper arms, the neck and the abdomen. Less common sites include axilla, groins, popliteal fossae and genitalia [2]. Clinical presentation with lesions confined to the acral parts has rarely been described. The author reports a rare clinical variant of this disease where the lesions are restricted to the dorsal aspects of hands and the wrist.

CASE REPORT

A 40 year old male visited our dermatology department with a chief complaint of multiple asymptomatic hypo pigmented macules over d orsal aspects of both hands and wrist for the last one and a half months. There were no such lesions on any other parts of the body. He had no such history in the past. He denied any such complaints in his family members. On examination, there were multiple discrete scaly hypo pigmented macules present on the dorsal aspects of both hands and wrist (Figs 1a - c). The scaling of the macules became prominent on stretching the affected skin (positive Zireli's sign). The examination of hair, nail and mucous membrane was unremarkable. Potassium hydroxide (KOH) examination of the skin scrapings was done which showed multiple short hyphae and spores. He was prescribed topical Sertaconazole 2%

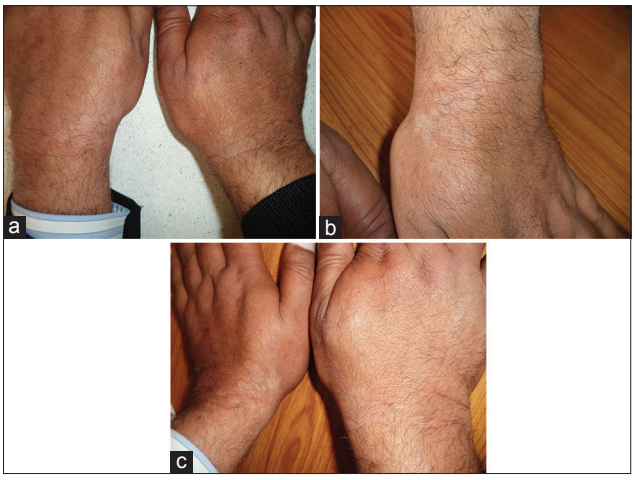

Figure 1 (a - c): Acral pityriasis versicolor: Multiple scaly hypopigmented macules on the dorsal aspects of the hands and the wrist

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cream twice daily. In addition, oral fluconazole 400 mg was given weekly for two weeks.

DISCUSSION

M. Furfur and the other related species of the genus Malassezia, the causative agents of Pityriasis versicolor, normally live on human skin in amounts which are undetectable on routine KOH examination of stratum corneum [3]. In most cases, Pityriasis versicolor represents a shift in the relationship between the yeast and the human skin. The factors which lead to the development of pityriasis versicolor are multiple. However, the environmental factors and the individual host susceptibility are amongst the major ones. A high temperature and increased humidity in the tropical climates favor the disease. Oily skin, poor nutrition, immunodeficiency, pregnancy and corticosteroid use are the risk factors in the temperate climate [1,2].

Clinically, patients of pityriasis versicolor present with well defined discrete or confluent scaly macules, which may be hypo pigmented or hyper pigmented [4]. The scaling of macules can be made prominent by stretching the affected skin and is called Zireli's sign [5]. There are many morphological types of pityriasis versicolor reported in the literature which include hypochromic (commonest), hyperchromic, combination of hypochromic and hyperchromic, circinate, erythematous, atrophying, follicular, parasitic achromia (intense skin depigmentation occuring in melanodermic individuals), involving inguinocrural region and simulating erythrasma. Another type resembling pityriasis rubra pilaris has rarely been reported [5-9]. Acral variant of the disease has been rarely reported. Ali Akbar, et al have reported an acral case of the pityriasis versicolor in which an 11 year old boy had reticulated hypo-pigmented macules on hands, feet, elbows and knees in a symmetrical distribution [6]. However, in the present case the lesions are confined to the hands and the wrist which adds more rarity to the present communication and inspired the author to report the same.

The diagnosis of pityriasis versicolor is a clinical one without requiring any laboratory documentation. However, the diagnosis can be confirmed by potassium hydroxide (KOH) examination of the skin scrapings, which demonstrates the characteristic short, cigar-butt hyphae and spherical, thick-walled yeasts referred to as "spaghetti and meatballs" appearance [4].

The treatment of pityriasis versicolor includes both topical and systemic agents. Various topical preparations include topical azole antifungals, terbinafine 1% cream, 2.5% selenium sulphide in a detergent base, 50:50 propylene glycol in water, 20% sodium hyposulphite solution, nystatin, salicylic acid, etc. The oral antifungals effective in pityriasis versicolor include ketoconazole, fluconazole, itraconazole, etc. [1,2]. In our case, the treatment given included topical sertaconazole 2% cream twice daily along with oral fluconazole 400 mg weekly for two weeks. The hypopigmentation took 2-3 months to recover after the institution of treatment.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

Atypical pityriasis versicolor case report

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ABSTRACT

Pityriasis versicolor is a superficial fungal infection caused by mycelial form of Malassezia spp, which is confined to stratum corneum.It usually present in the trunk as either hypo or hyperpigmented, aymptomatic, round to oval macules of varying sizes, which may merged to form geographic shape. Diagnosis is usually done clinically, or KOH examination which shows typical spagetti and meat balls appearances, or even by wood's lamp which shows orange to yellow fluorescence. The case series had been recording in between 2012 to 2013. Within that period, we had recorded 32 cases. All the patients which we had recorded presented with multiple, asymptomatic macules of small sizes varying from 1-2 cm in diameter to 3-4mm in diameter, usually round to oval, hypopigmented, non scaly lesions. 26 patients had lesions on forearms, 3 patients had lesions on dorsa of hands bilaterally, 3 patients had similar kind of lesions on thigh. Besnier's test was positive in 14 (43.75%) patients. KOH examinations showed fungal hyphae in 14 (33.33%) patients with typical spagetti and meat balls appearances in 9 (8.13%) patients. All of them were given and all of them got response and healed within 2-4 months.

Key words: Pityriasis versicolor; Malassezia; Besnier's sign

INTRODUCTION

Pityriasis versicolor is a superficial fungal infection caused by mycelial form of *Malassezia spp*, which is confined to stratum corneum. It usually present in the trunk as either hypo or hyperpigmented, aymptomatic, round to oval macules of varying sizes, which may merged to form geographic shape. Diagnosis is usually done clinically, or KOH examination which shows typical spagetti and meat balls appearances, or even by wood's lamp which shows orange to yellow fluorescence.The case series has been reported due to unusual sites and their appearances [1-6].

CASE REPORT

We had been recording the atypical pityriasis versicolor cases between 2012 to 2013.Within that period, we had recorded 32 cases. All the patients which we had recorded presented with multiple, asymptomatic macules of small sizes varying fromm 1-2 cm in diameter to 3-4mm in diameter, usually round to oval, hypopigmented, non scaly lesions.Among 32 patients,26 patients had lesions on forearms (Figs. 1 and 2), 3 patients had lesions on dorsa of hands bilaterally (Fig. 3), 3 patients had similar kind of lesions on thigh (Fig. 4). Besnier's test was positive in 14 (43.75%) patients. KOH examinations showed fungal hyphae in 14 (33.33%) patients with typical spagetti and meatballs appearances in 9 (8.13%) patients. 24 patients (75%) showed fluorescence on wood's lamp examinations. All of them were given oral fluconazole 450mg stat(as 400mg is not available in our setting) plus topical antifungals either miconazole or clotrimazole and all of them got response and healed within 2-4months. The lacunae of our study was that we did not have control site/patients. So, we could not ruled out spontaneous resolution.Clinically (by history and examinations, we ruled out other differential diagnosis which are mentioned in the discussion part as far as possible).

DISCUSSION

Pityriasis versicolor is a mild chronic superficial fungal infection (mainly *Malassezia spp*) of stratum corneum. The infection results from a change from its lipophilic

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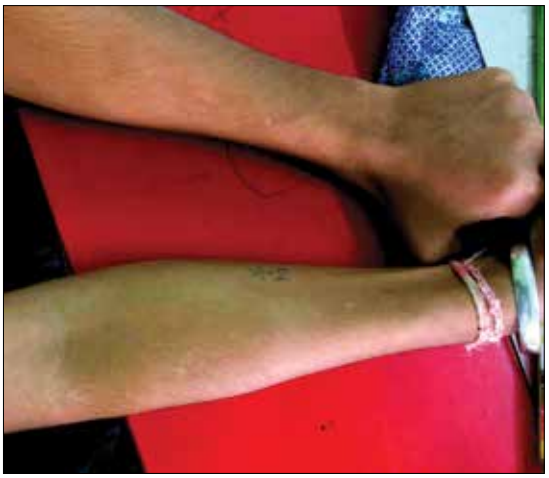

Figure 1: Atypical pityriasis versicolor at forearms

Figure 2: Atypical pityriasis versicolor at forearms

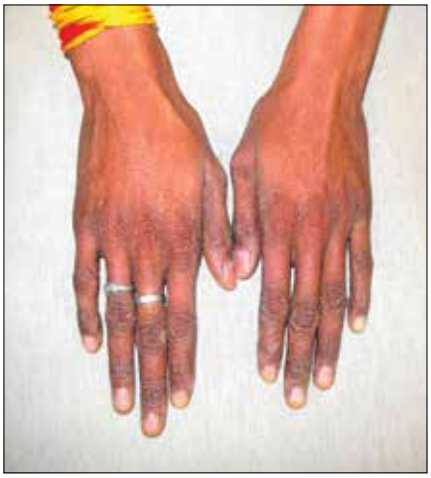

Figure 3: Atpical pityriasis versicolor at dorsa of hands

yeast form to mycelial form of *Malassezia*. Yeasts are found in the body where there is abundance of sebaceous lipids. The organism enter the follicles, begin to spread and produce fine scales. The factors contributing to the

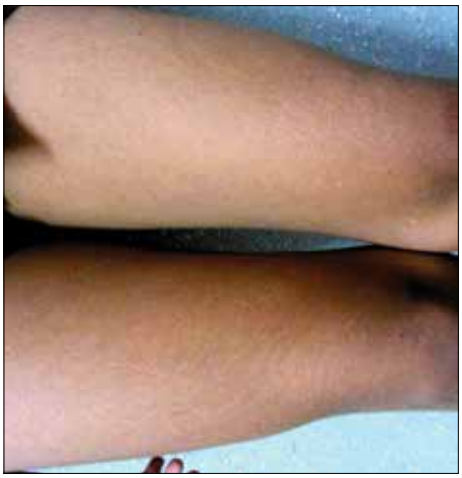

Figure 4: Atypical pityriasis versicolor at thighs

infection include humid environment, hyperhidrosis, malnutrition and immunocompromised state, diabetes mellitus, Cushing's diseases, patients on oral contraceptive pills as well as patients on corticosteroids. The pathomechanism is exact unclear. It may be associated with Delayed type hypersensitivity, release of lymphocytes by T cells, leukotrienes, which interferes with keratinocytes growth as well as collagen metabolism which may be particularly associated with atrophic type of pityriasis versicolor [1-7].

The condition is usually asymptomatic although mild itching is associated in some patients.It is characterized by patchy and scaly discloration of skin.It may be circular, oval, or even geographical due to merging of individual lesions. It may be hypopigmented due to production of dicarboxylic acid which inhibits tyrosinase, inhihibition of tanning due to overlying scales, or abnormally small melanosomes. It may be hyperpigmented also due to thicker stratum corneum, larger melanocytes and inflammatory reactions against fungus. Fluorochromes, especially pityriolactone, are linked with fluorescence in pityriasis versicolor. The typical site includes trunk, which may extend to upper arms, neck and abdomen. Atypical sites include face, genitalia, popliteal fossa, forearm and dorsa of hands and feet [3-8].

Diagnosis is done by clinical examination, KOH examination which shows typical spagheti and meat ball appearnance, and Wood's lamp examination which shows orange to yellow fluorescence. It can be confirmed by histopathology which shows yeasts in the stratum corneum and sometimes in the perifollicular region. PAS staining is also confirmatory. Culture is rarely needed which uses Sabouraud's dextrose agar with chloramphenicol, Acti-Dione, Tween-80

and layered with olive oil produces yellow colonies within 5-7 days. Serologically, Antibody specific to *M. furfur* can be determined by ELISA. Fluorescence microscopy shows green and orange fluorescent fungal elements[7-10]. The Differential diagnosis may include vitiligo, Pityriasis rosea, post inflammatory hypo or hyperpigmentation, sebhorreic dermatitis, pityriasis alba, polymorphic light eruption, secondary syphillis, and indeterminate leprosy [7-9].

Topical treatment includes 2.5% selenium sulfide, Ketoconazole shampoo for bathing, topical antifungals like clotrimazole, Miconazole, ciclopirox olamine etc, Whitfield ointment, Retinoids, Salicylic acid and Benzoyl peroxide. Systemic therapy includes Ketoconazole 200mg daily, A single dose of Fluconazole 400 mg, Itraconazole 200 mg per day for 5-7 days [11,12].

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

Acrodermatitis Enteropathica in an adult: a case report

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ABSTRACT

Acrodermatitis enteropathica (ADE) is an uncommon, inherited disorder occurring due to defective Zinc absorption. It can occur as an acquired condition secondary to impaired intestinal absorption in a wide variety of clinical conditions or due to nutritional deficiency. It is clinically characterized by triad of acral dermatitis, alopecia and diarrhoea. The preferential involvement of acral and peri-orificial skin is a feature that is pathognomonic for zinc deficiency. We report a case of ADE in a 22 year old female with no underlying comorbid conditions.

Key words: acrodermatitis enteropathica; zinc deficiency; adult

INTRODUCTION

Acrodermatitis enteropathica (ADE) is an uncommon, inherited disorder occurring due to defective Zinc absorption. It can occur as an acquired condition secondary to impaired intestinal absorption in wide variety of clinical conditions or due to nutritional deficiency. It is clinically characterized by triad of acral dermatitis, alopecia and diarrhoea. The preferential involvement of acral and peri-orificial skin is feature that is pathognomonic for zinc deficiency [1].

It can be hereditary or acquired secondary to gastrointestinal disorders or in patients with prolonged total parenteral nutrition or due to nutritional deficiency [2]. Classical clinical manifestation consists of triad of peri-orificial dermatitis, diffuse thinning of hair and diarrhea. Recognition of this condition is important as it can be fatal in severe cases. It occurs due to impaired Zinc absorption and patients respond dramatically when treated with Zinc [3].

We report a case of ADE in a 22 year old female with no underlying comorbid conditions.

CASE REPORT

A 22 year old patient presented with itchy lesions over face, neck, cubital fossa, hands and feet since 4 months. There was no history of oozing or bleeding. Patient gave history of fissuring with pain and burning. She also gave history of burning sensation and excessive lacrimation and inability to close her eyes. There was no blurring of vision. She complained of increased hair loss since 6 months. There was no history of diarrhea/oral ulcers/Raynauds phenomena and photosensitivity. She gave no history suggestive of any systemic illness. No contributory family history was present. She was not on any medications. She is a strict vegetarian and consumes mostly cereals.On clinical examination, well defined erythematous scaly and shiny plaques with crusting over the periorbital, perioral and perianal region and all around the neck were seen (Fig. 1). Erythematous fissured plaques were seen over bilateral cubital fossa, tips of fingers, toes and soles of feet (Fig. 2). Scalp showed diffuse thinning of hair. There was ectropion of both lower eyelids. Patient gave history of necrotizing fasciitis of the left foot for which debridement and amputation was done a year ago (Fig. 3).

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Biopsy was taken with a clinical differential diagnosis of acquired Acrodermatitis enteropathica and pellagrous dermatitis. Histopathological examination revealed mildly acanthotic epidermis with parakeratosis, dimunition of granular layer, with vacuolar change, and dyskeratosis, suggestive of acrodermatitis enteropathica (Fig. 4)

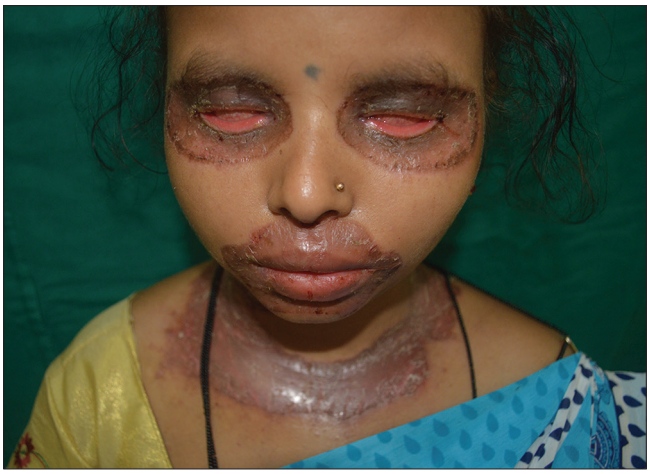

Figure 1: Clinical picture shows well demarcated erythematous scaly and shiny plaques with crusting over the periorbital and perioral region and all around the neck.

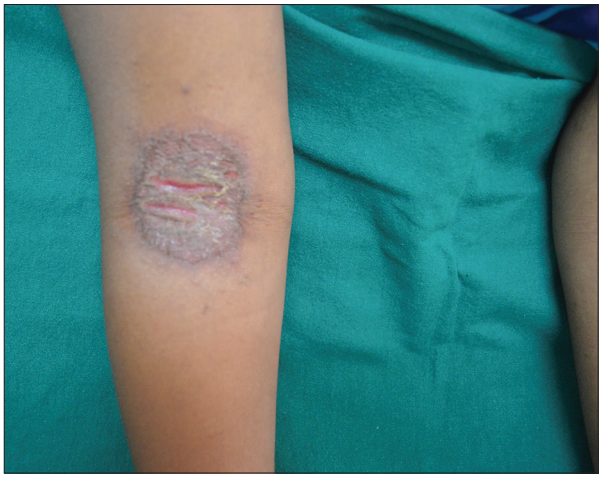

Figure 2: Clinical picture showing erythematous fissured plaques over cubital fossa.

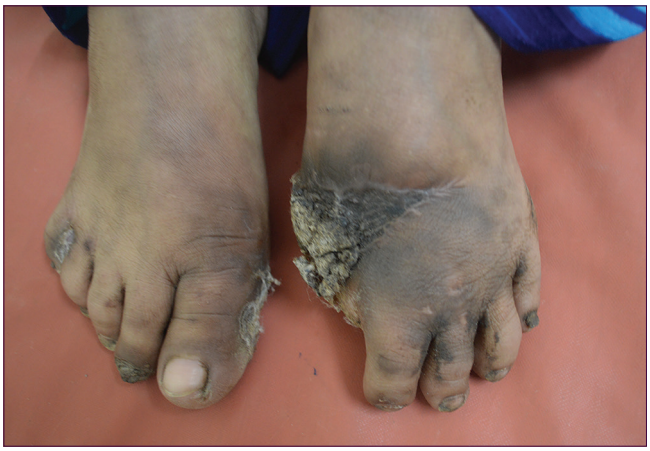

Figure 3: Clinical picture shows amputated great toe of the left foot,and acral scaly lesions

Her laboratory investigations revealed mild anemia (10.3 gm/dl) and raised erythrocyte sedimentation rate (45 mm/1hr).All other biochemical parameters including renal and liver function tests, blood sugar were within normal limits. Her HIV, HBsAg, HCV were non-reactive. ANA global was negative. Ultrasound abdomen, Chest X-Ray was normal. Serum zinc level was marginally low.

