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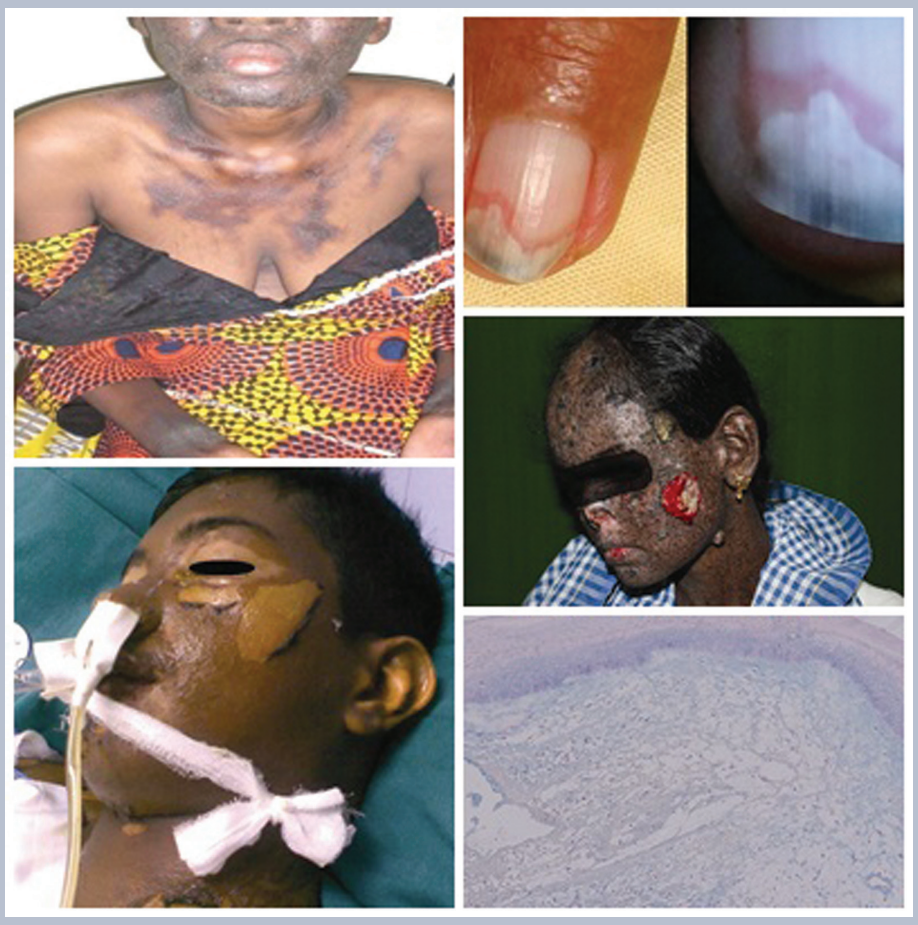

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Editorial Pages

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NASZA DERMATOLOGIA Online
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TRACE ELEMENTS HOMEOSTATIC IMBALANCE IN MILD AND SEVERE *PSORIASIS*: A NEW INSIGHT IN BIOMARKER DIAGNOSTIC VALUE FOR *PSORIASIS*

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Abstract
Introduction: The pathogenesis of psoriasis remains elusive and is a subject of interest to clinicians and scientists. Many studies have thrown light on the etiopathogenesis of psoriasis at both molecular and tissue concentrations. Of these, the role of trace metals has been of interest.
Objective: To evaluate the possible role of trace elements in mild and severe psoriasis.
Patients: Sixty patients suffering from psoriasis were included in the study and 30 healthy subject served as a control.
Methods: Serum sample analysis for some trace elements namely Na, K, Ca, P, Cu, Zn, and Fe using inductively coupled plasma-atomic emission spectroscopy (ICP-AES). In psoriatic patients and control, the severity of psoriasis was assessed by psoriasis area severity score (PASI score).
Results: In psoriatic patients the level of serum calcium and zinc were diminished while the level of serum copper, iron and organic phosphorous were increased. These changes were significantly evident in severe psoriasis compared to control and mild psoriasis ($P<0.05$).
Conclusions: There may be a role for trace elements in the etiopathogenesis of psoriasis.

Key words: psoriasis; trace elements; serum; homeostasis

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Nagat Sobhy Mohamad: Trace elements homeostatic imbalance in mild and severe psoriasis: a new insight in biomarker diagnostic value for psoriasis. Our Dermatol Online. 2013; 4(4): 449-452.

Introduction

Psoriasis is a hyperproliferative cutaneous disease of multifactorial etiologies: genetic background, environmental factors, vascular and immune system disturbances [1-3].
The clinical course is unpredictable, characterized by remissions relapses. Lesions are typically well-demarcated erthymatous, scaly plaques. Histopathologically,there is marked epidermal hyperplasia (acanthosis) accompanied by retention of keratinocytes nuclei in the stratum corneum (parakeratosis) and a mixed dermal infiltrate, including CD4+ T cells, dendritic cells, macrophages, and mast cells. Neutrophilic exudates are often seen (Munro microabscesses) and CD8+ T cells are present in the epidermis. Dermal papillary blood vessels are dilated and tortuous, and there is increased expression of angiogenesis-associated genes [4-7].
The pathogenesis of this disease remains elusive.
Trace elements are those found in such small amounts in the living tissues, of the trace element appearing in the body, ten have been designed essential trace elements: Zinc, copper, manganese, iodine, iron, cobalt, molybdenum, tin, selenium and chromium [7-9].
Although, by definition, trace elements are required in minutely small doses (less than 100mg/day) this does not mean they can be ignored. Trace elements are among the most important factors in maintaining and recovering health [10,11] .
In analytical chemistry, a trace element is an element in a sample that has an average concentration of less than 100 parts per million measured in atomic count, or less than 100 micrograms per gram.
In biochemistry, a trace element is a dietary mineral that is needed in very minute quantities for the proper growth, development, and physiology of the organism [12].

Aim of the work

The aim of this work is to detect any possible changes in the metabolism of some trace elements and their relation to the etiopathogenesis of psoriasis.

Patients and Methods

Sixty patients suffering from psoriasis and 30 healthy subject served as a control (age, sex, body mass index matched with the patients) were included in the study.

They were randomly selected from the outpatient clinic of dermatology and venereology department, Alexandria Main university hospital, they are subjected to:

1. History taking including: age -sex - occupation -duration of the disease -family history -history of drugs- predisposing factors like stress or trauma -receipt of previous of treatment.

2. Clinical examination including: morphology -distribution -extent of involvement -severity of the lesion.

- The selection criteria and the protocol were approved by Alexandria ethics committee.
- All the participants in the study signed an informed consent.