Patient has been treated with Zinc sulphate 200mg twice daily along with evening primrose oil 1 gm once a day, which contains essential fatty acid. Topically she was given white petroleum jelly twice a day along with diluted topical fluticasone propionate once at night. A diet containing leafy vegetables, nuts and legumes was advised. Patient is due for follow-up.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure

DISCUSSION

Acrodermatitis enteropathica (ADE) is an autosomal recessive disorder resulting in impaired zinc absorption or acquired, usually occuring in alcoholics. Zinc plays an essential role in catalytic, structural and regulatory functions in the human body. Deficiency of zinc manifests with multi-systemic manifestations, which can be fatal if not diagnosed and treated early.

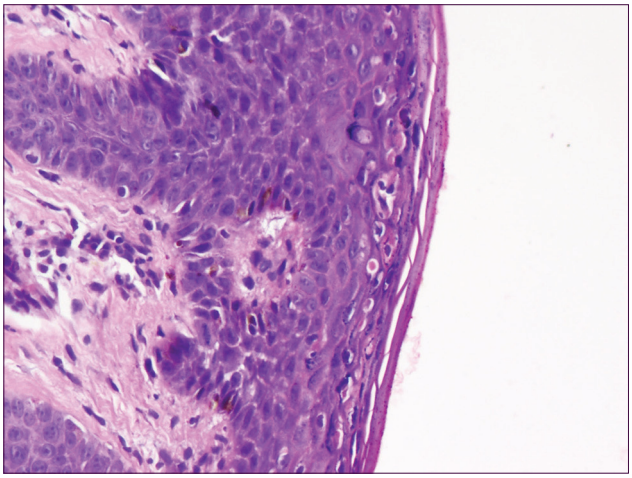

Figure 4: Photomicrograph showing vacuolar degeneration with ballooning of keratinocytes in upper epidermis with parakeratosis, H&E, 200X

ADE was first recognized by a Swedish dermatologist Thore Brandt in 1936 presenting with acral rash and diarrhoea. Later in the year 1973 Moynahan and Barnes associated the clinical finding with low plasma zinc level that responded dramatically when the patient was treated with zinc supplements [3].

Classical ADE is an autosomal recessive disorder and the defective gene is linked to a zinc transporting protein encoded on chromosome 8q24.3.5 by the gene SLC39A4. Since patients with hereditary acrodermatitis enteropathica may have minimal or no diarrhea and the correct diagnosis may be long delayed, the condition should not be considered strictly a disease of children.

Acquired zinc deficiency is widespread and is more common in populations who eat predominantly cereal proteins. It has been reported in a wide variety of clinical conditions including alcoholism, Crohn's disease and intestinal malabsorption syndromes, total parenteral nutrition,nutritional deficiency, defect of mammary zinc secretion (lactogenic ADE), pancreatic disorders, burns, malignancies and renal disorders [4]. Our patient had no underlying comorbid conditions, and we attribute the Zinc deficiency to deficient dietary intake.

The classical dermatological features of zinc deficiency include dry, scaly, sharply demarcated, erythematous patches in the peri-orifial areas that can become vesicular, pustular or desquamative. Psoriasiform plaques are typically seen in the acral region. Nails show paronychia and transverse ridging. Scalp can show diffuse alopecia with severe deficiency or dry, brittle hair in milder cases.

The associated systemic features of zinc deficiency are diarrhea, anorexia, growth retardation in children, photophobia,corneal opacities, hyposmia, hypogonadism, amenorrhea, anemia, impaired wound healing, neuropsychiatric problems, and perinatal morbidity in pregnancy. requirement in pregnancy. Our patient did not have any underlying systemic manifestations except mild anemia.

In the histopathology, necrolysis, characterized by cytoplasmic pallor, vacuolization,and ballooning degeneration of keratinocytes within the superficial epidermis of the epidermis which may subsequently lead to confluent necrosis of keratinocytes [5]. Other features are confluent parakeratosis, dimunition in the granular layer, dyskeratosis and psoriasiform hyperplasia. These findings need to be differentiated from necrolytic migratory erythema, seen in glucaganoma.

The most serious complication of ADE increased susceptibility to develop secondary infections, usually with Candida albicans, Staphylococcus aureus and Pseudomonas aeruginosa. Our patient had necrotizing fasciitis 1 year back for which she underwent debridement and amputation of great toe of left foot.

Establishing the diagnosis is by measuring plasma or serum zinc levels, although ADE with normal zinc levels has been reported. Treatment includes supplementation of elemental zinc at a dose of 2 mg/kg/day, at least two or three times the recommended dietary allowance of 15 mg/day.

CONCLUSION

This case highlights a case of ADE occurring in an adult, with no underlying comorbid conditions, presenting with peri-orificial erythematous rashes and diffuse alopecia.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Case Report

Occupational fingertip eczema from acrylates in a manicurist

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ABSTRACT

Occupational hand eczema due to acrylates present in the workplace is a disease frequently reported among dentists, printers, and fiberglass workers. Acrylate monomers are used in the production of a great variety of polymers, including nail cosmetics. Our case report demonstrates a rare clinical presentations of allergic contact dermatitis from acrylic nails. Our patient was working as a manicurist and the diagnostic analyses revealed sensitation to some of the (meth) acrylate compounds of her new nail cosmetics. Sculptured artificial acrylic and UV-hardened nails s are widely used in developed countries and they are gaining more and more popularity. We expect an increase in the number of cases of contact allergic dermatitis among manicurists and customers.

Key words: Acrylates; occupational; contact dermatitis; allergy; skin

INTRODUCTION

Acrylates are present in a wide variety of products and cause occupational and non-occupational allergic contact dermatitis. They are individual chemical molecules or monomers that bind together in a process called polymerization to form plastic materials (Table 1).

Occupational hand eczema due to acrylates in the workplace is a disease frequently reported among dentists, printers, and fiberglass workers [1]. The number of patients- manucurists or their customers is increasing, due to the new techniques in artificial nails- tips, silk, acrylic or gel nails. UV-hardened nails or photobonded nails also known as gel nails are gaining more and more popularity as a cosmetic enhancement to the natural nail. They are the newest type of artificial nails and are applied as an ordinary nail lacquer.

The diagnosis of occupational allergic contact dermatits is based upon clinical history, analyses of exposure and eliminating tests and performing specific patch testing. The golden standard is the last one as far as it can evaluate and prove the role of different compounds of the nail products in the pathogenesis of the disease.

CASE REPORT

A 31-year-old Caucasian woman developed erythema, scaling and fissuring of her fingertips (Fig. 1). The condition started 6 months ago when new nail lacquering technique was introduced in her practice as a manicurist. In the new technique she used gels containing monofunctional and multifunctional acrylate/methacrylate monomers/oligomers and primers based on methacrylic acid, but the specific identity of the ingredients was not revealed by the manufacturer for reasons of commercial secrecy. Thepatient noticed that the condition improved when she was on a vacation.

Upon admittance skin changes involved the pulps of all her fingers and they were presented with erythematous plaques, desquamation and fissures. Treatment with Clobetasol propionate 0.05% and barrier creams was introduced. The patient improved in the following 30 days. Patch testing was performed with European baseline series, acrylates and semi-open application of lacquering materials brought by the patient (Table 2). Readings at day 2 and day 3 yielded positive reactions to nickel, methylmethacrylate and 2 of her nail care

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products (Figs 2 and 3). The patient was advised on change of occupation.

DISCUSSION

Acrylate monomers are used in the production of a great variety of polymers, including nail cosmetics. Currently, there are three distinct types of sculptured acrylic nails: (i) acrylate monomers and polymers that polymerize at room temperature in the presence of an organic peroxide and accelerator, (ii) photo-bonded sculptured acrylate nails in which polymerization of the acrylate requires exposure to UV radiation; (iii) cyanoacrylate nail preparations. The acrylic compounds in gel nails are similar to those used in acrylic nails, except for 2-Hydroxyethyl methacrylate (2-HEMA), which is not present in all acrylic nails. Polymerization starts by a photo-bonding technique in the presence of a weak UV source, with benzophenone-3 and -4 as light absorbing activators (this is similar to restorative dental bonding).

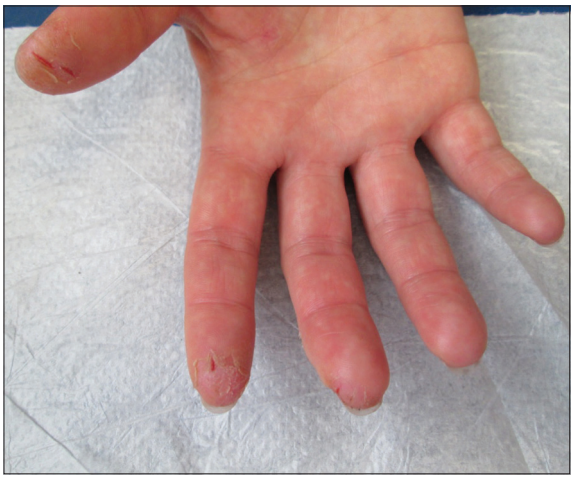

Figure 1: Clinical findings on the skin of the patient's fingertip presented by eryhema, desquamation and fissuring.

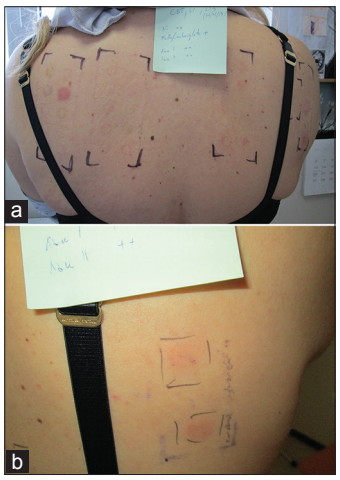

Figure 2: (a) Patch test results on day 3: positive reactions to nickel, methylmethacrylate and gel nail lacquers. (b) Closer view of the semi-open patch tested gel lacquers.

The diagnosis of contact dermatitis requires a careful history of possible contacts, including household, occupational, and recreational exposures. The skin changes include wide variety of clinical symptoms including erythema, fissuring, or also development of vesicules ot bulles [2]. It takes different period of time to diagnose and prove the agent that cause the eczema. Occupational exposure of beauticians and manicurists to acrylate-containing nail cosmetics may induce both allergic and irritant reactions [3-5]. Dermal exposures to acrylates usually induce type IV hypersensitivity reactions, manifesting mostly as hand (especially fingertip) eczema [6]. Reactions in sensitized patients include contact dermatitis, transient or permanent nail dystrophies, paronychial and subungual pain, and persistent peripheral paresthesias [7,8]. In our case the patient has only developed periungual and hand dermatitis without skin changes in any othe areas of the body. Eyelid and face dermatitis can be seen also and it's caused by airborne dusts of completely polymerized resins that have become depolymerized by the filing process or by exposure to organic vapors and polymethacrylate dusts [7,9]. However, eyelid dermatitis can be, in some cases, related to eyelid touching by the fingertips bearing acrylic nails [9]. Acrylate monomers (including residual

Table 1: List of the most common uses of acrylates

Acrylate	Applications/uses
Methyl methacrylate	Acrylic bone cements used in orthopaedic surgery; acrylic fibres, films, and inks; solvent-based adhesives and binders; medical spray adhesives; dental technology
2-hydroxyethylmethacrylate (HEMA)	UV inks; adhesives; lacquers; dental materials; artificial nails; coating for scratch-resistant glass; paint resins; binders for textiles and paper
Ethyl acrylate	Acrylic resin used in paint formulations, industrial coatings and latexes; acrylic rubber and plastics; denture materials; floor polishes, sealants; shoe polishes; adhesives; textiles and paper coatings
Ethyleneglycol dimethacrylate	Plastic bottles for soft drinks; dental materials; artificial nails; printing inks; automobile antifreeze and engine-cooling liquids

Table 2: Patch test results

Allergen	Day 2	Day 3
Nickel	+ +	++
Methylmethacrylate	+	+
Nail gel I (as is, semi-open patch test)	+	++
Nail gel II (as is, semi-open patch test)	+	++

unpolymerized monomers in the sculptured nails) may also be responsible for toxic reactions. For instance, methacrylic acid used in primer for acrylic nails may even produce third-degree burns [10].

Our patient has changed her occupation and 6 months later she has no complaints due to protection from new contact with acrylic products. We suppose that re-exposure to the same acrylic agents in a new occupation might induce recurrence of skin disorder so the patient is advised to prevent occupational setting in the field of dentistry, cosmetics, printing industry and construction industry.

Acrylates are all around us and despite the plethora of publications on (meth)acrylates, new information keeps surfacing about these fascinating chemicals. Patch testing with (Meth) Acrylate Series and semi-opened tests are the golden standard for diagnosis and detecting allergic contact dermatitis from acrylates. In conclusion this case report demonstrates the importance of good occupational advice about future occupations for employees who develop occupational skin disease. Nevertheless the acrylates have been found in the not so distant 1930s, the recent increase in the number of cases of ACD among manicurists and customers makes the acrylates The Contact Allergen of the Year according to the the American Contact Dermatitis Society in 2012 [11].

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article and any accompanying images.

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Our Dermatology Online

Opinion Article

Platelet rich plasma in dermatology and aesthetic medicine

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ABSTRACT

Platelet rich plasma is a promising therapy in dermatology and aesthetic medicine. In this article we will discuss the pros and cons of platelet rich plasma (PRP) and the usage of PRP in aesthetics. PRP is especially used for conditions like facial and neck rejuvenation, fine lines and wrinkles, abdominal striae and facial scarring.

Key words: Platelets; growth factors; granules; collagen; platelet rich plasma.

INTRODUCTION

Usage of platelet rich plasma (PRP) in aesthetic medicine is a new concept. In dermatology and cosmetic medicine, PRP has been used to treat acne, scarring, and alopecia (especially in women). It is also effective for skin rejuvenation and tightening around the eyes. Before injecting PRP to treat hair loss, a tiny scalp roller with spikes is used to stimulate the thinning areas. The rationale is that this sends a message to the hair follicles to start the healing process. Then, PRP is injected over the affected area to further stimulate stem cells in the follicle. Platelet-rich plasma is injected by multiple tiny punctures under the dermis, with or without topical local anesthesia [1,2]. The process is painless if sufficient topical anesthesia is applied. When PRP is injected into the damaged area, it stimulates the tissue, causing mild inflammation that triggers the healing cascade. As a result, new collagen begins to develop. As this collagen matures, it begins to shrink and tightens and strengthens the skin. Improvement in skin texture and tone is noticeable within 3 weeks. Full collagen regeneration requires 3 months [3,4]. The PRP treatments can be used on all skin types and tones. Minimal swelling, bruising, and redness for the initial 12 to 24 hours are expected. A bruise at the needlestick site may be visible for 2 to 3 days. Swelling from the fluid is what the patient will notice first. During several weeks, the platelets stimulate growth factors, which assists in more collagen stimulation. Treatment results vary but last up to 18 months in most patients.

In PRP, activated platelets release many other bioactive proteins responsible for attracting macrophages and mesenchymal stem cells. Inside the platelet are two types of granules, namely, alpha granules and dense bodies. Alpha granules contain the clotting and growth factors that are released in the healing process. Normally at the resting state, platelets require a trigger to activate and become a participant in wound healing and hemostasis.Growth factors and other cytokines in platelets include the following: platelet-derived growth factor, transforming growth factor, fibroblast growth factor, insulinlike growth factor 1, insulin like growth factor 2, vascular endothelial growth factor, epidermal growth factor, interleukin 8, keratinocyte growth factor, and connective tissue growth factor [5,6]. The platelets secrete growth factors, including platelet-derived growth factor and vascular endothelial growth factors. Platelet-derived growth factor is one of numerous growth factors or proteins that regulate cell growth and division [7-9]. In particular, it has a significant role in the formation of blood vessels (angiogenesis) and the growth of blood vessels from already existing blood vessel tissue. Vascular endothelial growth factor is a chemical signal produced by cells that stimulates the growth of new blood vessels. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate.

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DISCUSSION

Advantages of using PRP for aesthetic medicine include the following: tissue regeneration and rejuvenation, induction of cell differentiation, extracellular matrix formation, recruitment of other cells to the site of injury, and an increase in collagen production, which can increase skin thickness and overall skin health [10,11]. In addition, PRP is nonallergenic, is an autologous physiological product, eliminates donor transmissible infections, and is a biological glue for tissue adhesion, especially in skin flaps, bone grafts, and trauma.

Alhough PRP is a promising therapy for most patients, the practitioner must take into account some considerations during the initial assessment before suggesting this treatment. Contraindications include the following: sepsis, cancer, chemotherapy, platelet dysfunction syndrome, critical thrombocytopenia, hypofibrinogenemia, hemodynamic instability, anticoagulation therapy, acute and chronic infections, chronic pathological conditions of the liver, severe metabolic and systemic disorders, and skin disease (systemic lupus erythematosus, porphyria, and allergies), as well as heavy nicotine, drug, and alcohol consumption. Adverse effects of PRP treatment may occur, some of which are significant. The most common adverse effects are infection, skin discoloration and bruising, pain in the injected area, allergic reaction (a rare occurrence), and blood clot (because PRP therapy uses a needle, a vein could be damaged). Certain factors (eg, smoking and alcohol intake) diminish stem cell release. Avoiding these will increase the success of the PRP procedure. The platelets work by causing an inflammatory reaction. If this inflammatory reaction is diminished, the clinical outcome is significantly compromised [12,13]. For this reason, the use of anti-inflammatory drugs is not recommended. This restriction should be in place for about 1 to 2 weeks.

Platelet concentration is a rich source of various cytokines and growth factors, which are activated after its injection into the target tissue. Platelets are activated endogenously by coagulation factors (in some methods of preparing PRP, the activated PRP is injected to the tissue). Following their attachment to special receptors on the cell surfaces, some intracellular processes are activated, that facilitate extracellular matrix (ECM) accumulation and improve cell proliferation and differentiation. Tissue regeneration is resulted from cell proliferation, angiogenesis and cell migration [14,15]. Matrix metaloproteinas proteins (MMP) are involved in aging process by degradation of collagen and other extracellular matrix (ECM) proteins, this characteristic can be used to benefit rejuvenation. They can help regeneration of dermis through omission of collagen fragments that are harmful to the dermal connective tissue, and so, provide an appropriate foundation for new collagen deposition. In some studies aPRP (activated PRP) increases the expression of MMP-1 and MMP-3 protein. Thus, aPRP may cause ECM remodeling through stimulating the removal of photo-damaged ECM components and inducing the synthesis of new collagen by fibroblasts, which are in turn proliferated by their stimulation. Another mechanism of PRP for skin rejuvenization, is through acceleration of hyaluronic acid production. Hyaluronic acid absorbs water and makes hyaluronic acid matrix swelled which increases skin volume and turgor. It also promotes cell proliferation, extracellular matrix synthesis and helps to the adjustment of the collagen fibers diameter. Overall, it could enhance skin elasticity [16,17]. All these processes and some other unknown ones contribute to tissue rejuvenation through PRP.

Platelet Rich Plasma (PRP) is used for stimulation of both superficial and deep dermis layers. For superficial stimulation, the injection must be done in the superficial dermis. The PRP must be injected into the deep dermis or subdermal tissues when using as filler. The superficial injection might be done just like mesotherapy technique in order to improve the skin texture, volume and hydration. The technique is easy to be performed and has no important side-effects [18,19]. Side-effects might appear from mild bruising and occasional swelling to rarely infections. Compared with other skin rejuvenation therapies, the clinical experience using PRP can result in skin rejuvenation and global facial volumisation. PRP is a form of bio-stimulator that is safe and creates an immediate, long lasting volumetric effect with natural looking results.