Inclusion criteria:

-Male and female patients aged from 13 to 65 y (mean age 33.61 ± 17.12y.o.) with a clinical diagnosis of psoriasis of different severity.
-All patients had chronic psoriasis of different location on the upper extremities, lower extremities, and /or the trunk.
-An overall treatment free period of at least 2 weeks after any topical antipsoriatic (anthralin, corticosteroids, calcipotriol, retinoids) treatment and at least 2 months after systemic therapy (cyclosporines,methotrexate, retinoids, hydroxyurea, macrolides, corticosteroid, fumaric acid, biologics) must have elapsed before start of the work.

Exclusion criteria:

-patients with any chronic systemic diseases affecting the metabolism.
-patients with history of prolonged drug intake for any disease.
-recent phototherapy or systemic antipsoriatic treatment within the last 2 months before launching the work.
-recent topical antipsoriatic treatment within the last 2 weeks before launching the experiment except for Vaseline as an emollient.
-pregnancy and women using contraceptive pills .
-patients on vitamins or mineral therapy.

Assessment of the extent and severity of psoriasis:

The psoriasis area and severity index (PASI) score was first described in 1978 as a method of quantifying the extent of psoriasis and since then has been used frequently to assess disease severity [13].

- Psoriasis was graded according to the Psoriasis Area Severity Index (PASI), presenting at the time of blood collection. Among study patients, 30 subjects (50%) were with severe psoriasis (PASI range from 13-18), and another 30 (50%) with mild psoriasis (PASI range from 3-12). Patients (n=60) were assessed in comparison with the control group (n=30). The control group presented no clinical problems.

Venous blood samples (3–5 ml) were collected using metal-free Safety Vacutainer blood collecting tubes (Becton Dickinson, Rutherford ®, USA) containing >1.5 µg K2EDTA/ml and were stored at −20°C until analysis.

Seven trace metals: sodium (Na), potassium (K), Calcium (Ca) phosphorous (P), iron (Fe), Zinc (Zn) and Cupper (Cu) were estimated by atomic absorption spectrophotometrically following method of Fuwa et al [14], and Rodushkin [15].

Statistical analysis of the data

The clinical and laboratory results obtained are statistically analyzed using SPSS/PC* (Statistical package for social science for personal computers).Student's t- test was used and data were expressed as mean ± S.D, and $P<0.05$ was considered statistically significant.

Results

The studied patients aged from 13 to 65 y with a mean age of 33.61 ± 17.12 y.o.

The study was conducted on thirty (50%) male and thirty (50%) female patients.

The PASI score: severity of psoriasis was classified as mild in 50% of cases (PASI score rage from 3 – 12 with a mean of 7 ± 1.31.

Severe psoriasis in 50% of cases (PASI score rage from 13 – 18 with a mean of 11± 2.55.

The serum level of the 7 trace elements in psoriatic and control subjects (Tabl. I).

	Mild psoriasis	Severe psoriasis	Normal control	P value
No of cases	30	30	30	
Sodium (mmol/L) (Mean ± SD)	140±1.6	142.5± 3.1	136.5±4.6	0.14
Potassium (milliEquivalents per liter (mEq/L) (Mean ± SD)	4.51±0.5	3.72± 1.4	3.56± 0.7	0.07
Calcium (mg/dl) (Mean ± SD)	7.25±0.64	6.5±0.33	9.84±0.81	0.01*
phosphorous(mg/dl) (Mean ± SD)	5±1.26	6±0.74	3.55±0.48	0.02*
Iron (µg/dl) (Mean ± SD)	178±3.21	180±4.19	170±6.1	0.011*
Zinc (µg/dl) (Mean ± SD)	79.2± 2.3	70.3±1.55	86.7±8.4	0.031*
Copper (µg/dl) (Mean ± SD)	25±2.3.4	27±1.6	20±4.1	0.021*

Table I. The serum level of the 7 trace elements in psoriatic and control subjects.

*** P < 0.05 statistically significant**

No significant differences between the serum level of sodium and potassium in patients and controls (P>0.05)
The serum calcium and zinc levels were significantly diminished in psoriatic patients especially in severe psoriasis (P < 0.05).
The serum organic phosphorous, iron and copper levels were significantly increased in psoriatic patients especially in severe psoriasis (P < 0.05).
By correlation analysis no noticed effect of age, sex and body mass index on the previous results.

Discussion

Psoriasis is a chronic skin disease of multifactorial etiology. The exact pathogenesis of psoriasis has remained unclear, but some factors are known to trigger, participate or aggravate the disease process [3-6].
The stages of psoriasis as mild, moderate and severe are based on the PASI score. The PASI is a useful tool in monitoring response to treatment [13].
Normal trace (minerals) elements in the blood are important for maintenance of skin health, abnormality of trace elements can lead to many diseases [10,16]. Minerals play important role in the subtle biochemistry of the body as do vitamins [9,16]. Virtually, all enzymatic reactions in the body require minerals as cofactors [16].
Oxidative stress can result from deficiency of trace elements such as zinc, copper and selenium [11,16].
Trace elements and their compounds have been used since ancient times for their therapeutic as well as cosmetic effects on the skin [8,9]. The unique process of keratinization and melanin formation is enzyme-dependent and therefore could be influenced by trace element deficiencies or excesses as trace elements are involved in enzymatic activities and immunologic reactions [10].
We measured some of the trace elements in order to illuminate the possible role of trace metals in the pathogenesis of psoriasis. This study was conducted on 60 patients with psoriasis of different severity. And 30 healthy volunteer. On measurement of serum trace elements it was found many abnormality. The most important notice was that diminished serum calcium level in psoriasis mainly in severe type and this in agreement with the study done by Herizchi 2007 [17] and this inforced by the effect of calcipotriol in the treatment of psoriasis [17,18].
It is a must for every psoriatic patients to measure serum calcium and treatment by calcium if possible.
Also serum organic phosphorous level was found to be increase in a large percentage of psoriatic patients mainly in severe psoriasis, this in accordance to Sreekantha [18].
Hypocalcemia is responsible for triggering and aggrevation of psoriasis [19]. Calcium within the cell plays an important role in the regulation of proliferation and differentiation of keratinocytes. Calcium homeostasis may be involved in the development or exacerbation of psoriasis because hypocalcaemia may damage cell adhesion molecules, such as cadherins which were dependent on calcium [19,20].
In this study it was found that the serum level of free reactive serum iron was elevated especially in severe psoriatic patients, the same results were found by Arpita Ghosh 2008 [21]. In psoriatic plaque blood capillaries are dilated and become tortuous to form loops which may cause break down of erythrocytes to release hemoglobin also low level of glutathione peroxidase and super oxide dismutase may help to elevate the level of hydrogen peroxide which further causes break down of heamoglobin within erythrocytes to form non heme reactive iron. This free reactive iron can catalyze Haber-Weiss reaction and generate deadly damaging hydroxyl radical which in turn damaging cellular constituents [21,22]. However Nathalie et al in their study found that Iron serum concentrations were normal in psoriatic patients and in healthy subjects, whereas iron concentrations were high in psoriatic involved and uninvolved dermis compared to healthy dermis [23].
Serum zinc level was found to be diminished in a considerable percentage of psoriatic patients mainly in severe psoriasis and the same results were found in many studies [24-27].
This explained by that zinc used in rapid turnover of the skin and loss of zinc through exfoliation. And zinc deficiency may be the original cause of psoriasis. Some studies noted that psoriatic lesions retain a high content of zinc compared with the uninvolved skin, suggesting an imbalance in zinc distribution between serum and psoriatic lesions [24,25]. In fact zinc is a co-factor for DNA- and RNA polymerases required for protein synthesis in involved skin. Lowered level of serum protein or albumin which results from peeling off of a large quantity of scales from the body surface, may be also attributable to decreasing zinc level.
Contradictory to this, some authors found increase level of serum zinc & in some studies the serum zinc was equal in patients and control subjects [24-27].
There was a case report on improvement of psoriatic patient by oral zinc therapy [28].
This approach appears reasonable because copper and zinc are known to be among the constituents of the skin and to play essential roles in maintenance of its function in association with the enzyme systems activated by trace metals. A deficit of those elements may result in the decrease of antioxidant enzyme activity and the increases of oxidative stress induce cell damage [21].
As regard serum copper; in this study increase copper in severe psoriasis than mild and control this is in accordance to many studies [29,30]. Also increase in ceruloplasmin (copper carrying protien) [31,32]. There are several reports stating that the serum copper level is high in psoriasis [33,35]. Copper is present in the serum in at least two fractions: (1) a transport fraction (approximately 5%) loosely bound t albumin; and (2) ceruloplsmin (approximately 95%) firmly bound to globulin. The elevation of serum Copper in psoriasis may be ascribed to an increase in both fractions, especially an increase in ceruloplasmin, a Copper–binding protein,in response to inflammation. Opposite to this finding, a slightly low level of Copper was found in the study done by Lee et al [32] .
Psoriasis may be due to increase oxidative stress and most of trace elements enter in enzymatic process needed for anti oxidants.
Zinc is considered as an antioxidant because the extracellular enzyme superoxide dismutase is zinc- dependent, it plays a vital role in the protection against free radical damage [16].
The disturbance of trace elements not only in the level but also the disturbance in element to element ratio that lead to hemeostatic imbalance which lead to induction and severity of psoriasis [36-38].
Studying the level of trace elements in psoriatic patients gives an idea about the mollecular basis of psoriasis and cytokine etiology.