To prepare PRP, a small amount of blood is drawn from the patient's arm. The blood is then placed in a centrifuge that spins at high speed and separates the platelets from the rest of the blood components. The typical baseline blood platelet count is approximately 200 000 per microliter; therapeutic PRP centrifuges concentrate the platelets by roughly 5-fold. However, broad variability exists in the production of PRP by various concentrating equipment and techniques. The platelets collected in PRP are activated by the addition

of thrombin and/or calcium gluconate, which induces the release of these factors from alpha granules. The entire process takes less than 15 minutes and increases the concentration of platelets and growth factors up to 600%, along with an inherent rise in human stem cell proliferation due to exposure to concentrated platelets up to 10 times above native levels. The concentrated PRP is then injected into and around the affected area, jump-starting and significantly strengthening the body's natural healing signals. Injections of PRP heal the area over time, during 1 to 3 months. Because the patient's blood is used, there is no risk of a transmissible infection and a low risk of allergic reaction.

Aging of the skin, dermal components, and cells means that the skin texture and appearance deteriorate and have been damaged [20].Aging affects the hands and soft tissue of the face, neck, and decollete. This is characterized by sagging jowls, thinning of the skin, puffiness, age spots, and wrinkling.In dermatology and cosmetic medicine, PRP has been used to treat acne, scarring (Figs 1A and B), and alopecia (especially in women). It is also effective for skin rejuvenation and tightening around the eyes (for thin crepe-like skin and fine lines) and in the following areas: cheeks and midface, thinning skin on the neck, jawline and submalar regions, back of hands, decollete, and others (eg, knees, elbows, and upper arms, as well as for postpregnancy skin laxity). Platelet-rich plasma is injected by multiple tiny punctures under the dermis, with or without topical local anesthesia. The process is painless if sufficient topical anesthesia is applied. When PRP is injected into the damaged area, it stimulates the tissue, causing mild inflammation that triggers the healing cascade. As a result, new collagen begins to develop [21]. As this collagen matures, it begins to shrink and tightens and strengthens the skin, as well as the tendons and ligaments of the damaged area when it is injected at that level. Improvement in skin texture and tone is noticeable within 3 weeks. Full collagen regeneration requires 3 months. Topical skin care and light therapies can enhance these results. Advanced wrinkling cannot be reversed, and severe scarring may not respond to treatment. In my experience, surgical scars respond well cosmetically. The PRP treatments can be used on all skin types and tones. Minimal swelling, bruising, and redness for the initial 12 to 24 hours are expected. A bruise at the needlestick site may be visible for 2 to 3 days. Swelling from the fluid is what the patient will notice first. During several weeks, the platelets stimulate growth factors, which assists in more collagen stimulation. Treatment results vary but last up to 18 months in most patients. Biannual touch-up treatments will maintain the results. As an initial treatment strategy, up to 3 injections may be given within a 6-month time frame. These are usually performed 2 to 3 weeks apart. Certain factors (eg, smoking and alcohol intake) diminish stem cell release. Avoiding these will increase the success of the PRP procedure. The platelets work by causing an inflammatory reaction. If this inflammatory reaction is diminished, the clinical outcome is significantly compromised. For this reason, the use of anti-inflammatory drugs is not recommended. This restriction should be in place for about 1 to 2 weeks. Proponents of PRP therapy argue that negative clinical results are associated with poor-quality PRP harvest or concentration by inadequate devices. The specification that gathering devices capture a percentage of a given thrombocyte count is a marketing bias because significant individual variability exists in the platelet concentration of human plasma [22]. More is not necessarily better in this case. Variability in platelet concentrating techniques may alter platelet degranulation characteristics, which could affect clinical results.

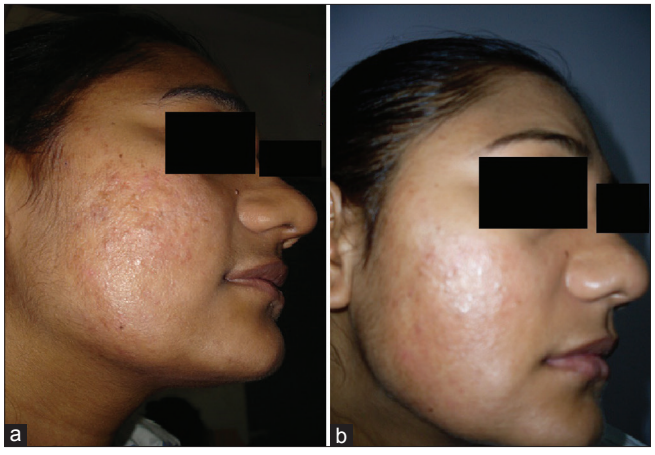

Figure 1: (a and b) Pre and post treatment of a 37 years old girl with acne scarring after 3 sessions of PRP.

There are various uses of PRP in aesthetic medicine:

- PRP has made the most significant progress in the facial area. Platelet Rich Plasma (PRP) with fat transfer is the surgical combination of injecting a patient's own plasma containing growth factors along with their own purified fat to augment areas of lost volume and wrinkles on the face.
- Containing beneficial growth factors, PRP may additionally be used with fat transfer or subcision to re-plump areas of lost volume or depressed scarring

from acne or trauma [23]. Subcision surgically releases the pulled down portion of the scar from within, inducing the body's healing response to create blemish free skin cells.Combined with fat transfer, PRP softens the appearance of depressed, roling scars.

- The latest facial rejuvenation procedure is the face lift which combines the power of new PRP technology and facial fillers to minimize the signs of facial aging. This non- surgical procedure promotes new tissue growth to improve overall facial skin tone for a more youthful appearance. The PRP is combined with a facial filler and then re- injected into areas of concern around the face [24]. Patients benefit from this procedure as there is minimal downtime and results can last for over a year. The true "lift" effect is achievable with a combination of fillers, layered with the PRP serum. The fillers provide an instant fill or volume correction and the PRP – injected above the filler – immediately kick-starts a skin regeneration process. Patients can see and feel the effects within minutes as their skin becomes tauter and smoother.The use of PRP with fillers not only enhances the skin tone and texture, but prolongs the effective filler correction for 3 to 6 months longer than when fillers are used alone. Monthly intradermal injections of PRP in 3 sessions have shown satisfactory results in face and neck rejuvenation and scar attenuation. A study showed that a combination of fractional non-ablative (erbium glass) laser therapy with topical application of PRP, resulted in objective improvement in skin elasticity, a lower erythema index and an increase in collagen density as well. Histological examination showed an increase in length of dermoepidermal junction, amount of collagen and fibroblasts in the treated skin.
- Patients who don't want or need fillers can benefit from PRP. The activated PRP serum can be injected just under the skin surface to stimulate the body to make a small amount of its own 'filler'. Although this will not approximate the same results as one gets from a gel filler, some improvement in textural changes can be seen.
- PRP in combination with fractional ablative lasers (carbon dioxide) for deep wrinkles and severe photodamaged skin, has also been shown to reduce commonly encountered, transient adverse effects and decrease the downtime. Fractional laser treatments are known for their ability to retexture skin. Adding PRP takes laser resurfacing to a new level by accelerating healing and increasing desired new collagen formation. Following your laser treatment,activated PRP serum is applied to skin that is ideally suited to accept the wound-healing platelet serum.
- PRP can also be used as 'PRP Facial'(Figs 2A and B) which consists of PRP applied to skin that has been prepared by an automatic microneedle. Thise micro-needling makes tiny "wounds" in the skin which accept the PRP serum and begins the process of collagen creation along with the tissue enhancement from growth factors found in the plasma serum. The micro needling based procedure is also producing great results in terms of minimizing the appearance of both scarring and stretch marks.In scarring, the micro needling is used to break up the fibrous tissues of the scar and the PRP spurs the growth of healthy tissue. For stretch marks, micro needling creates damage over the thinned skin of the stretch mark. PRP then promotes growth of thicker skin (Figs 2A and B).

Advantages of PRP Rejuvenation

- Uses bodys own natural platelets so there is no risk of allergic reaction
- Natural collagen is formed in response to the presence of the activated platelets
- PRP is ideal for the patient who does not want any synthetic fillers
- There is little to no swelling, bruising or lumping as the fluid assimilates in the natural skin environment
- PRP can be used to enhance Laser procedures for faster and improved healing
- PRP Therapy is equally as effective in men as in women

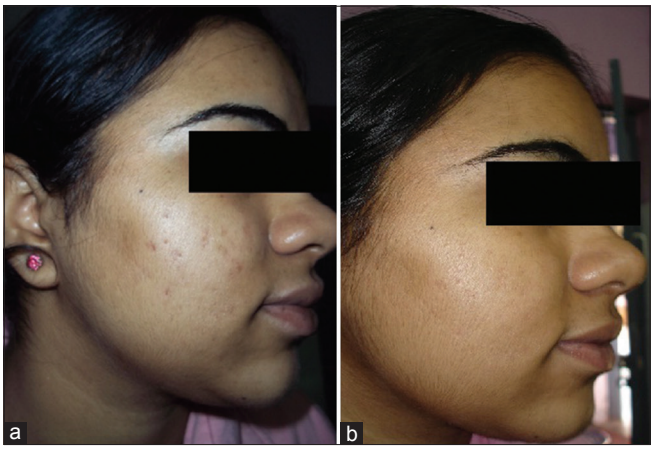

Figure 2: (a and b) Pre and post treatment of a 24 years old girl after 3 sessions of PRP

- Can provide outstanding results either with or without the use of underlying fillers.

CONCLUSIONS

As with all therapies, adequate training and experience are paramount. The beauty of the PRP technique, especially in dermatology and as an adjunctive tool in practice, is that it can be used as part of a multifaceted or layered approach. Significant clinical outcomes can be obtained with concomitant use of light therapies, fillers, and mesotherapy. Due to limited studies on clinical efficacy and safety, further studies are required to investigate the mechanism of action behind the therapeutic effects of these products and their long term safety.Still,the PRP has certain limitations as there is no standardisation in PRP preparation and specific quality parameters in PRP preparation are still lacking.

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Review Article

Antifungal drugs and resistance: Current concepts

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ABSTRACT

Recently, clinical failure and relapses have been observed in patients treated with antifungals. Drug resistance has become an important problem leading to significant negative social, psychological, and occupational health effects and quality of life. Early recognition and treatment is essential to reduce morbidity and possibility of transmission. The increased use, inappropriate prescribing and over the counter sale of antifungal agents has also added in the development of resistance to these drugs. The main biochemical and molecular mechanisms that contribute to antifungal resistance include reduced uptake of the drug, an active transport out of the cell or modified drug metabolic degradation of the cell, changes in the interaction of the drug to the target site or other enzymes involved in the process by point mutations, overexpression of the target molecule, overproduction or mutation of the target enzyme, amplification and gene conversion (recombination), and increased cellular efflux and occurrence of biofilm. Although, there is considerable knowledge concerning the biochemical, genetic and clinical aspects of resistance to antifungal agents, expansion of our understanding of the mechanisms by which antifungal resistance emerges and spreads, quicker methods for the determination of resistance, targetting efflux pumps, especially ATP binding cassette (ABC) transporters and heat shock protein 90, new drug delivery systems, optimizing therapy according to pharmacokinetic and pharmacodynamic characteristics, new classes of antifungal drugs that are active against azole-resistant isolates, and use of combinations of antifungal drugs or use of adjunctive immunostimulatory therapy and other modalities of treatment will clearly be important for future treatment strategies and in preventing development of resistance.

Key words: Antifungal, Resistance, Mechanism, Efflux pump, Measures

INTRODUCTION

Superficial dermatophytoses affecting skin, hair and nail are among the most common public health problem in hot and humid climate of tropical countries like India. Cutaneous mycoses are mostly caused by keratinophilic filamentous fungi called dermatophytes and are classified into three genera: *Trichophyton*, *Microsporum* and *Epidermophyton*. So far, about 30 species of dermatophytes have been identified as human pathogens [1].Although infections caused by dermatophytes are generally limited to the surface regions of the skin, these fungi can behave in a manner invasive, causing deeper and disseminated infection, especially in immunocompromised patients [2]. World Health Organization estimates dermatophytes affect about 25% of the world population [3]. It is also estimated that 30 to 70% of adults are asymptomatic carriers of these pathogens, and that the incidence of this disease increases with age [3]. The estimated life-time risk of acquiring dermatophytosis is between 10 and 20 percent [4]. Climatic factors, as well as social practices, population migration and individual characteristics, such as immune status, may affect the epidemiology of dermatophytosis [3]. In addition, some risk factors have also been associated with onychomycosis, such as age, morphological abnormalities in the nails, genetic factors, poor hygiene conditions and some diseases such as diabetes mellitus and immunodeficiency frames [4,5].

The most common dermatophytes that cause cutaneous mycoses are *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Microsporum canis* and *Trichophyton tonsurans* [6]. Among the fungi isolated from skin infections, the anthropophilic dermatophyte *T. rubrum* is the most frequent amongst clinical cases of tinea pedis, tinea unguium, tinea corporis and tinea

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cruris [4]. while *Trichophyton tonsurans* was the most likely etiologic agent in cases with tinea capitis [7]. *T. rubrum* accounted for 76 percent of all superficial fungal diseases in a representative sample of the U.S. population [7]. Epidemiological studies on occurrence of dermatophytes have also shown that *T. rubrum* is present in 80% of cases and *T. mentagrophytes* in 20% [8]. Among onychomycosis also, *T. rubrum* is the most prevalent dermatophyte and affects children and adults in about 33.2% of the cases identified, followed by *T. mentagrophytes* in 6.3% cases [9]. In a study conducted over a period of three years, Bright et al reported the isolation of dermatophytes in 12.99% of cases of onychomycosis, and *T. rubrum* isolated in 9.04% of patients and *T. tonsurans* and *T. mentagrophytes* 2.54% and 1.41% of subjects, respectively [10].

Mycoses may have significant negative social, psychological, and occupational health effects and can compromise the quality of life significantly. Early recognition and treatment is essential to reduce morbidity and possibility of transmission. Treatment of dermatophytosis is generally long and costly. Dermatophytoses are often associated with relapses following the interruption of antifungal therapy. Recently, clinical failure has been observed in patients treated with antifungals and drug resistance has become an important problem. Although the prevalence of drug resistance in fungi is below that observed in bacteria, mycologists now believe that selective pressure will, over time, lead to more widespread resistance [11].

ANTIFUNGAL DRUGS AND THEIR MECHANISM OF ACTION

The fungal cell wall is composed of multiple layers where mannoproteins and glucan make up more than 80% of the cell wall composition, while chitin represents less than 2% [12]. Mannoproteins are predominantly expressed at the external surface. The plasma membranes of fungi are primarily composed of ergosterol [12]. Keratinocytes are the most numerous cells in the epidermis, forming a physical barrier to micro-organisms and mediate the immune response [3]. Keratinocytes secrete various soluble factors capable of regulating the immune response, such as growth factors [basic fibroblast growth factor (bFGF), transforming growth factor (TGF- α, TGF- β), tumor necrosis factor, interleukins (IL- 1, IL-3, IL-6, IL-7, IL8), and colony stimulating factors [13].

Recent studies have demonstrated that keratinocytes have a different profile of cytokine expression when stimulated by different species of dermatophytes [3]. It was shown that Arthroderma benhamiae, a zoophilic and teleomorph of dermatophyte T. mentagrophytes, induces the expression of several cytokines by keratinocytes which may be involved in triggering an inflammatory response typical of these infections [14]. Both topical and systemic therapies may be used to treat dermatophyte infections. The binding and synthesis of ergosterol, the major cell membrane component, are the targets for several antifungal structures. Topical therapy is generally effective for uncomplicated tinea corporis of small areas and of short duration [15].

Antifungals are grouped on the basis of their structure and mechanism of action: The azoles and triazoles interfere with the ergosterol biosynthesis pathway by inhibiting cytochrome P450-dependent 14--demethylase and blocking the oxidative removal of 14--methyl from lanosterol resulting into the structural changes in the lipid membrane. They are directed against lanosterol 14-alpha-demethylase, a cytochrome P-450 enzyme containing a heme moiety in its active site, in the ergosterol pathway. Azoles have also been reported to inhibit membrane-surface enzymes and lipid biosynthesis [12]. Azoles, include imidazoles (ketoconazole and miconazole) and triazoles (fluconazole, itraconazole, and voriconazole). The topical azoles include clotrimazole, miconazole, oxiconazole, sulconazole, econazole, ketoconazole, sertaconazole. Sertaconazole is fungicidal and has anti-inflammatory and anti-itch properties [16]. Luliconazole is another FDA approved topical imidazole for treatment of interdigital tinea pedis, tinea cruris, and tinea corporis [17].Recently, US Food and Drug Administration (FDA) approved First Topical Triazole, efinaconazole 10% topical solution, for the treatment of onychomycosis [18]. Polyenes include amphotericin B and nystatin. They increase the permeability of the plasma membrane. They bind to fungal membrane sterol, resulting in the formation of aqueous pores through which essential cytoplasmic materials leak out and thereby destroying the proton gradient within the membrane [19,20]. Allylamines (naftifine, terbinafine and the related benzylamine butenafine) and thiocarbamates (tolnaftate and tolciclate) inhibit the conversion of squalene to 2,3-oxidosqualene by the enzyme squalene epoxidase [21-23]. This enzyme blocks ergosterol biosynthesis, leading to intracellular accumulation of squalene which is toxic to fungal cells and leads to cell death [21]. Allylamines are

lipophilic, bind effectively to the stratum corneum and also penetrate deeply into hair follicles [24]. Ciclopirox olamine is a topical fungicidal agent. It causes membrane instability by accumulating inside fungal cells and interfering with amino acid transport across the fungal cell membrane [25]. Candins function by inhibiting the synthesis of β 1,3-glucan which is the major structural polymer of the cell wall [26]. Echinocandins are semisynthetic lipopeptides that competitively inhibit β-glucan synthetase; the mechanism of action is not well defined but does not involve cytochrome P450 inhibition or P-glycoprotein transport [27].Flucytosine inhibits macromolecular synthesis [28]. Morpholines (fenpropimorph and amorolfine) are recently introduced new class of antifungal drug for topical use. The morpholines inhibit two enzymes in the ergosterol biosynthetic pathway, C-14 sterol reductase (ERG24) and C-8 sterol isomerise (ERG2) [29]. As it acts on two different enzymes involved in sterol biosynthesis leading to inhibition of ergosterol biosynthesis in the fungal cell membrane thus making it a potent fungistatic and fungicidal agent. Alteration in the membrane sterol content leads to changes in membrane permeability and disruption of fungal metabolic processes [30,31].In vitro studies have demonstrated that at concentrations of 0.1-100 μg/ml, topical amorolfine induces varying degrees of damage to the nuclear, mitochondrial and plasma membranes of both T mentagrophytes and Candida albicans [32]. An in vitro study has shown topical amorolfine to have the lowest minimum inhibitory concentration (MIC) against various strains of dermatophytes as compared to other topical antifungal agents [33].Thus, azoles, allylamines, and thiocarbamates, and morpholines act through inhibition of the ergosterol biosynthetic pathway by interacting with enzymes involved in the synthesis of ergosterol from squalene.