Our study was limited to a small number of the patients and many studies are needed on a larger numbers of patients to prove the role of trace elements in the pathogenesis of psoriasis.

Conclusion

1. In every patient with psoriasis: it is a must to measure trace element especially calcium, phosphorous, zinc, copper.
2. Correction of trace elements imbalance help in treatment of psoriasis.
3. Further study has to be done in larger population to show the effect of trace elements in psoriasis development and progression.

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RELATIONSHIP BETWEEN HEALTH BEHAVIORS AND QUALITY OF LIFE ON THE ONE HAND AND SATISFACTION WITH HEALTH CONDITION ON THE OTHER HAND IN PATIENTS WITH *PSORIASIS*

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Abstract

Introduction: Scientific research suggest that the more severe psoriasis symptoms are the poorer quality of life. Reviews show that appropriate health practices can reduce severity of symptoms of some diseases on the one hand and influence subjective assessment of quality of life on the other hand. The authors tried to assess the frequency of health behaviors in patients with psoriasis compared to the control group, as well as to analyze the relationship between health behavior and the quality of life.

Methods and Methods: The study was conducted on 61 patients with psoriasis and 60 respondents as a control group. Two tools were used in the study: Behavioral Health Inventory and author's questionnaire with questions concerning quality of life, satisfaction with health condition, number of medicines used and severity of psoriasis. Statistical analyzes were performed using Statistica SPPS 18.

Results: Patients with psoriasis assessed as worse their quality of life compared to the control group. In case of intensity of healthy eating habits the similar differences were revealed. Inverse relation was observed in case of prevention behaviors. There were no differences between the groups in terms of positive mental attitude and health practices. Quality of life in patients with psoriasis correlated with a positive mental attitude.

Conclusions: Our results suggest the need for comprehensive education in three areas: medical, nutritional and psychosocial.

Key words: quality of life; psoriasis; skin changes; health behaviors

Cite this article:
Mariusz Jaworski: Relationship between health behaviors and quality of life on the one hand and satisfaction with health condition on the other hand in patients with psoriasis. Our Dermatol Online. 2013; 4(4): 453-457.

Introduction

Health behaviors are defined as any behavioral activity undertaken by a person which have an impact on her/his health condition, both positive and negative. The division of these behaviors varies widely in the literature. One reason for this is that one faces many difficulties associated with defining this term depending on the approach [1]. The division based on the relationship 'cause – effect' is most often cited. Accordingly, the behaviors are divided into: favorable behaviors (pro-health behaviors) and unfavorable behaviors (anti-health behaviors) [2,3]. The present study analyzes only pro-health behaviors in case of patients with psoriasis. This is due to the fact that in the literature there are no scientific reports that analyze strictly these issues.

Psoriasis is a chronic, genetically determined disease. It is characterized by inflammatory changes of skin with periods of recurrence and remission. Four main factors associated with the pathogenesis of psoriasis are mentioned in the literature, namely auto-immunological, genetic, hormonal and psychosomatic ones [4]. The incidence of psoriasis affects from 1.5 to 3 percent of the population [5] and it is equally frequent in men and women [4].

Diagnosis of psoriasis is associated with the identification of characteristic skin changes in the form of red scaly rashes itching. The treatment of this disease presents one of the most difficult dermatological challenges. The most commonly used treatment methods include: external (specific and non-specific), general (including retinoids, immunomodulating and cytostatic medicines) and physical (including photochemotherapy, phototherapy, heliotherapy) [6].

During recent years scientists have attempted to identify behavioral markers which may directly or indirectly contribute to the severity of skin changes in psoriasis. It is suggested that undertaking activities with positive effect on health while limiting anti-healthy behaviors may reduce the severity of symptoms [7,8].

This observation is reported in case of various diseases such as cardiac or metabolic diseases [9]. However, there are no publications which would analyze the frequency of health behaviors in patients with psoriasis. Neither there were attempts to analyze the relationship between these behaviors and subjective assessment of quality of life on the one hand, and satisfaction with the current health condition on the other hand. Significant part of publications examine the role of psychological factors in the severity of psoriasis symptoms [10].
The objective of the present research was to assess the frequency of health behaviors in patients with psoriasis compared to the control group, as well as to analyze the relationship between various categories of these behaviors with the level of quality of life on the one hand, and satisfaction with the current health condition on the other hand.
The following research questions were developed in relation to the main objective of present research:

1) Do patients with psoriasis often undertake health behavior compared to the control group?
2) Is there any relationship between the subjective quality of life and health behaviors in patients with psoriasis?
3) Does frequency of health behaviors in patients with psoriasis correlate with their satisfaction with their health condition?
4) Is there any relationship between severity of skin changes in various parts of the body with the subjective assessment of the quality of life on the one hand, and satisfaction with the current health condition on the other hand?