Systemic therapy may be indicated for tinea corporis that includes extensive skin infection, immunosuppression, resistance to topical antifungal therapy, and comorbidities of tinea capitis or tinea unguium or when the infection involves hair follicles, such as Majocchi granuloma. The preferred treatment for tinea imbricata is griseofulvin or terbinafine, although some resistance has developed to oral griseofulvin [34]. The mode of action of griseofulvin is not completely clear, but it has been speculated that griseofulvin inhibits microtubule binding within the mitotic spindle in metaphase, causing arrest of fungal cell mitosis, weakening the cell structure [20]. A dose of 10 mg/kg/d is effective. In addition, griseofulvin induces the cytochrome P-450 enzyme system and can increase the metabolism of CYP-450–dependent drugs [25]. It is the systemic drug of choice for tinea corporis infections in children [25]. Oral terbinafine may be used at a dosage of 250 mg/d for 2 weeks; the potential exists for cytochrome P-450, specifically CYP-2D6, drug interactions with this agent [34]. Systemic azoles [eg, fluconazole (50-100 mg/d or 150 mg once weekly; itraconazole (100 mg/d); ketoconazole (3-4 mg/kg/d)] function similar to the topical agents, causing cell membrane destruction [34]. Based on E-test for susceptibility of T rubrum, voriconazole was the most active and fluconazole was the least active of the azole drugs [35].Use of oral agents requires attention to potential drug interactions and monitoring for adverse effects [25]. Voriconazole and Posaconazole are two broad spectrum triazole antifungal agents that were recently approved. Ravuconazole [36] is a new member of the azole family and Pramiconazole is another new member of triazole class in the stages of development for the treatment of superficial infections caused by dermatophytes, yeasts and many other fungi [37].

FUNGAL RESISTANCE AND MECHANISMS OF ANTIFUNGAL RESISTANCE

Dermatophytoses are frequently associated with relapses following the interruption of antifungal therapy. Clinical resistance to antifungal agents was rare until the late 1990s, with only isolated cases in patients with chronic mucocutaneous candidiasis [38,39]. The incidence of fungal infections, including resistant infections, has increased during the last few years, and may be due to inadequate or irregular use of drugs or increased incidence of immunodeficiency states [38,40]. The increased use and over the counter sale of antifungal agents in recent years has also resulted in the development of resistance to these drugs. Drug resistance in fungi, especially to azoles, is becoming more prevalent clinically. After the appearance of resistance to griseofulvin, a case of clinical resistance to terbinafine was reported in 2003 [3]. Antifungal-drug resistance is usually quantified using the minimum inhibitory concentration (MIC), in which growth in the presence of a range of drug concentrations is measured over a defined time period according to a standard protocol [41].The lowest drug concentration that results in a significant reduction of growth (usually either 50% or 90% reduction of growth compared with growth in the absence of the drug) is called the

MIC. One well-known limitation of the MIC as a measure of resistance is that it does not always predict the clinical outcome of antifungal therapy [42]. In 1997, the NCCLS proposed methods and guidelines for antifungal resistance testing of yeasts [43]. The NCCLS method for the determination of antifungal susceptibility is currently a standardized technique that can be used to determine the levels of resistance of a yeast strain. The NCCLS document M38-P proposes methods and guidelines for resistance testing of filamentous fungi. There is currently no susceptibility standard for dermatophytes [44].For aid in clinical interpretation of antifungal susceptibility testing, the NCCLS Subcommittee for Antifungal Susceptibility Testing recently established interpretive breakpoints for testing of fluconazole and itraconazole forCandida infections [45].

In vitro demonstration of resistance does not necessarily equate to in vivo resistance [44,46]. Other determinants in the selection of resistance include host-related factors, e.g. immunosuppression, the site and severity of infection and drug pharmacokinetics [47].

Martinez-Rossi described the antifungal resistance mechanisms in dermatophytes [48].The main biochemical and molecular mechanisms that contribute to antifungal resistance include reduced uptake of the drug, an active transport out of the cell or modified drug metabolic degradation of the cell, changes in the interaction of the drug to the target site or other enzymes involved in the same enzymatic process by point mutations, overexpression of the target molecule, overproduction or mutation of the target enzyme, amplification and gene conversion (recombination), and increased cellular efflux [48,49].

Ergosterol is the predominant component of the fungal cell membrane [50] and serves as a bioregulator of membrane fluidity and consequently of membrane integrity in fungal cells [51]. Changes in the sterol and/or the phospholipid composition of the fungal cell membrane and membrane fluidity may result into a decrease in azole uptake by the fungal cell. Similarly, reduced intracellular accumulation of the drug may occur due to increased active transport of the drug out of the cell. Azoles, polyenes, allylamine and thiocarbamates owe their antifungal activities to inhibition of synthesis of or direct interaction with ergosterol. There are as yet no reports of modification of azole antimicrobials as a mechanism of resistance [28]. Resistant strains either exhibit a modification in the quality or quantity of target enzyme, reduced access to the target, or a combination of these mechanisms [28]. Various mechanisms by which microbial cells might develop resistance include [28]. 1. The target enzyme is overproduced, so that the drug does not inhibit the biochemical reaction completely. 2. The drug target is altered so that the drug cannot bind to the target. 3. The drug is pumped out by an efflux pump. 4. The entry of the drug is prevented at the cell membrane/ cell wall level. 5. The cell has a bypass pathway that compensates for the loss-of-function inhibition due to the drug activity. 6, Some fungal enzymes that convert an inactive drug to its active form are inhibited. 7. The cell secretes some enzymes to the extracellular medium, which degrade the drug.

Several studies observed an alteration in the quantity or quality of 14α-demethylase in the expression of resistance to azole antifungal agents [28,52]. A recent study on resistance to fluconazole by comparing sterol composition, fluconazole accumulation, and inhibition of 14α-demethylase by fluconazole, no significant differences in the sterol content of C. krusei and C. albicans were detected [52,53]. Additionally, the enzyme had a low binding affinity for azole antifungals [54]. Overexpression of 14α-demethylase has also been implicated as a mechanism of resistance to azole antifungals [55].However, Ghannoum and Rice suggest that overexpression of target enzyme plays only a limited role in clinical resistance to the azoles [28].

The resistance of dermatophytes to agents inhibitors involves the participation of modifiers target enzymes, overexpression of ABC transporters and stress-related proteins [48]. In T. rubrum two ABC transporters, like TruMDR1 and TruMDR2 were identified as playing important role in development of resistance to many antifungal process and also in the secretion of enzymes [56,57].

A role of upregulation of the ERG11 gene, which encodes the major target enzyme of the azoles lanosterol 14α--demethylase, has been observed in azole-resistant C. albicans and C. glabrata isolates [58,59]. However, other studies have reported no significant change in expression levels of the ERG11 gene in azole resistant clinical isolates of C. glabrata [60,61]. White [62] investigated the target enzyme (Erg11p) susceptibility to fluconazole in cell extracts and observed that a substantial decrease occurred in one of the isolate, corresponding to resistance development. Sequence analysis identified a single

point mutation that resulted in a single-amino-acid substitution 'R467K' [63]. A second significant change observed in the ERG11gene of the resistant isolate was reported by White [63],namely, loss of allelic variation in the ERG11 promoter and in the downstream THR1 gene (which encodes homoserine kinase and is involved in threonine synthesis). The affinity of fluconazole for lanosterol 14α--demethylase containing the mutations Y132H, G464S or R467K was reduced as compared with the wild-type enzyme, confirming that these naturally occurring mutations indeed caused drug resistance in clinical *C. albicans* isolates [64,65]. Although these changes may account for resistance development, they are not the only factors involved and overexpression of the ERG11 gene probably is not critical for the development of azole resistance [66].

A mutation in the gene encoding the enzyme squalene epoxidase target antifungal terbinafine and gave high resistance to this drug against fungi *T. rubrum* [67]. Recently, Walsh et al [68] suggested that C. albicans may possess one or more additional genes encoding ATP-binding cassette MDR-like proteins that are distinct from CDR1, which could participate in the development of azole resistance. In this regard, five CDR genes (CDR1 to CDR5) which belong to the PDR family have been identified in C. albicans [69,70].

Considerable evidence implicating drug efflux as an important mechanism of resistance to azole antifungals is forthcoming recently. Studies [71-74] indicate that fungi possess at least two efflux systems: (i) proteins belonging to the major facilitator superfamily (MFS) and (ii) ATP-binding cassette (ABC) superfamily of proteins. The MFS drug efflux proteins are associated with the transport of structurally diverse compounds and account for a range of resistance to toxic compounds in microorganisms.

Parkinson et al [72] studied susceptible and resistant isolates of C. glabrata and observed that although there was no change in sterol biosynthesis between these two isolates, the resistant isolate accumulated less fluconazole than the susceptible one and the reduced ability of the resistant strain to accumulate fluconazole was a consequence of energy-dependent drug efflux. Clark et al [73] showed that resistant isolates accumulated less fluorescent dye rhodamine 123 (Rh123) than susceptible cells did. Furthermore, active efflux of Rh123 was observed in azole-resistant isolates of C. albicans and C. glabrata, consistent with the activity of an multidrug-resistant MDR transporter. The efflux mechanism associated with movement of Rh123 appears to play a role in azole resistance inC. glabrata but not in C. albicans, suggesting that azole resistance in C. albicans may be mediated by an alternative efflux pump [74].

Sanglard et al in there study of resistant C. albicans isolates obtained from five AIDS patients observed decreased accumulation of fluconazole associated with up to a 10-fold increase in the mRNA levels of the CDR1 gene in some resistant strains while other resistant isolates overexpressed mRNA from the gene encoding BEN^r (CaMDR1) and had normal levels of CDR1mRNA [75]. They suggested that CDR1 is involved in the export of several azole derivatives (including fluconazole, itraconazole, and ketoconazole) while BEN^r confers resistance specifically to fluconazole.

Redding et al in there study of a series of 17 C. albicans isolates cultured from a patient with recurrent episodes (relapses) of oropharyngeal candidiasis observed that patient required progressively higher doses of fluconazole to control the infection after each relapse [76]. The Fluconazole was ineffective after the 14th relapse. Analysis of all isolates by contour-clamped homogeneous electric field electrophoresis confirmed the persistence of the same C. albicans strain throughout all infectious episodes [76]. The sterol content did not differ between susceptible and resistant isolates in this collection, suggesting that the mechanism(s) of resistance does not involve alteration in sterol composition [76].White examined the expression of several genes of interest in all 17 of these isolates, and found that no expression of ERG1 and ERG7 (genes involved in the ergosterol biosynthetic pathway) was detected [62]. He suggested that high-level azole resistance, at least in this series of isolates, results from the contributions of several mechanisms and prolonged exposure of a strain to one azole may lead to overexpression of genes, such as ERG16and CDR1, that result in cross-resistance to other azoles.

Another emerging source of antifungal resistance is the occurrence of a biofilm, the extracellular matrices produced by microbes themselves which serve to help organisms attach to living or non-viable surfaces [66]. It is estimated that about 65% of all human microbial infections involve biofilms and the majority of invasive diseases produced by C. albicans are associated with

biofilm growth [77-79]. It has been demonstrated that drug efflux pumps play a role in the drug resistance of early biofilms [80,81]. In contrast, resistance of mature biofilms does not rely on the known antifungal efflux pumps [80]. It has been hypothesized that a change in membrane sterol composition during biofilm formation might explain resistance to amphotericin B and the azoles [81]. In addition, the MAPK Mkc1p seems to be a regulator of azole resistance in mature biofilms [82].

Resistance to polyene antibiotics is rare, with resistant isolates being confined mostly to the less common species of Candida, such as C. lusitaniae, C. glabrata, and C. guilliermondii [83]. Fryberg suggested that development of resistance occurs by selection of naturally occurring resistant cells, present in small numbers in the population [84]. These naturally resistant cells produce modified sterols that bind nystatin with lower affinity. Athar and Winner, however, have suggested that resistance results from mutation rather than selection [85]. Hamilton-Miller [86] proposed a "biochemical" hypothesis that resistance arises due to changes, either quantitative or qualitative, in the sterol content of the cells. According to this hypothesis, resistant cells with altered sterol content should bind smaller amounts of polyene than do susceptible cells. This decreased binding of polyenes in C. albicans mutants could be attributed to [28] (i) a decrease in the total ergosterol content of the cell, without concomitant changes in sterol composition; (ii) replacement of some or all of the polyene-binding sterols by ones which bind polyene less well, e.g. substitution of ergosterol, cholesterol, or stigmasterol by a 3-hydroxy or 3-oxo sterol [87]; or (iii) reorientation, or masking, of existing ergosterol, so that binding with polyenes is sterically or thermodynamically less favored. Molzahn and Woods [88] reported the isolation and characterization of S. cerevisiae mutants which were resistant to polyenes including nystatin, filipin, and pemaricin. The mutants were allocated to four unlinked genes, pol1, pol2, pol3, and pol5.

Although clinical failure has been observed in patients treated with terbinafine, allylamine resistance in association with clinical use of terbinafine and naftifine has not been found in human pathogenic fungi. However, with the increased use of this agent, resistance may be expected, since Vanden Bossche et al [89] have reported a C. glabrata strain that became resistant to fluconazole and expressed cross-resistance to terbinafine. Sanglard et al reported that CDR1 can use terbinafine as a substrate [90].

Fungi also show adaptive responses to environmental stimuli by activation of several signal transduction pathways in stress conditions [3]. The antifungal drugs induce cellular stress responses needed to overcome its toxic effects, allowing the survival of the fungus [3]. A number of genes involved in adaptation and response to stress and to elucidate the mechanism of action of drugs such as terbinafine, acriflavine, amphotericin B, fluconazole,etc, have been identified [91,92]. Gene expression studies have also contributed to the assessment of the effect of new antifungal agents for T. rubrum, as PHS11A and PH11B recently developed, which act by inhibiting the enzyme fatty acid synthase [93].

CLINICAL IMPLICATIONS, PREVENTION OF ANTIFUNGAL RESISTANCE AND FUTURE DIRECTIONS

The primary factor driving the emergence of antifungal resistance appears to be resulting from the increased use and inappropriate prescribing of systemic antifungal agents [94]. There is no clear evidence as to what dosing strategy should be used during treatment and prophylaxis to best avoid resistance [95]. Ghannoum and Rice [28] suggested measures to avoid and suppress the emergence of antifungal resistance which include (i) prudent use of antifungals, (ii) appropriate dosing with special emphasis on avoiding treatment with low antifungal dosage, (iii) therapy with combinations of existing agents, (iv) treatment with the appropriate antifungal (in cases where the etiological agent is known), and (v) use of surveillance studies to determine the true frequency of antifungal resistance. An increased emphasis on rapid diagnosis of fungi and optimizing therapy according to pharmacokinetic and pharmacodynamic properties and thus reducing exposure to low concentrations of systemic agents should be focussed upon [94,96]. The recent approval of a reference method for the antifungal susceptibility testing of yeast is encouraging and provides a means for performing surveillance studies [97].

Use of combinations of antifungal drugs or use of adjunctive immunostimulatory therapy may be more effective in preventing development of resistance. A variety of immunosuppressive compounds, including cyclosporin and D-octapeptides [98], have been tested and found to counteract antifungal resistance due to efflux pumps. Cernicka, et al. screened a synthetic compound library and identified a chemical that increased

the sensitivity of a drug-resistant strain of S. cerevisiae to fluconazole [99].The compound also increased sensitivity of the pathogenic yeasts Candida albicans and Candida glabrata that expressed efflux pumps [99].

Recently, a team of researchers using detailed genetic, biochemical, and molecular approaches, identified a mechanism controlling multidrug resistance in fungi [100]. They found that yeast induce multidrug resistance via a molecular switch similar to one that removes drugs and other foreign substances from human cells. When the yeast protein Pdr1p binds to anti-fungal drugs or other chemicals, it switches on molecular pumps that remove the drugs from the cell. The research team also showed that this chemical switch also controls drug resistance in an important human pathogenic fungus, Candida glabrata. In humans, a protein called PXR is the drug sensor that turns on genes involved in detoxifying and removing drugs from cells [100].After binding to drugs, the Pdr1p protein partners with another key mediator of genetic switches called Gal11p. In-depth molecular and structural studies identified the specific area of Gal11p that binds to Pdr1p to induce multidrug resistance [100,101].

A new way to fight drug-resistant fungal infections targeting heat shock protein 90 has been suggested [102]. The Hsp90 chaperone protein provides one mechanism to link temperature with the signalling cascades that regulate morphogenesis, fungal development and virulence. Targeting the molecular chaperone Hsp90 or its downstream effector, the protein phosphatase calcineurin, abrogates resistance to the most widely deployed antifungals, the azoles, which inhibit ergosterol biosynthesis [103]. It was observed that the fungal pathogen Candida albicans is able to resist drug treatment because of an associated molecular chaperone protein called heat shock protein 90 (Hsp90) whose compromising function renders the fungal-fighting drugs known as echinocandins more effective at killing C. albicans laboratory strains and clinical isolates. Hsp90 acted as a kind of thermostat for C. albicans and shutting down the protein's temperature-sensitivity can shut down the spread of infection. It has been suggested that interfering with Hsp90 function provides a powerful and much-needed strategy to render existing antifungal drugs more effective in the treatment of life-threatening fungal infections [98]. Due to the high degree of conservation in Hsp90, many of the connections in C.albicans may be extrapolated to other fungal pathogens or parasites [98,99].

Photodynamic therapy has been suggested as an alternative treatment for therapy resistant patients, however, the data on this are still limited and in some cases, the aggravation rates are higher than with other methods [104,105,106]. An alternative non-invasive treatment protocol utilizing combinations of VIS-NIR laser beams in association with broadband beams of UV, B and R- LEDs, without usage of photosensitizers, with minimal side effects, for therapy resistant patients suffering from Tinea Pedis, Pityriasis versicolor, or Mycetoma has been demonstrated [107].

CONCLUSION

At this time, antifungal drug resistance is clearly becoming a common problem in patients and is inevitable due to wide availability and use of these agents. There is considerable knowledge concerning the biochemical, genetic and clinical aspects of resistance to antifungal agents. However, sample selection and inadequate information regarding denominators limit current epidemiological data [108,109]. Several variables need to be considered when trying to minimize the risk for development of resistance, including type of drug, intermittent versus continuous dosing during prophylaxis or treatment, the amount of drug administered, the length of treatment, and the immune status of the patient [29]. The availability of molecular genetic tools has led to a rapid expansion in our understanding of the mechanisms by which antifungal resistance emerges and spreads and promises help to develop novel and effective compounds for future use. Research works to study the mechanisms of antifungal resistance, the development of experimental systems in which individual resistance mechanisms can be studied, and establishment of a reproducible method of susceptibility testing will be important components of a strategy to limit the emergence of resistance to these agents and to develop safer and more potent compounds for the future. The current techniques to determine the MIC of a drug include both macro- and microdilution broth methods. However, these remain a time-consuming techniques and quicker methods for the determination of resistance are needed. Targetting efflux pumps, especially ATP binding cassette (ABC) transporters and heat shock protein 90 are the new ways under investigation to fight drug-resistant fungal infections. There is a clear need for the next generation of antifungal agents. New classes of antifungal drugs that are active against azole-resistant isolates, such as the cationic peptide histatin [110] will clearly be

Table 1: Antifungal agents against dermatophytes

Chemical group	Site of action	Target
Allylamines (Terbinafine, Naftifine)	Ergosterol biosynthesis	Squalene epoxidase
Azoles	Ergosterol biosynthesis	Cytochrome P450
Imidazoles		14α- Lanosterol
Bifonazole, Clotrimazole, Econazole, Ketoconazole, Miconazole		Demethylase
Triazoles		
Fluconazole, Itraconazole, Terconazole		
Morpholines (Amorolfine)	Ergosterol biosynthesis	Sterol reductase and Isomerase
Polyenes (Amphotericin B, Nystatin)	Ergosterol	Membrane barrier function
Thiocarbamate (Tolnaftate)	Ergosterol biosynthesis	Squalene epoxidase
Griseofulvin	Fungal mitotic apparatus	Sliding of microtubules

important for future treatment strategies [29]. It is likely that the future of antifungal drug therapy lies in drug combinations and improving the immune status of the host. A combination of azoles and cytokines may be an important therapeutic strategy for fungal infections in immunocompromised individuals [111].Finally, new drug delivery systems may have a place in the treatment of antifungal-drug-resistant infections [29]. As drug resistance continues to develop in pathogenic fungi, ongoing research and developments in the understanding of resistance will find ways to formulate strategies to overcome the resistance.