Materials and Methods

The study was conducted on 61 patients with psoriasis (30 women and 28 men) aged 18 to 67 years. The research was conducted from November 2011 to January 2013. All patients were treated in clinics and hospitals in the region of Mazovia, Poland. Patients were selected using purposive sampling method on the basis of the selection criteria. The subjects were recruited from patients who: 1) were over 18, 2) had psoriasis diagnosed, 3) were subject to ongoing therapy, 4) and gave informed consent to be part of the study. All patients gave their informed consent.
Control group was included in present research. This group consisted of 60 adults who had not been diagnosed psoriasis. The subjects in this group were recruited from persons who: 1) were over 18, 2) had no psoriasis diagnosed, 3) and gave informed consent to be part of the study. The control group was introduced in order to compare the frequency of health behaviors with regard to patients with psoriasis. Age of the control group ranged from 18 to 66 years.
The gender analysis has not been conducted. This is because the number of men and women participating in the research were inadequate.
Behavioral Health Inventory (BHI) by Z. Juczynski was used in the study. This inventory was designed to examine both healthy and sick subjects. BHI consists of 24 items describing four categories of health-related behaviors. These are: proper eating habits, preventive behavior, positive mental attitude and health practices. BHI is characterized by satisfactory reliability and validity parameters [11].
Proper eating habits assess the frequency of consumption of selected health-related product groups including whole wheat bread, vegetables and fruit. Preventive behaviors facilitate the assessment of the extent to which respondents follow recommendations concerning health, as well as how patients obtain information about health and disease from various sources. Health practices concern the assessment of frequency of eating habits associated with rest, sleep and physical activity. And finally the positive mental attitude makes it possible to characterize behavior aiming at the avoidance of too strong emotions, stresses and strains, as well as of any situation that can lead to depression [11].
Patients assessed the subjective level of quality of life influenced by health in accordance with 5-point scale (1 - very poor, 2 - poor, 3 - neutral, 4 - good, 5-very good). Patients also assessed the subjective level of satisfaction with their health condition using 5-point scale (1 – highly non-satisfactory, 2 – non-satisfactory, 3 - neutral, 4 - satisfactory, 5 - very satisfactory). In addition, patients were asked to indicate the amount of medicines used, as well as to determine the severity of psoriasis in various parts of the body such as head, trunk, arms and legs with the buttocks. The severity of skin changes on various body parts was assessed using 6-point scale (0 - no change, 1 - to 10%, 2-over 10% to 30%, 3 - from 30% to 50%, 4 - over 50% 70% 5 - above 70% to 90%, 6 - more than 90% to 100%). Socio-demographic variables such as age, gender, weight, height were monitored during the research. Body mass index (BMI) was calculated on the basis of the anthropometric data (ie, weight and height) according to WHO guidelines [12].
The data was analyzed statistically using StatSoft Statistica 9.0 software. The $p \leq 0.05$ criterion of statistical significance was adopted. Since ordinal and interval scale data were analyzed, both parametric and nonparametric statistics were applied. Correlations between variables were analyzed using the Spearman's rank-order coefficient.

Results

The average age of the analyzed clinical group was 35.13 years (SD = 14.08), while in case of the control group it amounted to 34.92 years (SD = 11.54). There was no statistically significant difference between both groups ($t = - 0.092$, $p = 0.927$). Body weight of persons participating in the research from the clinical group ranged from 51 to 112 kg, while in the control group it fell within the range of 47 to 92 kg. The average body weight was significantly statistically different in case analyzed groups ($t = - 5.314$, $p = 0.000$). It amounted to 69.46 kg (SD = 12.20) for the clinical group and 59.15 kg (SD = 8.84) for the control group. The average value of body mass index (BMI) was slightly higher in the clinical (24.16 kg/m2) than in the control group (21.33 kg/m2) (Tabl. I).
The average level of severity of skin changes did not exceed 30% in each of the analyzed parts of the body. However, the greatest severity of skin changes was observed in case of head and legs, where changes involved over 90% in some people. The lowest severity of these changes was observed in case of arms and trunk. These changes did not exceed 10% (Tabl. II).
The average level of subjective quality of life in patients with psoriasis was neutral (Me = 3.00), whereas 14.8% (n = 9) of respondents indicated that their quality of life was poor. Neutral quality of life was indicated by 36.1% (n = 22) of patients. 49.2% (n = 30) indicated good quality of life. None of the patients indicated that their quality of life was very good or very bad. The level of subjective quality of life was good (Me =4.00) in case of the control group. The observed differences were statistically significant ($z = - 5.864$, $p = 0.000$).
The average level of satisfaction with the current health condition was neutral (Me = 3.00).

		Clinical group				Control group			
		Age	Body mass	Growth	BMI	Age	Body mass	Growth	BMI
Mean		35,13	69,46	169,44	24,16	34,92	59,15	34,99	21,33
Std. Deviation		14,08	12,20	8,46	3,55	11,54	8,841	67,279	2,44
Median		33,00	68,00	168,00	23,44	33,00	57,00	168,00	20,55
Minimum		18	51	154	17,87	18	47	152	18,51
Maximum		67	112	187	32,03	66	92	180	31,10
95% Confidence Interval for Mean	Lower Bound	31,52	66,33	167,28	23,25	31,93	56,87	17,61	20,70
	Upper Bound	38,74	72,58	171,61	25,07	37,90	61,43	52,37	21,96

Table I. Characteristics of the groups in terms of anthropometric parameters.

		Head	Arms	Trunk	Legs
Mean		2,30	0,92	1,36	1,89
Std. Deviation		1,783	1,085	1,291	1,644
Median		2	1	1	2
Minimum		0	0	0	0
Maximum		6	4	4	6
95% Confidence Interval for Mean	Lower Bound	1,84	0,64	1,03	1,46
	Upper Bound	2,75	1,20	1,69	2,31

Table II. The severity of skin changes in different parts of the body.

Nobody declared highly satisfactory level. Approx. 11.5% (n = 7) of patients indicated that they were very dissatisfied with their health condition. Prevailing part of respondents (37.7%, n = 23) indicated their satisfaction with health condition. Neutral appraisal of health condition was showed by 23% (n = 14) of patients. 27.9% (n = 17) of patients was satisfied with their health condition.

Number of medicines used by participants in the research ranged from 1 to 6. Average number of medicines used by patients was 2 (Me =2.00).

Using Spearman correlation coefficient no significant correlation was revealed between the amount of medicines and subjective quality of life (rho = -0.110, p = 0.200), as well as satisfaction with health (Rho = -0.066, p = 0.306) in the clinical group.