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Our Dermatology Online

Review Article

Targeted Phototherapy (newer phototherapy)

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ABSTRACT

Conventional phototherapy uses a whole body cabinet or body part machine such as hand, foot or scalp machines. They have many disadvantages due to which new phototherapy technique was then developed to overcome this situation. This new technique is called targeted phototherapy which includes excimer laser, intense pulse light system (IPL), photodynamic therapy and ultraviolet (UV) light source with a sophisticated delivery system which is easy to be operated by hands. The mechanisms of action of targeted phototherapy systems are similar to those in conventional UVB/UVA therapy. They have many advantages like less chances of side effects, avoidance of exposure of unnecessary sites, faster response, shortening of the duration of treatments. But they have disadvantages like high costs and inability to use for extensive areas. This review article discusses targeted phototherapy in considerable to the mechanism of actions and advantages and disadvantages in comparison to the conventional phototherapy.

Keywords: Conventional phototherapy; targeted phototherapy; excimer laser; intense pulse light system (IPL); photodynamic therapy; ultraviolet (UV) light

INTRODUCTION

Phototherapy is a therapeutic strategy in dermatology for treating several skin diseases. Conventional phototherapy uses a whole body cabinet or body part machine such as hand, foot or scalp machines [1,2]. It includes Broadband UVB therapy, Ultraviolet A (UVA) therapy, SUP or selective ultraviolet phototherapy (310-318) therapy, Narrowband UVB (311 nm). Ultraviolet A1(UVA1) therapy Phototherapy is used for a wide variety of skin diseases. There has been considerable progress in cellular and cutaneous photobiology leading to improved understanding of different photodermatoses and their treatment. However, the developments in phototherapy have been comparatively slow, as reflected in a recent publication that "developments in phototherapy have not kept pace with scientific progress, as has been the case with radiotherapy" [3].

The conventional phototherapy have many disadvantages like exposing uninvolved areas, slow delivery system and lengthy treatment sessions, multiple and frequent visits to clinic, difficulty in treating certain areas (such as genitalia, oral mucosa, ear, etc.), difficulty in treating children who may feel intimidated by the large machines, large office space required to house the bulky machines [4]. Due to those disadvantages of conventional phototherapy, a new phototherapy technique was then developed to overcome these situations. This technique was called targeted phototherapy or also known as concentrated phototherapy, focused phototherapy, micro phototherapy and localized phototherapy. This review mainly focussed on this newer technique called targeted phototherapy.

Targeted phototherapy is defined as a therapeutic method using a device that delivers laser light or ultraviolet light spectrum of a specific wavelength focused on specific body areas or lesions. This definition includes different technologies used such as excimer laser, intense pulse light system (IPL), photodynamic therapy, and ultraviolet (UV) light source with a sophisticated delivery system which is easy to be operated by hands [3].

MECHANISM OF ACTIONS

Most targeted phototherapy devices (laser or non-laser type) emit radiation in the UVB range with

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peak emission in the narrowband wavelength (around 308-311 nm), while some light-based non laser machines emit UVA radiation also. Hence mechanisms of action of targeted phototherapy systems are similar to those in conventional UVB/UVA therapy [2,5-8]. Ultraviolet light has a spectrum which is divided into 3 parts according to their wavelengths, namely UVC with the shortest wavelength (200-290 nm), UVB with the intermediate wavelength (290-320 nm) and UVA with the longest wavelength (320 -400 nm). UVA is then divided into UVA1 (340-400 nm) and UVA2 (320-340 nm)[9,10]. The light sources include broadband UVB (BB-UVB) with a wavelength of 290-320 and a peak at 313 nm, narrowband UVB (NB-UVB) with a wavelength of 311-313 nm, UVA (320-400 nm, peaks at 355 nm) and UVA1 (340-400 nm, peaks at 365 nm). Excimer laser which emits monochromatic UV light has various wavelength ranges depending on the molecules used, especially in the field of dermatology XeCl laser with a wavelength of 308 nm. Various mechanisms were found and it was proposed that phototherapy can give either in systemic or local effect. Ultraviolet B rays have shorter wavelengths so that they do not penetrate as deeply as UVA rays do, but UVB rays have more energy. Ultraviolet B phototherapy primer effect is on the function of keratinocytes and Langerhans cells. The effectiveness of UVB therapy in psoriasis especially lies on its anti proliferative effects. The decrease of pruritus after the treatment with both BB-UVB and NB-UVB is caused by cell mast apoptosis [11]. In the use of targeted BB UVB phototherapy, NB UVB and excimer laser, T cell apoptosis was found [12-14]. The apoptosis mechanism may be caused by the damage of the epidermis and dermis cells which are susceptible to UV light exposure. Ultraviolet B rays cause DNA damage and formation of pyrimidine dimer [15]. In addition to T cell apoptosis, UVB radiation triggers changes in cytokine production, local immunosuppression, stimulation of melanocyte-stimulating hormone (MSH), increases migration, proliferation of melanocytes and melanogenesis [16,17]. A two-step effect of NBUVB has been proposed – both of them may occur simultaneously although. Firstly, there is immunomodulation (local as well as systemic), leading to down regulation of immune attack against the melanocytes. Subsequently, the melanocytes are stimulated to migrate to the epidermis and synthesize melanin [18]. NBUVB phototherapy increases synthesis of IL-1, TNF-α and LTC-4 and these cytokines induce melanocyte mitogenesis, melanogenesis and melanocyte migration. However, the roles of IL-1 and TNF-α in melanogenesis are controversial and contradictory, as has been observed in some studies. It was proposed that TNF-α inhibits the expression and activity of tyrosinase, the key enzyme in melanin synthesis. This inhibition of melanogenesis induced by TNF-α is secondary to activation of nuclear-factor κB [19]. IL-1 stimulates synthesis of endothelin-1, which is mitogenic and melanogenic. The contradiction is that IL-1β has been found to decrease proliferation of melanocytes and melanogenesis, while IL-1β decreases melanocyte tyrosinase activity without any effect on proliferation [20]. It was also observed that the increase of expression of endothelin-1, IL-1 and tyrosinase in human keratinocytes *in vivo* and *in vitro* after UVB irradiation suggested the possible mechanism of repigmentation [21]. Release of prostaglandins (PGE_2 and PGF_2) is another mechanism of action of phototherapy [22]. PGE_2 is synthesized in the skin and regulates melanocyte and Langerhans cell function, and promotes melanocyte mitogenesis [23]. Ultraviolet A has a longer wavelength, so it can reach the dermis and have an effect on fibroblasts, dermal dendritic cells, endothelial cells, T lymphocytes in the dermis and granulocytes. In atopic dermatitis, UVA is shown to cause apoptosis of T helper cells in the skin with eczema lesions through FAS/FAS ligand system [24]. In addition, UVA and UVA1 irradiation may also decrease histamine release by basophils and mast cells [25]. The combination between UVA and psoralen (PUVA) has a more complex mechanism. Psoralen undergoes intercalation in the double-stranded DNA. Ultraviolet A exposure causes the formation of 3,4 or 4',5' cyclobutane mono adduct with pyrimidine bases on a single photon absorption. The double helix DNA then undergoes a cross linking process when the absorbed second light photon by 2monoadducts forming a bifunctional adduct. DNA replication is inhibited by the cross-linking results in cell cycle disruption and decreased epidermal proliferation. Once psoralen excited by the photons, it can react with oxygen molecules to form reactive oxygen species (ROS),which can cause mitochondrial dysfunction and apoptosis of Langerhans cells, keratinocytes and lymphocytes. Both UVA and UVB cause decreased expression of ICAM-1 and increased levels of immunosuppressive cis-urocanic acid that it can depress cellular immune response and inhibit Langerhans cells activities [26]. Although the mechanism of action of targeted phototherapy is similar to the mechanism of action of conventional UVB/UVA phototherapy, it is thought to be more aggressive because the dose given can be higher than

the erythemogenic dose, which results in a greater efficacy due to its ability to deliver the energy to the deeper dermis layer [27-33].

Advantages [30]

Several advantages have been claimed for targeted phototherapy: Exposure of involved areas only and sparing of uninvolved areas, thus minimizing acute side effects such as erythema and long-term risk of skin cancer over unaffected skin; quick delivery of energy and thereby shortened duration of treatment; delivery of higher doses (super-erythemogenic doses) of energy because uninvolved areas are not exposed, higher doses of energy can be delivered selectively to the lesions, thereby enhancing efficacy and achieving faster response; shortening of duration of treatment, leading to less frequent visits to clinic and is more convenient for the patient; the maneuverable hand piece allows treatment of difficult areas such as scalp, nose, genitals, oral mucosa, ear, etc; easy administration for children as delivery is hand-held and it also occupies less space.

Disadvantages [30,31]

Targeted phototherapy devices have certain disadvantages; they are more expensive. Also, they are not adequate to treat extensive areas in view of the cost of treatment and time involved in treatment. They are not recommended for use if lesions occur over more than 10% of the body area.

CONVENTIONAL PHOTOTHERAPY

Scherschun, et al retrospectively analyzed their experience of treating vitiligo with NB-UVB administered as monotherapy 3 times a week [34]. Five of their seven patients achieved more than 75% repigmentation with a mean of 19 treatments, whereas the remaining two patients had 50% and 40% repigmentation after 46 and 48 treatments respectively. In a recent meta-analysis of non-surgical therapies in generalized vitiligo by Njoo, et al [35] higher success rates were observed with NB-UVB (63%) than with oral PUVA (51%). As in the western population, NB-UVB phototherapy produces a cosmetically good color match in Indian patient [36]. Its distinct advantages over PUVA include the lack of psoralen related side effects and precautions, cosmetically better color match, and its safety in children. However, the relative stability of NB-UVB induced repigmentation over PUVA, its maximum safe duration and cumulative dose allowed still remain to be determined.

The NB-UVB lamp was developed as a 'new' UVB phototherapy source with an emission spectrum within the therapeutic waveband for psoriasis phototherapy. NB-UVB phototherapy has a higher ratio of therapeutic to erythemogenic activity, resulting in increased efficacy, reduced incidence of burning and longer remission. Results from two therapeutic action spectroscopy studies indicated that wavelengths of the range 295-320 nm are effective in clearing psoriasis, whereas shorter wavelengths are more erythemogenic and wavelengths longer than 320 are less therapeutic [37,38]. Subsequent clinical studies have tended to report significantly greater improvement of psoriasis with NB-UVB including reduced incidence of burning episodes, increased efficacy and longer remission when compared with broad band sources [39]. When NB-UVB phototherapy and PUVA were compared, there was little overall difference in efficacy [40,41].

Prophylactic low dose NB-UVB has been found to be useful in various predominantly UVA induced photosensitivity disorders like polymorphic light eruption, actinic prurigo, hydroa vacciniforme and the cutaneous porphyrias by providing a 'hardening photoprotective' effect. A typical course involves 10-15 treatments given in early spring [42]. We have also observed a beneficial role of NB-UVB in patients with airborne contact dermatitis to Parthenium hysterophorus, a frustrating problem for both the patient and the physician [43].

NEWER/TARGETTED PHOTOTHERAPY

Excimer laser/excimer light (308 nm)

The various uses of Excimer laser include palmoplantar pustular psoriasis, plaque-type psoriasis, nail psoriasis, chronic atopic dermatitis of the hands, non-atopic dermatitis of the hands and alopecia areata. The common side-effects include intense erythema and, more rarely, blisters, but these were are usually well tolerated [32].

Steven Paul Nisticò M.D., Rosita Saraceno M.D., Caterina Schipani M.D, et al (2009) showed different applications of Monochromatic Excimer Light in skin diseases on 152 patients with stable and localized plaque psoriasis, 47 with palmoplantar psoriasis, 7 with palmoplantar pustulosis, 32 with vitiligo, 11 with prurigo nodularis, 9 with mycosis fungoides

stage Ia, 8 with alopecia, 5 with localized scleroderma, 5 with genital lichen sclerosus, and 3 with granuloma annulare showed complete remission in more than 50% of patients with plaque psoriasis and palmoplantar dermatoses, respectively, complete remission in all patients affected by mycosis fungoides, excellent repigmentation in one third of vitiligo patients, hair re growth in three patients with alopecia areata, an overall improvement in prurigo nodularis, a partial remission in patients affected by localized scleroderma and a complete remission in most of the patients with genital lichen sclerosus and granuloma annular [33].

DUALIGHT

(Previously called Theralight) emits both UVA radiation in the range 330-380 nm and UVB in the range 290-330 nm with peak at 303 nm [5]. The system has a 2-meter long fiber-optic delivery system with a spot size of 4 cm^2. UVA intensity is 10-550 mW/cm^2 for 3.63-cm^2 exit aperture, while UVB intensity is 50-250 mW/cm^2 for 3.63-cm^2 exit aperture.

B CLEAR TARGETTED PHTOCLEARING SYSTEM

B clear system is mercury-based noncoherent UVB radiation with a therapeutic wavelength of 290 to 320 nm and pulse width of 0.5 to 2.0 seconds. Fluence ranges from 50 to 800 mJ/cm^2 in increments of 10 mJ/cm^2. Its disadvantage is that only UVB range is available, unlike Dualight, which delivers both UVA and UVB ranges [2,44].

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) involves the use of photochemical reactions mediated through the interaction of photosensitizing agents, light and oxygen for the treatment of malignant or benign diseases. Photodynamic therapy is a 2-step procedure. In the first step, the photosensitizer is administered to the patient by one of several routes (eg, topical, oral, intravenous) and it is allowed to be taken up by the target cells. The second step involves the activation of the photosensitizer in the presence of oxygen with a specific wavelength of light directed toward the target tissue. Then, sunburn reaction will occur which usually heals by 4-8 weeks. Because the photosensitizer is preferentially absorbed by hyperproliferative tissue and the light source is directly targeted on the lesional tissue, photodynamic therapy achieves dual selectivity, minimizing damage to adjacent healthy structures. The photosensitizers are aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), Porfimer sodium (Photofrin™), Benzoporphyrin derivative monacid ring A, Tin ethyl etioporphyrin, Lutetium texaphyrin [45-48].

Light at a wavelength corresponding to a peak of the porphyrin excitation spectrum in tissues is used to most efficiently generate a therapeutic effect. The Soret band (approximately 405-420 nm) is the most important excitation peak of protoporphyrin IX and is included in the spectral output of the US Food and Drug Administration (FDA)– approved Blu-U device, which is used with ALA. Another peak in the excitation spectrum of porphyrins includes a red peak at approximately 635 nm, which is targeted by different devices, including those approved to be used with MAL [34,36-38].

Light sources used in PDT include laser or non laser light. Laser light has the advantages of being [45]:

- monochromatic (exactly one colour/wavelength that corresponds with the peak absorption of the photosensitising agent)
- coherent (able to focus light waves to specific site)
- intense (high irradiance allowing for shorter treatment times)

The only FDA-approved indication for ALA photodynamic therapy (PDT) and MAL photodynamic therapy in dermatology is currently the treatment of AKs. Common off-label uses include the treatment of BCC, photoaging, acne vulgaris, and Bowen disease [49-51].

Side effects from PDT are due to the treated area being sensitive to light. The photosensitivity usually lasts about 24 hours (depending on the specific agent). Side effects may include [45]:

- Burning/stinging sensation
- Swelling and redness
- Crusting
- Itchiness
- Peeling and blisters
- Skin infections

The treated area should be protected from light exposure using a dressing. A local anaesthetic such as lignocaine (lidocaine) spray may be applied to

the treatment area before or during Stage 2 of the procedure to help relieve pain [52].

The author experience is, although excimer light is effective for treatment of stable localised vitiligo and psoriasis, its efficacy is limited for treatment of alopecia areata.

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Our Dermatology Online

Clinical Image

Holter induced contact dermatitis

Tasleem Arif

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CLINICAL IMAGE

A 15 year old boy visited our dermatology outpatient department (OPD) with two days history of multiple reddish papules and pustules on his chest referred from General Medicine department. There is history of pruritis associated with the eruption. On detailed history, patient revealed that he had recurrent episodes of syncope. His documents revealed an electrocardiogram (ECG) with premature atrial contractions (PAC's). With this clinical background, the general physician had referred him to a tertiary care hospital for cardiological consultation where he was advised 24-hour Holter monitoring. Patient admitted that during Holter monitoring he had mild itching and on the day of Holter removal he noticed mild erythema associated with itching on the chest where Holter was applied. Next day, he experienced severe itching and there were multiple reddish raised lesions on the chest. On examination his vitals were stable. Dermatological examination revealed multiple bright red erythematous papules and pustules present on the upper central chest with some lesions present more towards on the left side (Fig. 1). Many of these papules and pustules were present in a follicular distribution (Fig. 2). With such a history and further supported by cutaneous examination, a diagnosis of Holter induced contact dermatitis was made. However, the author couldn't document contact dermatitis by patch testing due to the unavailability of the same. The patient was prescribed levocetrizine 10 mg daily. For topical application, he was prescribed a combination of mometasone furoate 0.1% w/w and fusidic acid 2% w/w cream. After one week, the lesions regressed completely.

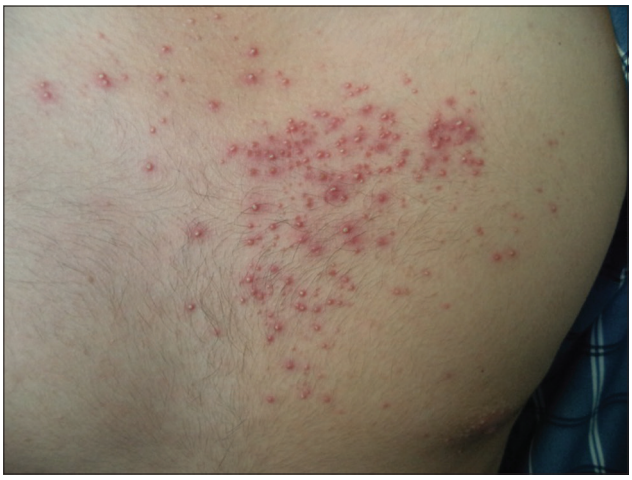

Figure 1: Multiple erythematous papules and pustules over chest in a 15 year old boy

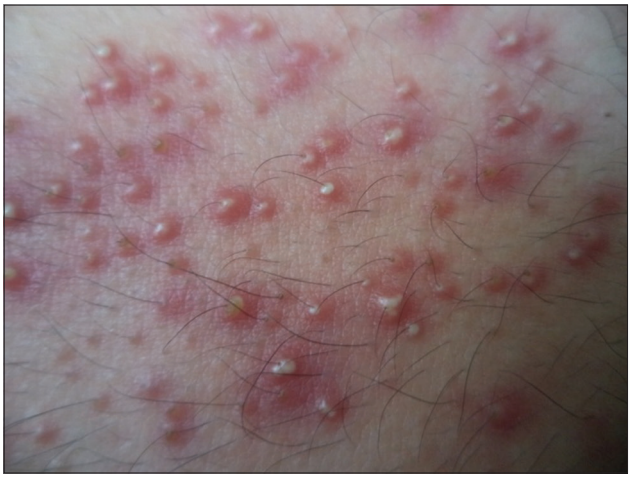

Figure 2: Close view of bright red erythematous papules and pustules with many of these lesions in a follicular distribution

This was probably a case of Holter induced contact dermatitis. Such cases are not so uncommon but they are rarely reported in the medical literature. Probably, ECG jelly used for Holter, continuous mechanical occlusion caused by the machine on the skin and material make up of the Holter itself can be

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contributory in causing such eruption. Therefore, a patch test can help to find the actual cause.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article and any accompanying images.

Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Clinical Image

Neuroglial heterotopia of the scalp in an adult

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Sir,

We report a 50 year-old man who presented with a swelling of the occipital scalp which was noticed at birth and increased progressively in size. At physical examination the lesion was firm and alopecia (Fig. 1). Clinically, the diagnosis of benign adnexal tumor was suggested and a surgical resection of the lesion was performed. Preoperatively, the lesion did not adhere to the occipital bone and had no connection with the brain. Grossly, the tumor was nodular, white, ill-defined and measured 1.2 cm of diameter. Histological examination showed a well-circumscribed lesion of the deep dermis composed of mature glial tissue (Fig. 2). It consisted of a dense network of columns and clusters of neural cells within a fibrillar, fibrous and hyaline tissue (Fig. 3). Sections of nerves were also seen. The immunohistochemical study showed a diffuse and intense staining of cells with GFAP (glial fibrillary acidic protein) and S100 protein (Fig. 4). The cytokeratin was negative. These features confirmed the diagnosis of a neuroglial heterotopia. At 3 years of follow-up, the patient was asymptomatic and there was no recurrence.

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

Neuroglial heterotopia is a rare, non-hereditary malformative lesion, defined by the presence of an ectopic glial or neuroglial tissue outside the brain. It must be distinguished from meningeal heterotopias that are more frequent and derived from the brain and the spinal cord meninges [1].

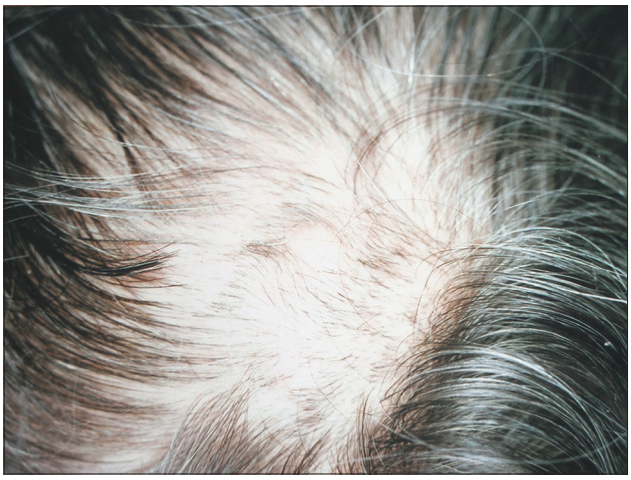

Figure 1: Occipital bald scalp plaque.

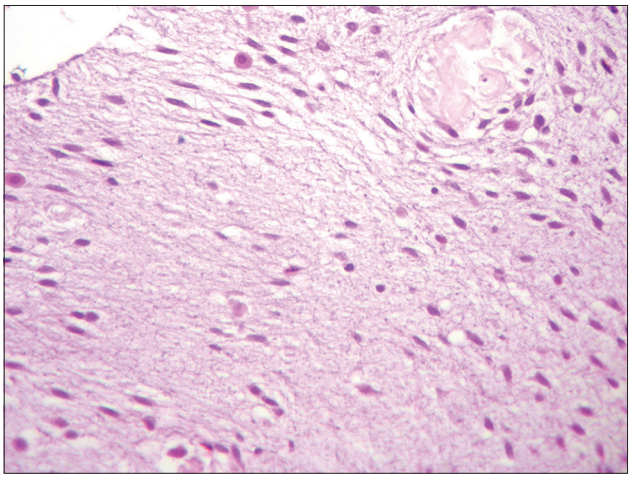

Figure 2: Range of neural and glial cells with eosinophilic fibrillar cytoplasm, and small, rounded nuclei, without atypia and mitosis (HEX40)

This congenital lesion is found mainly in the nose and less frequently on the palate, tongue, orbit, lung and chest wall [1]. The location at the scalp is extremely rare. Only 13 cases were described in the English medical literature.

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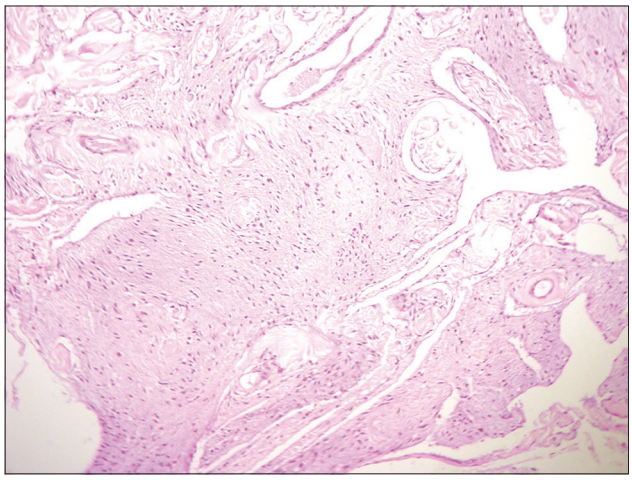

Figure 3: Cells arranged in layers within a hyalinized fibrous tissue (HEX20)

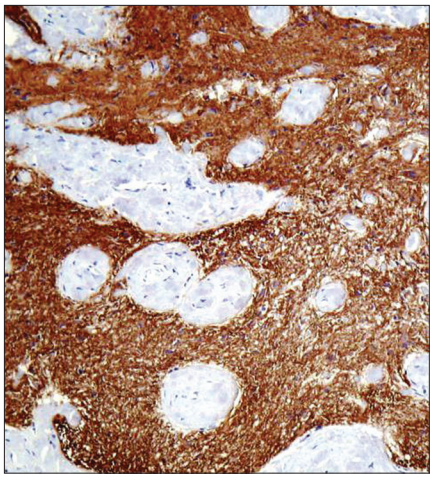

Figure 4: Diffuse and intense staining of neuroglial cells with GFAP

The exact pathogenesis of these lesions is unknown.

Neuroglial heterotopia is usually diagnosed in children, rarely in adults [1].

Clinically, it is a nodular lesion often discovered at birth, measuring 2 and 4 cm in diameter and increasing proportionately with the child's growth. It is solitary, circular, skin-colored, pink or bluish, mobile [1-3].

Grossly, the lesion is firm, nodular and has a grey-white cut surface. Histological examination showed a glial proliferation made of clusters of round or oval cells, composed mainly of astrocytes sitting in a neurofibrillary and richly vascularized tissue. These cells have central nuclei, without atypia and nucleolei. The cytoplasm is fibrillar and finely granular. Some astrocytes are giant and multinucleated like ganglion cells. An associated neural component or sometimes ependymal or choroid plexus structures can be found. However, purely glial appearance is most frequently described in the literature [2].

The immunohistochemistry witch shows positivity of glial component to GFAP (glial fibrillary acidic protein) and S100 protein [1,2].

The main differential diagnosis is with encephalocele which have the same clinical and histological appearance but encephalocele is connected to the sub-arachnoid space by a cavity [1].

The treatment consists of total excision of the tumor. Incomplete excision may cause recurrences. Furthermore, no malignant transformation has been reported in the literature.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Letter to the Editor

Morphea and vitiligo-A very uncommon association

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Sir,

Morphea represents a localized form of scleroderma where there is predominant skin involvement, with occasional involvement of subjacent muscles. However, it usually spares the internal organs [1]. Morphea has been associated with several autoimmune diseases like mixed connective tissue disease, dermatomyositis, pemphigus, myasthenia gravis, bullous pemphigoid, systemic sclerosis, Hashimoto's thyroiditis, etc [2,3]. The association of morphea with vitiligo has been rarely reported. In this article we report a 29 year female with concomitant vitiligo and plaque type morphea over her lower back.

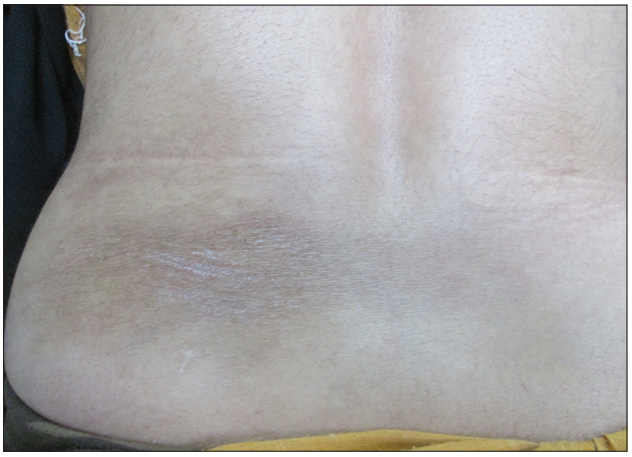

Figure 1: Ill-defined brownish hyperpigmented indurated plaque over lower back.

CASE REPORT

A 29 year female reported to our dermatology department with a chief complaint of brownish hyperpigmentation, thickening and hardening of the skin on the lower back on the left side for the last three months. There is history of mild pruritis. There is no history of any discoloration in the digits on exposure to the cold. There is no history of sour eructation's, epigastric discomfort or constipation. There are no similar complaints of hardening of skin on hands and feet. She denied any history of preceding trauma or application of some topical medications prior to the complaints. There is no such history in her family members. The patient gives history of vitiligo for the last five years localized to scalp with associated whitening of hair. On examination, there was an ill-defined hyper pigmented, indurated, shiny plaque around the size of 8cm × 4cm on the lower back towards the left side extending up to the midline (Fig. 1). The plaque showed loss of appendages. There was no associated digital pallor or cyanosis. Nail fold capillaroscopy was unremarkable. The scalp on the occipital region of the patient revealed a hypo pigmented patch about the size of 5cm× 4cm with associated leucotrichia (Figs 2 and 3). A 5mm punch skin biopsy on the back was sent for histopathological examination which showed atrophy of the epidermis, perivascular lymphocytic and plasma cell infiltrates in the dermis and subcutaneous tissue. There were thickened and closely packed bundles of collagen. The adnexal structures were scanty. The typical clinical findings and further supported by histopathology confirmed the diagnosis of morphea in our patient. Her routine laboratory tests were unremarkable. Her anti-nuclear antibody was within normal limits. Her thyroid function tests were unremarkable. She was prescribed topical tacrolimus 0.1% ointment to be applied twice daily. After three months of treatment, her skin pigmentation and induration improved.

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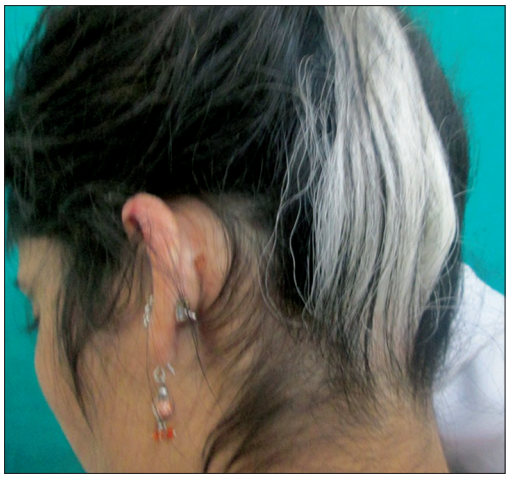

Figure 2: Vitiliginous patch with associated leucotrichia on the occipital region.

Figure 3: Close view of the vitiliginous patch and the associated leucotrichia.

DISCUSSION

Scleroderma comprises a spectrum of disorders which is characterized by thickening and/or hardening of the skin eventually leading to the fibrosis of the tissues. Broadly, it has been divided into the systemic and localized forms. The localized type of the scleroderma is called as morphea. In morphea, there is predominant skin involvement, with occasionally involving the subjacent muscles. The internal organs are usually spared in morphea in contrast to the systemic sclerosis [1]. However, extra cutaneous features have been reported from childhood morphea cases [4]. Paterson, et al has classified morphea into morphological types viz., plaque, linear, generalized, deep and bullous [5,6]. Our patient had plaque type of morphea.

Morphea is considered to be an immune-mediated disease which has been suggested by various studies. This is supported by increased levels of circulating cytokines in the patients of morphea including interleukin-2 (IL-2) receptor, soluble CD4 and CD8, CD23, CD30, IL-6 receptor, IL-13 and toxic necrosis factor (TNF), soluble vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, antiendothelial cell antibodies, etc. Various organ-specific auto antibodies have been demonstrated in the serum of these patients and their relatives. Another evidence is the association of morphea with other autoimmune diseases. Morphea has been seen in association with carpal tunnel syndrome, nephritis, dermatomyositis, pemphigus, primary biliary cirrhosis and myasthenia gravis [2]. The association of morphea with vitiligo is an uncommon one and hence inspired the authors to report the same.

Bonilla-Abadia (2012), et al have described a peculiar case of morphea as a part of multiple autoimmune syndrome (MAS) in which a 53 year-old female patient with plaque type morphea over legs was associated with vitiligo, pneumonitis, autoimmune thrombocytopenic purpura and central nervous system vasculitis [7]. When three or more well-defined autoimmune diseases are present in a single patient, the condition is known as MAS [8]. However, in our case, there was no systemic involvement other than the associated vitiligo. Moreover, her anti-nuclear antibody and thyroid function tests were unremarkable. However, the antibody profile specific for other organs was not done.

Generally, the prognosis of morphea is considered to be good. Rarely, it has been reported to evolve into the systemic sclerosis. The disease activity may last for three to four months in most cases [9]. However, regular follow up is warranted to screen for the development of other concomitant systemic autoimmune disorders like MAS.

The treatment of morphea has been updated. Various treatment options include topical tacrolimus, Imiquimod, phototherapy, calcipotriol in combination with betamethasone dipropionate, cyclosporine, D-penicillamine, photopheresis, etc [10]. Our patient was already receiving treatment for vitiligo. For morphea, she was prescribed topical tacrolimus 0.1% ointment applied twice daily. After three months of treatment, skin pigmentation and induration of the plaque on the back improved.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

Written informed consent was obtained from the patient for publication of this article and any accompanying images.

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Letter to the Editor

Recurrent targetoid hemosiderotic hemangioma

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Sir,

Targetoid hemosiderotic hemangioma (THH) which is also known as hobnail hemangioma is a rare benign vascular neoplasm [1]. Although episodic and cyclic morphological changes can occur, spontaneous regression and recurrence is very rarely reported [2,3]. We report a case of THH that recurred after previous complete resolution.

CASE REPORT

A 43-year-old women presented with a 5-mm violaceous papule with a surrounding annular, eccymotic halo on the right side of the flank (Fig. 1). The patient stated that the lesion had appeared 1-week ago. She described the onset of a similar lesion at the same place 1-year ago and the lesion had regressed completely within 2 months without any treatment. The patients past medical history included diabetes mellitus, depression and lower extremity venous insufficiency and she had been using metmofine, sertraline and calcium dobesilat therapies. The patient did not give any history of trauma to the area of the lesion. Histopathology of the lesion revealed ectatic vascular spaces lined with a single layer of prominent plump endothelial cells protruding in to the lumen of vessels and the patient was diagosed as THH (Fig. 2).

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure

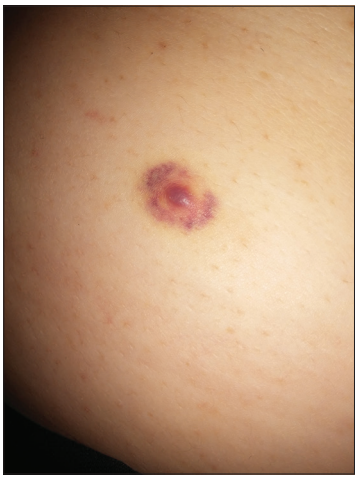

Figure 1: Violaceous papule with a surrounding annular, eccymotic halo

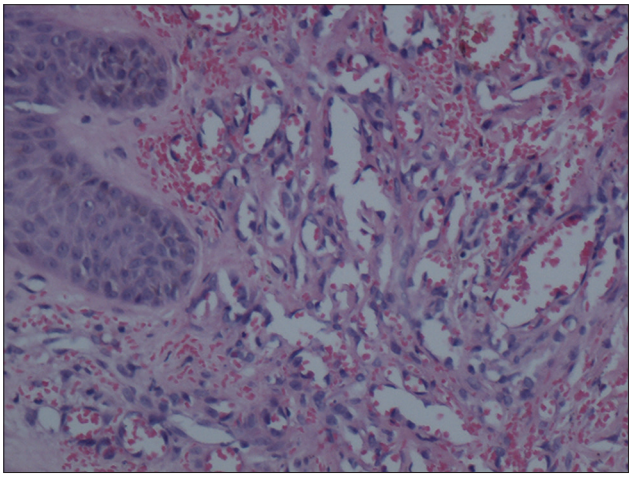

Figure 2: Ectatic vascular spaces which lined with a single layer of prominent plump endothelial cells protruding in to the lumen of vessels (H&EX20)

DISCUSSION

THH is a solitary vascular neoplasm which was first described by Santa Cruz and Aronburg in 1988 [4]. Though the etiology of THH is not clear trauma to a pre-existing hemangioma and influence of sex hormones have been proposed [5,6]. THH occurs

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predominanly on the proximal extremities and trunk and often presents as a small violaceous papule or nodule with an ecchymotic halo, which leads to a targetoid appearance [2,3]. The halo may expand peripherally and eventually disappear [3]. However the halo may not be present in all cases and the term hobnail hemangioma is used to describe the non-targetoid variant [2]. Cyclic changes have been described in palpability, size and color of THH [5,7].

Histopathologically ectatic vascular spaces which are often lined with a single layer of prominent plump endothelial cells protruding in to the lumen of vessels are observed in the papillary dermis and vascular spaces and collagen dissecting narrow vessels are observed in the deeper dermis [5,6].

The clinical differantial diagnosis includes melanocytic nevus, melanoma, dermatofibroma, hemangioma, insect bite reaction and the histopathological differential diagnosis includes Kaposi's sarcoma, retiform hemangioendothelioma, eosinophilic hemangioma, progressive lymphangioma and angiokeratoma [6,7].

THH may be removed for diagnostic and cosmetic purposes and there is no recurrence after excision [3].

We present this case as complete and spontaneous regression with subsequent recurrence has been very rarely reported in the literature.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article

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Our Dermatology Online

Letter to the Editor

Lipoid Proteinosis treated as post acne scars - A clinical diagnostic error

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Sir,

Lipoid proteinosis is a very rare disorder in which there is infiltration of an amorphous hyaline material into the skin, oral cavity, larynx and various internal organs. It usually presents in infancy with hoarseness due to laryngeal infiltration. These patients usually develop acneiform or pock-like scars on the face either spontaneously or due to trauma. In this article, we describe a 27 years old female who was treated as a case of post-acne scars. However, a meticulous history and thorough clinical examination guided us to diagnose it as lipoid proteinosis which was further supported by histopathology.