Patients with psoriasis rarely applied health-promoting eating behavior compared to the control group. The observed relationship was statistically significant (z = - 3.513, p = 0.000). The reverse relationship was observed in case of prevention behaviors (z = -2.268, p = 0.023). There were no statistically significant differences between the analyzed groups in terms of positive mental attitude (z = - 1.798, p = 0.072) as well as health practices (z = -0.451, p = 0.652). The detailed description of severity of various health behaviors by participants in the research is presented in Table III.

	Clinical group				Control group			
	Health-promoting eating behavior	Prevention behaviors	Positive mental attitude	Health practices	Health-promoting eating behavior	Prevention behaviors	Positive mental attitude	Health practices
X	19,20	21,46	19,59	18,84	22,20	19,77	20,78	18,73
SD	4,69	4,16	4,21	4,25	4,31	3,71	3,44	2,80
M	20,00	21,00	20,00	18,00	23,00	19,50	21,00	18,50
Min	8	13	10	11	12	11	12	12
Max	30	30	29	28	30	27	27	24

Table III. Characteristics of groups in terms of health behavior.

X- Mean / Średnia, SD- Std. Deviation/ Odchylenie standardowe, Min. - Minimum/Minimum, Max- Maximum/ maksimum, M- Median/ Mediana

The severity of all four categories of analyzed health behavior was calculated in this research. It was then compared with different groups of patients. The severity of behavioral categories ratio was calculated according with the guidelines of the BHI author [11]. Our results were compared to research results among patients with diabetes and dialysis patients presented by Juczynski [11].

The comparative summary presented in table 4 is for information only. This is a more complete outline of discussed problem in clinical practice.

Patients with psoriasis were characterized by lower average values of severity of all analyzed categories of health behavior ratios compared to patients with diabetes. In case of dialysis patients, the differences were recorded for the three health behaviors such as eating habits, preventive behaviors and health practices. The severity of positive mental attitude ratio was slightly higher in patients with psoriasis than in dialysis patients (Tabl. IV).

	Psoriasis		Diabetes		Dialysis patients	
	X	SD	X	SD	X	SD
Health-promoting eating behavior	3,20	0,78	3,87	0,70	3,65	0,99
Prevention behaviors	3,58	0,69	4,00	0,63	3,67	0,80
Positive mental attitude	3,27	0,72	3,84	0,62	3,11	0,55
Health practices	3,14	0,72	3,70	0,75	3,47	0,82

Table IV. Comparison of health behaviors in patients with psoriasis with other diseases.

Positive mental attitude of patients with psoriasis is characterized by positive relationship with the level of subjective quality of life (rho = 0.281; p <0.05) and satisfaction with health condition (rho = 0.217; p <.05). Results of own research have shown that general level of health behaviors is characterized by a relationship with level of quality of life in clinical group (rho = 0.217, P <0.05), but there was no relationship with satisfaction with the current health condition. The amount of medicines shows positive relationship with health practices (rho = 0.219, p <0.05) (Tabl. V).

The study showed positive relationship between severity of skin changes on shoulders with frequency of positive mental attitude (rho = 0.225; p <.05). On the other hand, the severity of skin changes in the area of trunk was positively correlated with health practices (rho = 0.217, p <.05). There was no correlation between the severity of skin changes on head and feet and the frequency of analyzed health-related behaviors (Tabl. VI).

		Health-promoting eating behavior	Prevention behaviors	Positive mental attitude	Health practices	The general health behaviors
Quality of live	rho	,102	,092	,281	,204	,217
	p	,216	,239	,014	,057	,046
Satisfaction with health	rho	,088	-,097	,217	-,078	,038
	p	,251	,229	,044	,276	,384
Number of drugs	rho	,060	,128	-,017	,219	,106
	p	,322	,164	,449	,045	,209

Table V. Relationship between health behavior and the quality of life on the one hand and satisfaction with health condition on the other hand in patients with psoriasis.

		Health-promoting eating behavior	Prevention behaviors	Positive mental attitude	Health practices	The general health behaviors
Head	rho	,075	-,178	-,118	-,058	-,069
	p	,282	,085	,182	,330	,299
Arms	rho	,086	,018	,225	,128	,193
	p	,255	,446	,041	,162	,068
Trunk	rho	-,171	,142	,037	,217	,128
	p	,094	,137	,389	,047	,164
Legs	rho	-,121	,135	,137	-,109	,015
	p	,177	,150	,145	,201	,454

Table VI. Relationships between health behavior and severity of skin changes.

Discussion

Health behaviors belong to basic factors that facilitate the maintenance of appropriate health condition. This position is confirmed by many scientists who analyze relations between frequency of these behaviors and health condition in the general population and some disease entities [13,14].

This applies in particular to diseases, in case of which significant correlation between lifestyle and severity of symptoms was shown.

Eating habits, which are one of the categories of health behavior have received special attention during recent years.

The proper diet can reduce the risk of developing certain diseases, especially diet-related ones, as well as can minimize the severity of disease symptoms. This is particularly relevant in case of psoriasis. Preliminary reports suggest that abnormal dietary composition may increase skin changes in psoriasis [15]. According to experts in clinical dietetics and medical nutrition, dietary composition may increase inflammation in psoriasis. It is therefore advisable to combine compatibly proper diet with pharmacotherapy [16]. In addition, nutrients in daily food ration may also affect the functioning of central nervous system, both in terms of functional and structural aspects [15,16]. Nevertheless, there are few publications highlighting the importance of science in the field of nutrition in dermatology.

Our results did not confirm the existence of the relationship between the severity of skin changes in psoriasis and healthy eating behaviors. Moreover, the frequency of healthy eating habits for this patients group was significantly lower compared to the control group (i.e., healthy individuals), as well as to certain other diseases. This phenomenon may be explained by the lack of knowledge about impact of diet on the severity of skin changes on the one hand, and lack of obligatory participation of specialists in the field of nutrition, especially clinical dieticians, in complex treatment of psoriasis on the other hand.

Such a view is upheld by the fact that some patients deliberately restrict consumption of certain groups of products, such as dairy products, in their diet. The main factor motivating patients to apply such restrictions is the association between consumption of these products and the intensity of skin changes [15,16]. It should be stressed that the patients act in these instances rather intuitively.

The foregoing observations may suggest the need for more nutrition education directed to patients with psoriasis, as well as the need to develop obligatory standards concerning the composition of treatment teams and the role of clinical dietitian in the treatment of psoriasis. The main task of a dietitian in this team would be nutritional education and developing appropriate individualized diet taking into account specific individual needs and comorbidities.

Health-related practices showed positive correlation with the amount of medicines and the severity of skin changes in the area of trunk. There was however no relationship between health practices (e.g. rest, sleep and physical activity) with the level of subjective quality of life and satisfaction with the current health condition.

The results of the research showed positive relationship between positive mental attitude and quality of life on the one hand, and satisfaction with current health condition on the other hand in patients with psoriasis. The more patients with psoriasis showed behavior aimed at avoiding too strong negative emotions, stress and tension the more often they indicated higher quality of life and satisfaction with their health condition.

The observed relationships are consistent with the reports of other researchers who have shown that psychological factors may influence the severity of skin changes in psoriasis [8,9]. The foregoing relationship is especially associated with stressors and ability to cope with stress. If the intensity of stress is greater and patient less able to deal with it, the severity of skin lesions is higher. The very fact of illness is a major source of stress. Additionally, the level of stress is compounded in situations when the disease significantly affects interpersonal relationships (what in fact is occurring in case of psoriasis) [17].

Conclusion

The results of our research suggest the need to take actions aimed at improving quality of life of patients with psoriasis, as well as the need to conduct education aimed at increasing awareness among these patients on the relationship with their lifestyle and the severity of skin changes in psoriasis, especially in the area of proper nutrition and the ability to cope with the disease itself. The presented results are of preliminary nature and in order to be more reliable, further detailed study with better control of confounders, larger sample, etc. is required.

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CUTANEOUS TB PROFILE IN NORTH WEST PUNJAB, INDIA: A RETROSPECTIVE DATA ANALYSIS

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Abstract
Introduction: Previous studies from India concluded that the incidence of cutaneous tuberculosis has fallen from 2% to 0.15%, whereas more recent reports suggest that cutaneous tuberculosis is again becoming more prevalent.
Aims: To study the patterns of clinical presentation of cutaneous tuberculosis, to correlate them with histopathology, Mantoux reactivity and BCG vaccination status in the north-west region of Punjab.
Methods: Analysis of the records of patients with cutaneous tuberculosis who attended the hospital between Jan 2009 to Dec 2012.
Results: A total of 36 (0.02%) of dermatology patients had cutaneous tuberculosis. The type of cutaneous tuberculosis in decreasing order of incidence was lupus vulgaris 16 (44.44%) followed by tuberculosis verrucosa cutis 10 (27.77%), scrofuloderma 7 (19.44%) and tuberculids 3 (8.33%). There were no cases of erythema nodosum or miliary tuberculosis. Multiple sites were involved in 17 (47.22%) patients. Face and neck were the most common sites affectedMost of the patients (52.77%) presented with single lesion. Active tuberculosis in other organs were observed in 8 (22.22%) patients. Mantoux test was positive in 23 (63.88%). BCG scar was present in 23 (63.8%) patients. 29 cases (80.55%) showed characteristic histopathological changes of cutaneous tuberculosis.
Conclusions: The incidence of cutaneous tuberculosis in the present study was found to be 0.02% which is far lower as compared to previous reports. Reason for this observation could be the effective implementation of the National Program for tuberculosis at primary and secondary level leading to early diagnosis and treatment, hence lesser number of cases reaching to a tertiary center. This study also depicts the histopathological correlation evident in 80.55% of the histopathological specimens which is highly significant.

Key words: cutaneous tuberculosis; histopathology; Mantoux test; BCG

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Introduction

Tuberculosis is a disease of antiquity. Mycobacterium, the organism responsible was identified about 100 years ago, vaccine and chemotherapy are available for over 50 years. Despite the availability of effective diagnostic tools and treatment, the number of new cases of tuberculosis is rising again [1]. About 1/3rd of the world's population has latent *M. Tuberculosis* infection. And 5-10 % of those having latent infections develop symptomatic infection, but the risk of developing the clinical manifestations of the disease is greatly increased by HIV co-infection [2]. The rise in cases of tuberculosis may be attributed to the emergence of (MDR-TB) Multidrug resistance tuberculosis and (XDR-TB) extensively drug resistance tuberculosis. With the advent of the AIDS epidemic and the introduction of immunosuppressive agents, the incidence of (NTM) non-tuberculous mycobacterial associated disease has increased dramatically [3]. Early studies from India concluded that the incidence of cutaneous tuberculosis has fallen from 2% to 0.15% [4], whereas more recent reports suggest that cutaneous tuberculosis is again becoming more prevalent [5]. Diagnosis of cutaneous TB is challenging as its manifestations are varied, typical dermatologic lesions are rare, and the bacterium is seldom identified by staining or culture. Cutaneous tuberculosis can present with unusual clinical and histopathological features causing delay in diagnosis. Strong clinical suspicion, family history of pulmonary/extrapulmonary TB, a positive Mantoux test and histopathological features aid the diagnosis.

Materials and Methods

This was a retrospective data analysis where the data of 4 years duration from Jan 2009 to Dec 2012 was analyzed. The detailed history regarding age, sex, occupation, education, marital status and socioeconomic class was analyzed. History of trauma was taken into consideration.

Materials and Methods

Data regarding general and systemic examinations in addition to dermatological examination for evidence of tuberculosis elsewhere in the body was taken. Reports of smear from the affected area and sputum for acid-fast bacilli, chest X-Ray, routine haemogram with ESR, Mantoux test, and histopathological examination were retrieved.

Results

The demographic profile of the patients is shown in Table I. During the 48 months of our study 36 patients were found to be suffering from cutaneous tuberculosis out of approx 1,80,000 patients with skin diseases attended the skin OPD, giving an incidence of 0.02%. The age varied from 4 to 85 years, the majority of patients belonged to younger age groups (16 - 30 years) comprising 36.11% of total patients. In 8 cases (22.22%) disease was noted to appear before the age of 15 years. Among adults there were 15 (41.66%) female patients and 12 (33.33%) male patients giving female to male ratio of 5:4. Among children 4 (11.11%) were male and 5 (13.88%) were female. The duration of disease varied from 4 months to 5 years.

Demographic feature	No. of patients (n=36)	%
Age		
0-15	8	22.22
16-30	13	36.11
31-45	7	19.44
46-60	6	16.66
>60	2	5.55
Sex		
Male	12	33.33
Female	15	41.66
Male child	4	11.11
Female child	5	13.88
Rural/ Urban		
Rural	13	36.11
Urban	23	63.88

Table I. Demographic profile of the study cases.

The type of cutaneous tuberculosis in decreasing order of incidence was lupus vulgaris 16 (44.44%) followed by tuberculosis verrucosa cutis 10 (27.77%), scrofuloderma 7 (19.44%) and tuberculids 3 (8.33%). There were no cases of erythema nodosum or miliary tuberculosis. Multiple sites were involved in 17 (47.22%) patients. Face and neck were the sites affected in 15 (41.66%) patients; trunk in 11, buttocks in 5, legs in 4, hand in 3 and foot in 2 patients, (Fig. 1).

Mantoux test was positive in 23 (63.88%) with an induration > 10mm, and negative in the remaining. BCG scar was present in 23 (63.8%) patients. Biopsy reports of 29 cases (80.55%) depicted characteristic histopathological changes of cutaneous tuberculosis. In rest of cases (19.44%) the histopathological features were non-specific. Active tuberculosis in other organs (Lung, bone and lymph nodes) was observed in 8 (22.22%) patients. All the patients were negative for HIV, (Fig. 2).