A 27 year old female, product of consanguineous marriage, presented with history of progressive skin and mucous membrane thickening since childhood and a history of weak cry and hoarseness of voice since infancy. She also had restricted tongue movements and speech impairment. Her skin lesions started at the age of 4 years when she developed multiple warty papules over the dorsum of hands, face and eyelid margins that progressed to form diffuse, yellowish waxy scarring of the skin over the face, shoulders, upper back and extremities. There was a history of increased scarring even with mild injury. There was no such history in the family. There was no history of convulsions, neuropsychiatric complaints or history suggestive of any other systemic involvement. The clinical rarity of this disease inspired us to report this case.

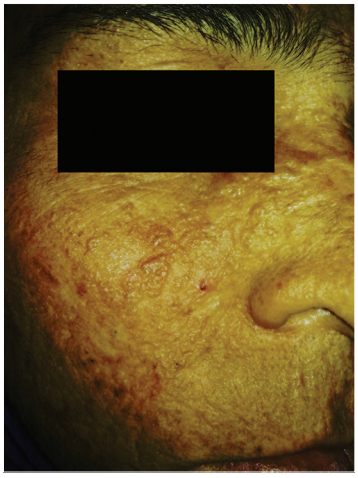

Figure 1: Lipoid Proteinosis in a 27 year old female. There are multiple infiltrated, yellowish colored papules and plaques on the face with areas of atrophic scarring.

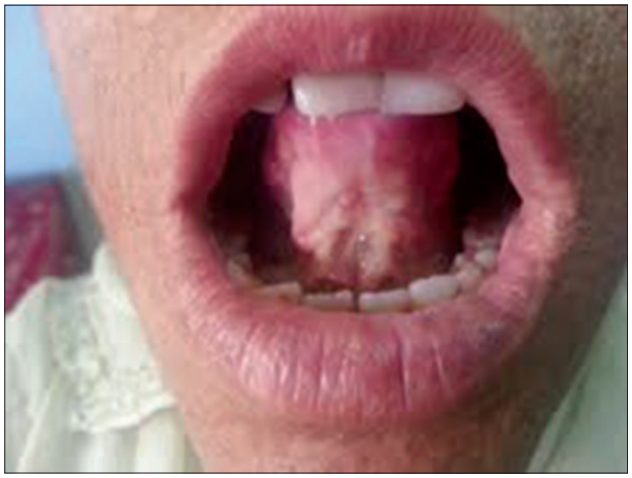

Figure 2: Infiltrated plaque on the undersurface of the tongue.

On examination, a yellowish tinge and waxy texture of face was noted. Extensive atrophic scars, glossy, infiltrated, yellow papules and plaques were present on forehead and cheeks (Fig. 1). Similar scars were found on her shoulders, upper back, around elbows

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and on the dorsum of hands. Yellow infiltrated plaques were covering the mucosa on hard palate and floor of mouth, which along with thickened frenulum limited her tongue movements (Fig. 2). She was also having bulbous swelling of fingers and toes along with flexion deformity of little fingers (Fig. 3). The patient had a hoarse voice. Opthalmological examination was normal except for the presence of beaded papules along the eyelid margins (Moniliform Blepharosis). Hair and nails were normal. Systemic examination did not reveal any abnormal finding.

Routine laboratory investigations were unremarkable. Fibre-optic laryngoscopy (FOL) revealed thickened base of the tongue, obliterating the valleculae with thickening of epiglottis. The pharyngeal walls were granular with hypertrophic tonsils. Both the vocal cords were hypertrophic with restricted movements (Fig. 4). Evaluation of central nervous system with computed tomography showed calcification in basal ganglia (Fig. 5). The skin biopsy of the patient revealed epidermal hyperkeratosis, eosinophilic, amorphous infiltrate throughout the dermis and thickening of basement membrane. The infiltrate showed strong staining with periodic-acid Schiff (PAS). With such a history and clinical findings and further supported by histopathology, a diagnosis of lipoid proteinosis (LP)was made. Immunohistochemistry, polymerase chain amplification and direct nucleotide sequencing of ECM-I gene could not be performed due to unavailability.

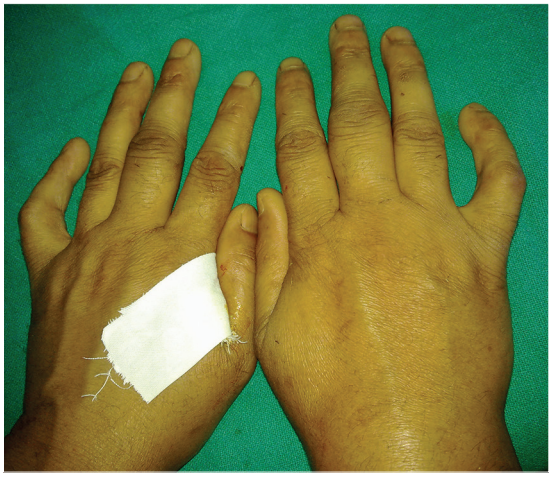

Figure 3: Spindle shaped fingers (especially right middle) along with flexion deformities of both little fingers.

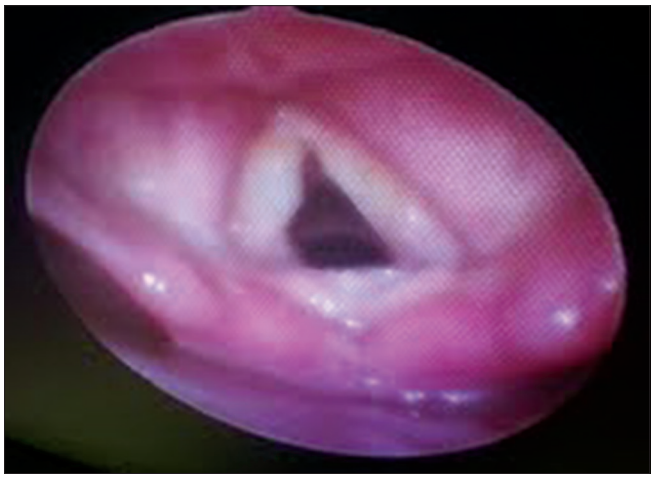

Figure 4: FOL showing visible thickening of vocal cords.

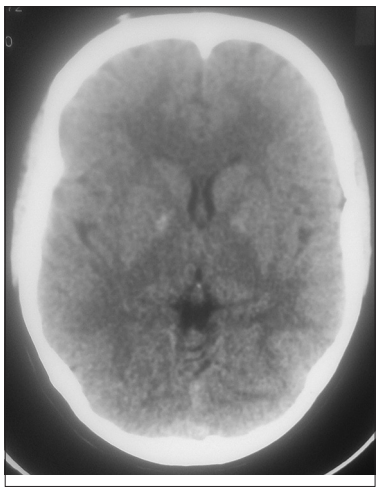

Figure 5: CT brain showing areas of calcification in basal ganglia.

DISCUSSION

Hyalinosis cutis et mucosae also known as Lipoid proteinosis (LP)or 'Urbach-Wiethe' disease was first described by Seibenmann in 1908, but the first detailed report was made by Urbach and Wiethe in 1929. The exact etiopathogenesis of LP is not known. Loss of function mutation in the extracellular matrix protein 1 gene (ECM-1)of LP patients, located on chromosome 1q21 next to the epidermal differentiation complex has been recognized as a cause in recent years [1].

It is a rare, autosomal - recessive disease characterized by hoarseness of voice from early infancy, together with widespread cutaneous scarring, more prominent at the sites of minor trauma and on sun-exposed areas. The most easy recognizable sign is the beaded papules on the eyelid margins (Moniliform Blepharosis)occurring in about two-third of the cases. Eyelid beading, skin lesions and hoarseness are attributed to infiltration of hyaline material into the skin, larynx and various internal organs [2]. The

skin lesions usually develop within the first few years of life, leading to an appearance of chicken-pox like scars or acneiform scars primarily involving the face. The hoarseness of voice is one of the most striking clinical features. The mucosae of pharynx, tongue, soft palate, tonsils and lips are also infiltrated and there is thickening of the sublingual frenulum and tongue, causing limited tongue movements and speech difficulties [3]. In our patient all the essential clinical features along with histopathological changes proved the diagnosis.

The eye changes that have been reported and other extracutaneous features including epilepsy, memory loss and neuropsychiatric abnormalities [4,5] were not present in our patient, who only had intracranial calcification in the temporal lobes or hippocampus, as detected by brain computed tomography.

There is currently no effective therapy available for LP. Microlaryngoscopy and dissection of the vocal cords and excision of deposits may be performed to preserve or improve the voice [3]. Dermabrasion, chemical skin peeling, blepharoplasty and CO2 laser therapy may be helpful for dermatological problems concerned [6]. Therapeutic approaches reported in the literature include oral steroids, dimethylsulphoxide, intralesional heparin, etretinate, and penicillamine [7].

Essentially LP is categorized as a dermatologic disease, runs a chronic course, that severely diminishes the quality of life. Our case had all the features suggestive of LP but was misdiagnosed and treated as a case of post acne scars. Moreover, clinical rarity of this condition prompted this communication.

As skin lesions are an early and prominent manifestation, establishing a correct and timely diagnosis by a dermatologist, and a multidisciplinary approach involving several medical specialties like an otolaryngologist, neurologist, psychiatrist and ophthalmologist may play a more effective role in the management of individuals with this disease.

This article draws the importance of a thorough history and clinical examination by a dermatologist for arriving at the correct diagnosis.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article and any accompanying images.

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Letter to the Editor

A unique case of tiny disseminated angiomas from childhood: a variant of "petechial" angiomata?

Yuka Hanami, Toshiyuki Yamamoto, Mikio Masuzawa

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Sir,

A 14-year-old girl was referred to our department complaining of a number of angiomas on the extremities. The patient stated that the angiomas had appeared on the upper limbs at the age of 10 and had gradually increased in number. Physical examination revealed a number of pin-sized to 2-mm-diameter reddish angiomas on the outer side of the upper arms, forearms, and thighs. She refused to undergo a skin biopsy. Three years later, she visited us again because of a further increase in the number of the angiomas. On physical examination, a number of small reddish nodules were scattered on the thighs, back, upper limbs, and abdomen (Figs. 1-3). Telangiectasia was also observed on the upper arm and chest (Fig. 4). Results of laboratory examinations including liver and renal function were normal. Other findings, suggestive of POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin changes) syndrome or Fabry disease, were not accompanied. Unfortunately, the patient once again refused examination by skin biopsy.

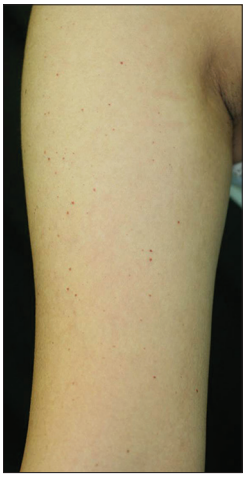

Figure 1: A number of small reddish papular lesions on the upper arm

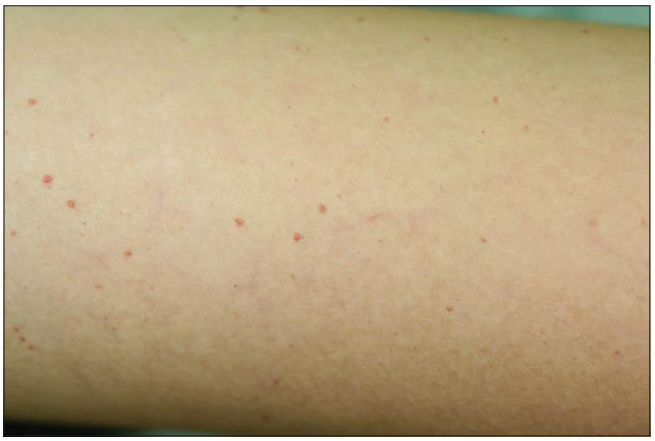

Figure 2: Close-up view of the arm, showing multiple small angiomas accompanied by telangiectasia

Recently, Miyabe et al. [1] reported two cases of disseminated angiomas on the entire body, which demonstrated several characteristics, *e.g.* tiny angiomas covering the entire body except for the palms and soles, childhood onset with a gradual increase in number, familial occurrence suggestive of autosomal dominant inheritance, and absence of other systemic disorders such as Fabry's disease. Histological features in the aforementioned study showed mild hyperkeratosis and vessel ectasia in the papillary dermis. These observations were similar to our own case, although histological evaluation could not be carried out because our patient decisively refused skin biopsy. Familial occurrence was not observed in the present case. Although Miyabe et al. did not exhibit the diagnosis of their cases, there is an old paper termed 'petechial' angiomata by Brannen et al. [2], who collected 23 patients that presented multiple small, punctate, vascular lesions on the trunk and extremities.

How to cite this article: Hanami Y, Yamamoto T, Masuzawa M. A unique case of tiny disseminated angiomas from childhood: a variant of "petechial" angiomata? Our Dermatol Online. 2015;6(2):240-241.

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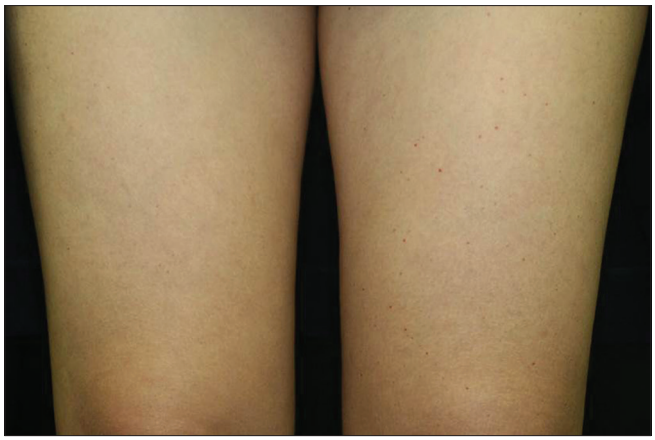

Figure 3: Numerous tiny angiomas developed also on the thighs

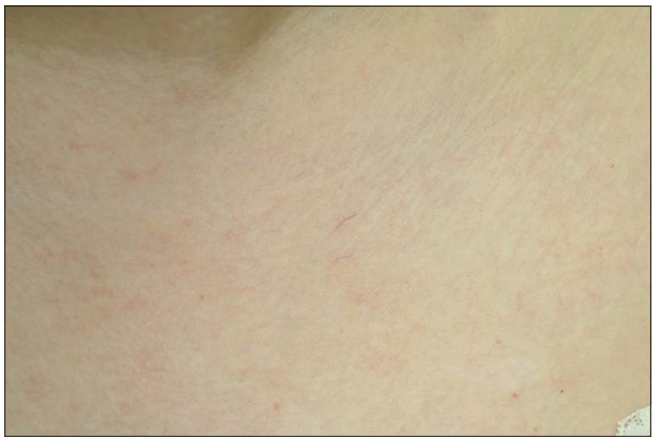

Figure 4: Telangiectasia was scattered on the trunk, unassociated with angiomas

The age of the patients ranged from 20 to 73 years, with a predilection for female. Histological examination showed a simple localized dilatation of a vessel in the subpapillary venous plexus. The cases reported by Miyabe [1] and the present case may be similar to those cases reported by Brannen et al. [2]. Furthermore, linear telangiectasias were scattered on the surface of the extremities and chest. Further accumulation of similar cases is needed and whether those cases may be more common in the Japanese population than was considered should be determined in the future.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Letter to the Editor

Localised facial pityriasis versicolor-A very uncommon presentation of a common disease

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Sir,

Pityriasis versicolor is a common superficial fungal infection of the skin which is caused by various species of yeast of the genus Malassezia and is clinically characterized by scaly hypo pigmented or hyper pigmented macules usually involving the upper trunk, upper arms, neck and abdomen [1]. Lesions of pityriasis versicolor confined to face has rarely been reported. In this article the author reports a 17 year old boy who had pityriasis versicolor localized to the face.

CASE REPORT

A 17 year old boy presented with three months history of multiple asymptomatic hypo pigmented macules over both cheeks. He denied any previous history of similar complaints. On examination, there were multiple discrete hypo pigmented macules with fine branny scaling present on both cheeks (Figs 1a, 1b). There were no such lesions on any other parts of the body. When the affected skin was stretched, the scaling of the lesions became prominent showing the positive Zireli's sign. The examination of hair, nail and mucous membranes was normal. KOH examination of skin scrapings from the lesions showed multiple short hyphae and spores. Skin biopsy was not done. A diagnosis of localized facial pityriasis versicolor was made. He was treated with topical sertaconazole 2% cream applied twice daily. In addition, he was prescribed oral fluconazole 300 mg weekly for two weeks. The hypo pigmentation took about two months to recover.

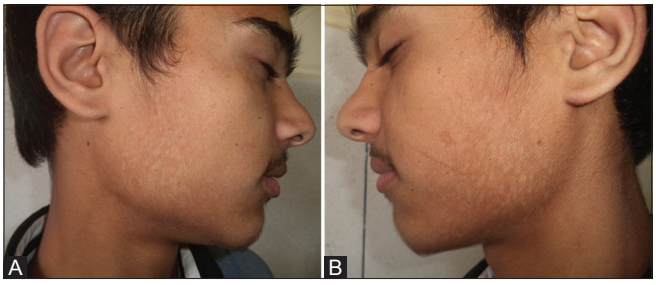

Figure 1: Facial pityriasis versicolor in a 17 year old boy. There are multiple hypopigmented macules on right (a) and left (b) cheeks

DISCUSSION

Pityriasis versicolor mostly affects the upper trunk, but commonly the lesions spread to upper arms, neck and abdomen. Less commonly, it involves axillae, groins, thighs and genitalia. Lesions involving palms have been reported from the tropics but rarely described from temperate zones. Pityriasis versicolor involving face is well recognized in the tropical areas but lesions restricted to the face have rarely been reported [1].

Morphologically, various types of pityriasis versicolor have been reported. These include hypochromic (commonest), hyperchromic, combination of hypochromic and hyperchromic, erythematous, circinate, atrophying, acral, parasitic achromia, follicular, involving inguinocrural region and simulating erythrasma. A clinical variant resembling pityriasis rubra pilaris has been described [2,3]. Localized facial pityriasis is a rare presentation and hence reported. The scaling of macules of pityriasis versicolor can be made prominent by stretching the affected skin. This is called Zireli's sign [4]. Various mechanisms have been proposed for hypopigmentation in pityriasis versicolor. Production of dicarboxylic acids like azaleic acid by Malassezia species causing a competitive inhibition of

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the enzyme tyrosinase and a probable cytotoxic effect on hyperactive melanocytes have been suggested by some researchers [5]. The importance of this clinical type lies in differentiating this entity from the lesions of pityriasis alba in children as both can present with hypopigmented scaly macules. However, type of scaling, Zireli's sign, woods lamp examination and KOH examination of skin scrapings will differentiate between the two entities.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article and any accompanying images.

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Source of Support: Nil, **Conflict of Interest:** None declared.

Letter to the Editor

A pedunculated protruding lesion of the back

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Sir,

A 24 year-old man presented with a pedunculated protruding mass of the back evolving for three years. At physical examination, the tumor was polypoid, pedunculated and measured 2,5cm. Grossly, it was myxoïd and contained cystic and hemorrhagic changes at cut surface.