All patients were referred to directly observed treatment, short-course (DOTS) center of the institution and were given anti-tuberculosis treatment. Patients showed significant clinical response and in most of the cases healing with scarring within a period of 6-9 months.

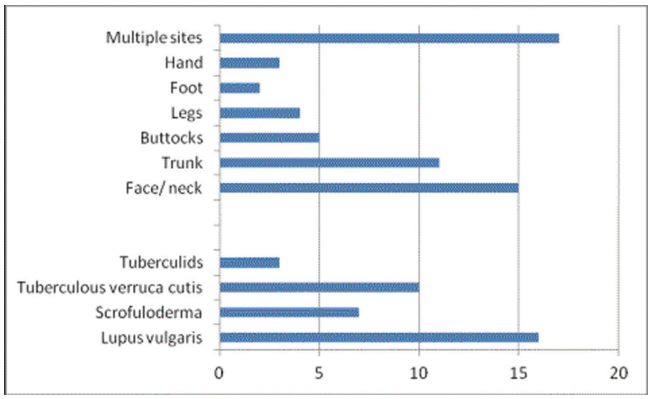

Figure 1. Figure depicting the site and type of cutaneous tuberculosis among study cases.

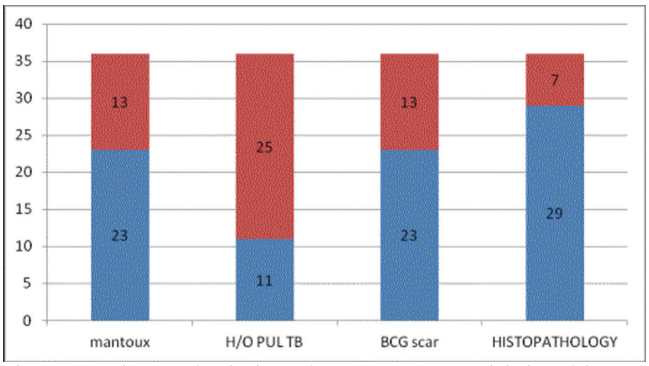

Figure 1. Figure depicting the Mantoux positivity, history of pulmonary tuberculosis, presence of BCG scar and histo-pathological corelation (n=36).

Legends: red colour - Negative; blue colour - Positive

Discussion

The genus *Mycobacterium* contains more than 80 species, most of which are harmless environmental saprophytes. A few species are important pathogens of humans and other vertebrates. The most important obligate human pathogens are *Mycobacterium tuberculosis* and *M. leprae*, but others such as *M. avium* and *M. ulcerans* are also significant.

M. tuberculosis can cause skin infection by direct inoculation into the skin, by haematogenous spread from an internal lesion or by direct contact with tuberculosis in an underlying deeper structure. To date, histopathology testing and isolation of *M. tuberculosis* in culture of skin samples or by PCR have been considered the best diagnostic tools for the detection and diagnosis of cutaneous TB. The definitive criterion for cutaneous TB is the isolation of the bacterium in culture or the identification of mycobacterial DNA by PCR. Unfortunately, few institutions or laboratories can afford this procedure, particularly in developing countries [6].

The wide clinical spectrum of cutaneous tuberculosis is dependent on the route of infection (endogenous or exogenous), the immune status of the patient and whether or not there has been previous sensitization with tuberculosis. *M. tuberculosis* is the main organism responsible for cutaneous tuberculosis.

In the skin, tuberculosis presents itself in an astonishing variety of forms, which has given rise to an unwieldy, overextended number of descriptive terms and bewildering classifications. The potential of the skin to react in many different ways to a single disease agent is nowhere better illustrated than in tuberculosis [7].

Primary inoculation produces tuberculous chancre and tuberculous verrucosa cutis in non-immune and immune host respectively. Lupus vulgaris occurs mainly through haematogenous, lymphatic or contiguous spread. Scrofuloderma results from contiguous involvement of skin overlying tuberculosis in deeper structures, for example lymph node, bone or joint. Metastatic tuberculous abscess (tuberculous Gumma) can occur due to haematogenous spread from primary focus. Ingestion of bacteria from swallowing sputum or milk contaminated with *M. bovis* can result in orificial, perioral or perianal tuberculosis. Tuberculids results from immunological reaction to haematogenous spread of antigenic components of *M. tuberculosis* [8].

The incidence of different forms of cutaneous tuberculosis varies among gender, age group, socioeconomic strata and geographical location globally. The incidence of cutaneous tuberculosis in the present study was found to be 0.02%, which was far lower as compared to previous reports of 0.28% [9] and 0.59% [10]. The duration of disease varied from 4 months to 5 years.

The commonest type of TB was lupus vulgaris in the present study (36%), followed by tuberculosis verrucosa Curtis and scrofuloderma by 32% and 28% respectively. Similar findings have been reported by other authors [10-12]. However, some authors have reported Scrofuloderma to be the most common variety [13,14], while others have reported TVC [11] to be most common.

The minimum incidence was that of tuberculids in our study, as reported by other authors previously [4]. History of pulmonary TB could be elicited in 30.55% of the patients, which was comparable to that reported previously (10% to 45%) [15,16].

In agreement with previous studies, the majority of the Scrofuloderma lesions was located in the neck area (41.66%) [17,18].

Biopsy reports of 29 cases (80.55%) showed characteristic histopathological changes of cutaneous tuberculosis. In 7 cases (19.44%) the histopathological features were non-specific. Early, non-specific inflammatory changes give rise after 3–6 weeks to a characteristic tubercle. The fully formed tubercle consists of a focus of epithelioid cells containing a variable, but usually sparse, number of Langhans' giant cells and a surrounding infiltrate of mononuclear cells. The center of the tubercle undergoes caseation necrosis and sometimes calcifies. Endovascular or perivascular changes in the vicinity of the tubercle become more marked as necrosis proceeds, and are accompanied by a cellular reaction leading to fibrosis. Such granulomas vary greatly in appearance, depending on the virulence of the organism, the size of the inoculum and the immune status of the patient [19].

Conclusion

The incidence of cutaneous tuberculosis in the present study done at a tertiary care center was found to be 0.02% which is far lower as compared to previous reports of 0.28% [9] and 0.59% [10]. Reason for this observation could be the effective implementation of the National Program for tuberculosis at primary and secondary level leading to early diagnosis and treatment, hence lesser number of cases reaching to tertiary center like ours. This study also depicts the histopathological correlation evident in 80.55% of the histopathological specimens which is highly significant.