Histological examination revealed a well-circumscribed, unencapsulated tumor, located in the middle and deep dermis. It was composed of dense cellular areas alterning with myxoïde zones. The cellular areas were formed by long bundles of spindle-shaped cells, with their nuclei arranged back to back in a parallel pattern (Figs 1 and 2). Vessels were numerous and their walls were thick and hyalinized. Immunohistochemically, the tumor cells stained strongly and diffusely for S100 protein (Fig. 3).

The diagnosis of a pedunculated cutaneous schwannoma.

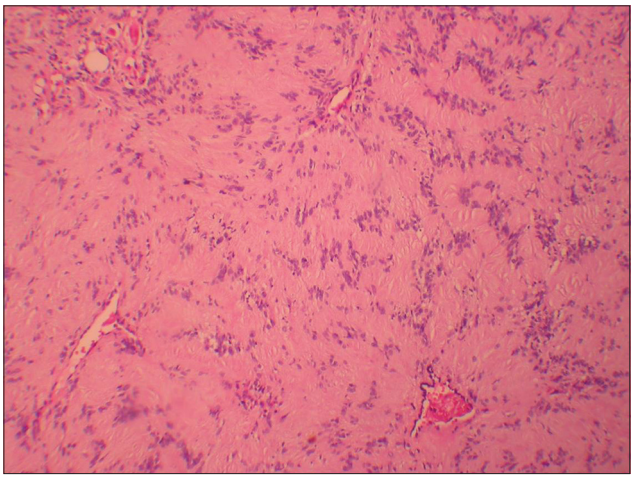

Figure 1: Sparse proliferation made of spindle shaped cells showing nuclear palisading (HE x 100)

The patient's informed consent was obtained.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

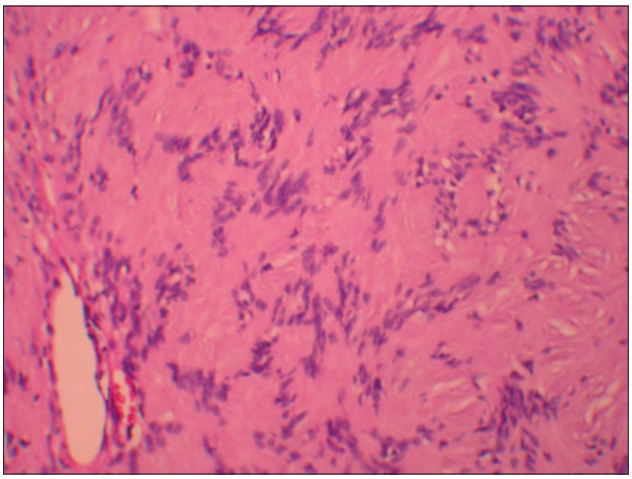

Figure 2: Verocay bodies: nuclei aligned in palisades, surrounding an eosinophilic material (HE x 400)

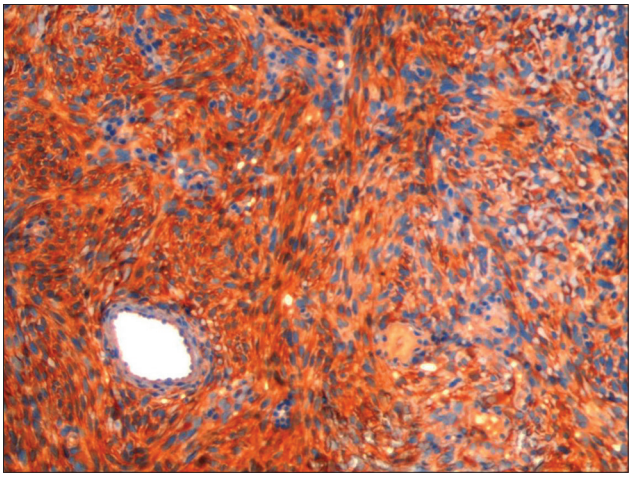

Figure 3: The tumor cells stained strongly and diffusely for S100 protein.

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DISCUSSION

Schwannoma (also known as neurilemmoma or neurinoma) is a benign nerve sheath tumor which arises from Schwann cells, thus; it can be located anywhere in the body. Cutaneous schwannomas are uncommon [1]. Limbs are their site of predilection [1]. The tumor affects equally the two sexes [2] and is most common in patients aged between 20 and 50 years. Cutaneous schwannomas occur at random without a known cause and are usually solitary. Schwannomatosis is rare and is defined by the presence of multiple diffuse or localized tumors. Some authors considered it as a rare form of neurofibromatosis [3].

Clinically, cutaneous schwannomas grow slowly for several years and are often asymptomatic, but pain, tenderness or paresthesia may occur in up to one third of patients; due to the neural compression by the tumor.

It generally presents as a deep seated nodule located in the deep dermis or in the subcutis. Schwannomas presenting as a pedunculated protruding mass as in our case are exceptional. In our best knowledge, only Seongmin and al reported a similar presentation [4].

Macroscopically, the tumor is encapsulated, gray-white in color, with a smooth, shiny appearance. Cystic changes are sometimes present, particularly in high-sized and deep tumors [4]. In our case, they may be explained by a vascular insufficiency because of the tumor particular form.

The diagnosis of schwannomas is histological. They are well circumscribed, encapsulated by perineurium, and usually located in the deep dermis and the subcutaneous tissue. They are characterized by two types of areas.

Antoni A areas are made of spindle-shaped Schwann cells arranged in interlacing fascicles. The cells have indistinct cytoplasm borders. The nuclei may be aligned in rows or palisades, between which the cytoplasm is fused into eosinophilic material forming Verocay bodies.

Antoni B zones are loosely cellular, myxoïd and edematous. At immunohistochemical study, the tumor cells stain strongly for S 100 protein and are encircled by the type IV collagen [1].

Cutaneous schwannoma must be differentiated histologically from PEN (Palisated and Encapsulated Neuroma) but -in case of pedunculated protruding mass- neurofibroma is the main differential diagnosis because it can present as a pedunculated tumor [1].

Schwannomas treatment is complete surgical removal. In case of incomplete excision, post operative radiotherapy was proposed by some authors [5] but it has not shown its efficacy [2].

By conclusion, in front of a patient with a pedunculated cutaneous mass, schwannoma must be evocated and this unusual clinical feature of this tumor must be included into cutaneous schwannoma‘s appearances to avoid misdiagnosis.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Letter to the Editor

Balanitis evoked by abuse of intimate washing: Two case reports where circumcision encourages the solution of the problem

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Sir,

In nineteenth century penile inflammations characterised by red erosions and pain on glans and on foreskin and foul smelling discharge, were baptized as mal napolitain (by French militaries that had contracted the disease in Italy, or mal franzoso, by the Italian soldiers that had contracted this syndrome during campaigns in France), despite all Catholic and Christian cultures of Old Continent have been coining several epithets for balanitis as Grosse Verole, Grandcor, Bœsen Blattern, Bubās, Pudendagra, Passio Turpis saturnine, Gorra and this means that this urological malady has been always existing for centuries throughout all the aforesaid populations.

It is fascinating moreover that urologists belonging to religions not allowing circumcision, refer that balanitis is more frequent in circumcised than in uncircumcised men. Van Howe [1] found that circumcised boys need to be closely monitored for balanitis than uncircumcised boys.

Weiss et al assumed that male circumcision were a potential risk of syphilis, chancroid, and genital herpes [2]. Øster reported no balanitis in 9,545 observations of uncircumcised Danish boys [3].

There are indeed some A.A. that assume neonatal circumcision should be mandatory to the prevent from urinary tract infections in infancy [4], or preconize general male circumcision as a normative practice to have to be hallowed by the World Health Organisation [5].

Apart from these statistical divergences, it is ascertained that an usual cause, amongst the various ones of balanitis, is the excess in washing [6] especially when aggressive bath intimate foams containing cationic surface active agents are employed, which are characterised by a very wide antibacterial spectrum.

I am strenuously persuaded that circumcision (e.g. the Khatna) reduces almost to half the incidence of balanitis.

CASE REPORT

Here follow two case reports of two waiters, employees at the canteen of a college (36 years) the former circumcised, the latter uncircumcised, that suffer from balanitis, because of excess of washing, due to their job indoor that coerces them to wash deeply every evening, using aggressive syndets.

Before to introduce my dermal-cosmeticological method to solve the two cases, it is better to clarify that the anaerobic microflora of the prepucial area amounts to 95.% of the total colony-forming units per square centimeter (peptococci, peptostreptococci, propionibacteria, bifidobacteria, eubacteria, and bacteroides, that after all represent the symbiontic bacterial component) and that the aerobic flora consisting most commonly of nonhemolytic streptococci and diphtheroids, represents the fraction of the commensal and pathogenic bacteria.

Cationic surfactants, ingredients of intimate bath foams, boast the eradication of all bacteria of human

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mucosa, and therefore all symbionts bacteria sojourning in the prepucial area are destroyed.

It is well known that lactic acid producing lactobacilli are welcome for the care of internal mucosae both in man and in woman and this is an exemplary reason why drinking yogurth, kefir and Koumīs in equatorial disctricts is advisable), some of the aforesaid lactobacilli are pathogens or commensals, albeit *Lactobacillus delbrüecki subsp. bulgaricus* is the sole capable to transform lactose of milk in lactic acid and is an excellent symbiont.

A nouvelle vague coming from Australia and Canada that will invade all the world, forecasts the employ of raw unpasteurised cow milk as biological cosmetic.

Unpasteruised milk plus *Lactobacillus delbrüecki* is the method I ideated to nurse the two waiters' balanitis: lactose in unpasteurised milk is present is under its osazonic form, so that lactobacillus is able to transform it in acid more copiously.

The treatment I propose consists in spreading onto the glans and let it stand overnight a toffee-like-mousse made up with raw milk and lactose, where finally lactobacillus delbrüecki is dispersed, for two weeks.

DISCUSSION

Unequivocal positive results are observed in case I, the circumcised man, after the third night of application, meanwhile some potential amelioration is visible in uncircumcised man (Case II) only after the 11st night, but it is amazing to observe that after two weeks Case II's aspect of penis does not appear safe and well treated as Case I's one.

I deem the hypothesis I proposed could be reputed right, and, statistically, almost according to the empirical observations of these case reports, circumcision can reduce the risk of incidence of balanitis to 79%.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Historical Article

Romana's sign

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Romaña's sign is the first symptom of american trypanosomiasis (or Chagas' disease). When the route of inoculation of parasites (*Trypanosoma cruzi*) is the ocular mucosa, edema of the eyelids and conjunctivitis may occur. This unilateral periorbital edema which does not pit on pressure and with a dry skin is thought to be pathognomonic for early Chagas'disease. Chagas'disease is a zoonosis, caused by *Trypanosoma cruzi*, which was discovered by Carlos Chagas in Brazil in1909. About 18 million persons are infected in south America, mostly in Brazil and Argentina. Cecilio Felix Romaña (1899-1997) was an Argentinean researcher dedicated to tropical diseases firstly in the area of Santa Fe then in Oswaldo Cruz Institute (Rio da Janeiro) with S. Mazza. Romaña became famous when he described this symptom in 1935. But, the director of the Institue, S. Mazza, never accepted neither the specificity of this sign nor its popular name as Romaña's sign.

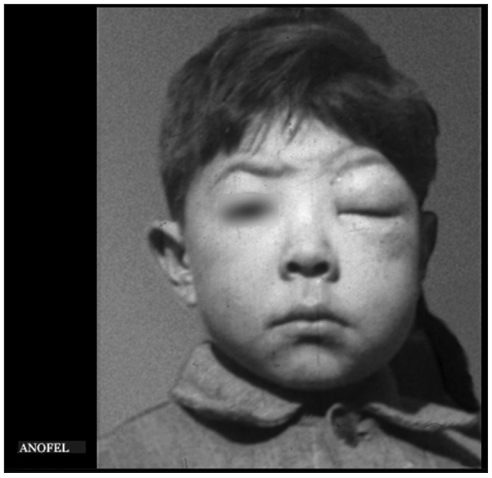

Figure 1: Romaña's sign.

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Obituary

Aliis inserviendo consumor - Professor Kovalchuk Leonid Yakymovych

Press Center of the I. Ya. Horbachevsky Ternopil State Medical, Ternopil, 46001, Ukraine

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Figure 1: Professor Kovalchuk Leonid Yakymovych

Dedicated to the memory of the prominent scientist, leader - Corresponding Member of NAMS of Ukraine, Honored Worker of Science of Ukraine, the rector of I.Ya.Horbachevsky Ternopil State Medical University, Professor Kovalchuk Leonid Yakymovych.

October 1, 2014 stopped beating the heart of the Corresponding Member of NAMS of Ukraine, Honored Worker of Science of Ukraine, the rector of I.Ya.Horbachevsky Ternopil State Medical University, Professor Kovalchuk Leonid Yakymovych (Fig. 1).

All his life he devoted to medicine, helping patients and developing medical university.

Leonid Yakymovych was born on March 15, 1947 in the village Ternivka Izyaslav district Khmelnytskiy region.

The head of Ternopil State Medical University finished Bereshany Medical College (1967). Specialty "physician" with qualifications "surgeon" has gained in Ternopil State Medical Institution and received the diploma in 1973. After graduation internship took place in Ternopil Regional Hospital. In 1974-75 he worked as a surgeon in the village Ustya-Zelene Monastyrskyi district, Ternopil region, and in 1975-78 - a surgeon, head of surgical department of Velykodederkalskiy hospital Shumsk district, Ternopil region. Since that time Leonid Kovalchuk was not limited only by medical activities and the range of his scientific interests covered issues of current medical techniques and technologies.

In 1977 L.Ya.Kovalchuk defended his thesis on the theme "The activity of a number of neutrophils oxidative enzymes and lymphocytes in patients with thyrotoxicosis." Due to this he started his Ternopil surgical school that has a strong scientific foundation.

In 1978, the fate brought him to Kirovohrad region, where during two years Leonid Kovalchuk worked as the head of surgical department Znamyanka Central Hospital. In 1980 he returned to the surgeon position at Ternopil hospital No 1. Already since 1981 to 1983 Leonid Yakymovych worked as an assistant at Surgery Department Advanced Medical Faculty of Ternopil Medical Institutoon. Later (1983-1987), he was the chief surgeon of Ternopil regional health department. In September 1987, Leonid Kovalchuk became head of the Department of Surgery Hospital No 1 Ternopil Medical Institution. In 1994-1997 he served as vice-rector with clinical work of this institution.

In August 1997, taking into account the significant contribution to the development of then still Ternopil State Medical Academy his leadership, the ability to predict the institution staff entrusted leadership to Leonid Kovalchuk.

As rector Leonid Yakymovych demonstrated an innovative approach in the organization all activities of TDMA, which under his leadership has received university status and was published in the leading medical universities in Ukraine. His efforts opened

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3 new departments: pharmacy, dental, foreign students; four educational and research institutions on the basis of theoretical departments and the first educational institute of nursing and educational institute of postgraduate education in Ukraine.

Material and technical base of the university was enhanced radically, publishing house "Ukrmedknyha" with its own printing complex was established, which is the base for CMC with WMO Ministry of Health of Ukraine and is now the largest specialized medical publishing house in Ukraine, issued by the regional newspaper "Medical Academy" and "University Hospital". "Chervona Kalyna" was created as an educational and recreational complex, with the Congress Centre, the hotel, food complex, sports and physical training base and students dispensary.

Ternopil State Medical University Rector deservedly gained such rewards and honors: Corresponding Member of NAMS of Ukraine, Order "For Merit" third degree, Honored Worker of Science of Ukraine. He was awarded the Diploma of the Supreme Council of Ukraine, the Cabinet of Ministers of Ukraine and the Ministry of Health, the Diploma rating "Zolota Fortuna" was included in "Zolota knyha elity Ukraiiny." In 2008 he was awarded the title of Honorary Professor of South Carolina University (USA), in 2014 - the title of Honorary Professor of Tbilisi State Medical University (Georgia). Also he awarded nominal Jubilee Medal Medical University, Bratislava (Slovakia), honors "European quality" European Business Assembly.

Since 2009, he headed the permanent commission of Ternopil Regional Council on questions of Health Care, Family, Motherhood and Childhood. He was particularly concerned about necessity of changes in the existing health care system. Results of his work were "The concept of reforming health care in Ternopil region." Leonid Yakymovych worried about the issue of medical personnel training. To resolve this problem, he approached unconventionally, namely using the latest innovative techniques - methods of a single day, practically oriented model of the learning process (Z-model), lines of practical skills OSKI (OSPI), test technology assessment, computer technology, virtual computer programs. Ternopil State Medical University Rector made a special emphasis on obtaining practical skills by medical students. It was the first time in Ukraine launched a project to create university hospitals based on a cooperative model. To prepare family physicians Leonid Kovalchuk initiated the creation of a network of practical training centers of primary health care. This Leonid Yakymovych saw the way the integration of higher medical education at Ukraine international educational medical space. That he firstly launched a project to create university hospitals based on a cooperative model in Ukraine. Leonid Kovalchuk initiated the creation of a network of practical training centers of primary health care for preparing family physicians. In that Leonid Yakymovych saw the way of integration higher medical education at Ukraine into international educational medical sphere.

The innovation study and analysis of international experience, establishing close cooperation with leading foreign universities were based.

Leonid Yakymovych is well known expert in the field of medicine with a strong reputation among colleagues and friends, students and patients. The main scientific activity was associated with the study of fundamental problems of gastric ulcer and duodenal ulcer. He developed the original pathophysiological based methods of surgical treatment of gastric ulcer and duodenal ulcer, which reduced recurrence postresection disorders in four times. He developed methods which improve the safety and efficacy of surgical treatment of pathology of major arteries and extracranial vessels, including methods for preventing thrombosis segment reconstruction of the arterial system.

He is the author of 234 scientific works including 7 monographs, atlases, 4 surgeries, 6 books, 3 manuals, 32 inventions and patents. He prepared 8 doctors and 30 candidates of science. Leonid Kovalchuk also served as editor of scientific and practical journal "Hospital Surgery" and member of the editorial board of "Yzdatelskiy dom" (Russia).

His major works are: "The choice of methods of surgical treatment of gastroduodenal ulcers" (1997); "Laparoscopic surgery of the biliary tract" (1997); "Hospital Surgery" (textbook, 1999); "Clinical Surgery" (textbook, 2000); "Organ blood flow in precancerous lesions of esophagus and stomach" (2001); "Surgery Dumping Syndrome" (2002); "Anaesthesiology and intensive care emergency conditions" (2003); "Atlas of surgical interventions on the gastrointestinal tract and the anterior abdominal wall" (2004); "Surgery combined and multiple atherosclerotic occlusions of extracranial arteries and aorto-femoral segment" (2005); "Clinical phlebology" (2008); "Surgery" (textbook, 2010); "Venous thrombosis" (2010).

He attituded to his work with great responsibility, trying to save life and health of each patient and worked for Ukraine's prosperity. Rector believed in every student and sincerely rejoiced achievement and achievements of its graduates.

This year TSMU through wise and careful management Leonid Kovalchuk was recognized by the Ministry of Health of Ukraine as the best university among all medical schools in our country.

The death of Leonid Kovalchuk is an irreparable loss for Ternopil State Medical University named after I. Horbachevskiy. Only with time everyone who worked together with this extraordinary man, declare all the greatness Leonid Yakymovych figure and fully appreciate his contribution! Faculty and student team also expresses sincere condolences to the family at the loss of Kovalchuk as wise and loving husband, father, and grandfather!

Press service of the I.Ya.Horbachevsky Ternopil State Medical University.

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