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CUTANEOUS TB PROFILE IN NORTH WEST PUNJAB, INDIA: A RETROSPECTIVE DATA ANALYSIS

by Tejinder Kaur, Alpna Thakur, Kritika Pandey, Suresh Kumar Malhotra, Karan Jit Pal Singh Puri

comment:

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Although it is a "disease of antiquity", nicely described by Kaur T et al, tuberculosis is still a challenge in the modern medicine. The authors highlighted the role of HIV coinfection, but we don't have to forget about the role of anti-TNF therapies (widely prescribed nowadays) in reactivating tuberculosis infection, especially in endemic regions [1].

Another important point that we could observe here is the important number of cases with a negative Mantoux test (approximately 36%). As we showed previously, Mantoux or tuberculin skin test (TST) is not a reliable technique in detecting the infection. We registered positive tuberculin skin test (defined in the context of biologic therapy as induration >5 mm) in 51% of nondermatologic subjects, respectively 70% of the patients with psoriasis [2]. Among them, 50% of psoriatic patients and 28% of nondermatologic subjects had an induration >10 mm (unpublished data).

We have also reported the reactivation of TB under anti-TNFα therapy [3]. According to World Health Organization, the incidence rate of tuberculosis in Romania was estimated to 101/100000 population [4]. However, even if Romania is an endemic country, we mostly see pulmonary tuberculosis, cutaneous tuberculosis being very rare.

Thus, we need to compliment the authors for a very clear and didactic presentation of different forms of cutaneous tuberculosis.

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EVALUATION OF THE EFFICACY OF A COMBINATION – *MEASLES*, *MUMPS* AND *RUBELLA VACCINE* IN THE TREATMENT OF *PLANTAR WARTS*

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Abstract
Introduction: The treatment of patients with plantar warts continues to be a frustrating matter for both primary care physicians and dermatologists. There are new trends towards the use of immunotherapy in treatment of warts, as the immune system seems to play an important role in the control of warts infection.
Aim: Assessing the efficacy of intralesional injection of MMR vaccine (measles, mumps, rubella) in the treatment of plantar warts.
Patients: One hundred patients complaining of plantar warts were included in this study.
Methods: The patients were divided into two groups:
Group 1: This group included 50 patients subjected to intralesional injection of measles, mumps, rubella vaccine (MMR).
Group 2: This group included 50 patients as a control group and subjected to intralesional injection of 0.3 ml saline.
Only single wart was injected. Injections were done at 3-weeks interval until complete clearance or for a maximum of 3 treatments.
Follow up of patients was done every month for six months for clinical assessment of results and to show any recurrence.
Results: Regarding the response of the target wart, MMR- treated group showed significantly higher rate of complete clearance compared with the control group (82% versus 0% respectively). The rate of partial response was 6% versus 30%, and the rate of no response was 12% versus 70%, respectively. Regarding the response of untreated distant warts, MMR-treated group showed 86.9% complete and 13.1% partial clearance of the warts whereas the control group showed 100% no response. This strongly indicates the development of a widespread HPV-targeted immunity as a response of antigen injection and represents a major advantage of the intra lesional immunotherapy.
Conclusions: We found that treatment of plantar warts by MMR vaccine is effective, with good cure rates and excellent safety profile.

Key words: Immunotherapy; MMR vaccine; plantar warts

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Introduction

Plantar warts are benign epithelial proliferations on the sole of the foot most frequent over pressure points [1,2].
Plantar warts are caused by Human Papilloma Virus (HPV), a small non-enveloped double stranded DNA virus [1].
The treatment of patients with plantar warts continues to be a frustrating matter for both primary care physicians and dermatologists. They are usually treated by a wide variety of methods including cryotherapy, surgical excision, podophyllin, bleomycin and lasers. Each mode of therapy has its own complications and failure rates [3-5].
Previous mentioned methods are not always successful and may be associated with adverse events. Even when existing warts are successfully eradicated, patients may develop new warts in other areas [1,2].

There are new trends towards the use of immunotherapy in treatment of warts, as the immune system seems to play an important role in the control of warts infection. Although the exact mechanisms are unclear but most evidences suggest that cell mediated immunity plays an important role in control of HPV infection as the incidence of warts increases in subjects with cell mediated immune defects e.g (HIV infection patients, malignant diseases. etc….) [6-8].
Various methods have been used to stimulate the immunological response as oral levamisole, cimetidine, zinc sulfate, cidovir, intralesional interferons, topical dinitrochlorobenzene, squaric aciddibutyl ester, imiquimod, intralesional immunotherapy with mumps, candida and trichophyton antigens, intradermal BCG vaccine, and intralesional MMR vaccine [9-11].

The aim of this study was

Assessing the efficacy of intralesional injection of MMR vaccine (measles, mumps, rubella) in the treatment of plantar warts.

Patients

One hundred patients complaining of plantar warts were included in this study (their age ranged from 17 to36 years with a mean of 23.88 ± 4.66 and they were 50% males and 50% females 50% of patients with single wart and 50%of patients with multiple warts and the duration of warts ranged from one to six months).

They were selected from the outpatient dermatology clinic of Alexandria Main University Hospital.

All patients gave informed consent to participate in this work. The study was approved by Ethical Committee of scientific research, Faculty of Medicine, Alexandria University.

They were divided into two groups:

Group 1: This group included 50 patients subjected to intralesional injection of measles, mumps, rubella vaccine (MMR) .

Group 2: This group included 50 patients as a control group and subjected to intralesional injection of 0.3 ml saline.

Inclusion Criteria:

· Patients should have single or multiple plantar warts (from 2 up to 7 warts).
· The age is more than 12 years.
· No concurrent systemic or topical treatment of warts

Exclusion criteria:

· Patients with fever or signs of any inflammation or infection.
· Children < 12 years.
· Pregnancy.
· Lactation.
· Immunosuppression.
· Patients who received any other treatments for their warts in the last month before enrolment.
· Past history of asthma, allergic skin disorders, meningitis or convulsions

Methods

All the patients in the study were subjected to the following:

1. History taking:

- Personal data: name, age, sex, occupation and marital state.
- Present history: pain, disfigurement, interference with function.
- Past history: previous treatments, recurrence and duration of the wart.
- Medical history: systemic diseases as HIV, diabetes, asthma and cutaneous diseases as generalized eczema or urticaria.
- Drug history: corticosteroids or chemotherapeutic drugs.

2. Clinical examination:

For identification of the characteristics of the warts including site, size, number and presence or absence of distant warts before the first treatment session and 3 weeks after the last one.

3. Photography of the lesions:

Before the first treatment session and 3 weeks after the last one.

4. Injection of the target wart with either MMR or saline according to the group assignment.

Group 1:

Patients are subjected to intralesional injection of 0.3ml of measles, mumps, rubella vaccine (MMR) in the target (usually the largest wart). Injections were done at 3-weeks interval until complete clearance or for a maximum of 3 treatments.

There are two available forms of MMR vaccine (Trimovax Merieux):

1. Single dose vial of freeze-dried vaccine. It should be reconstituted with 0.5 ml of diluent (water for injections).
2. Ten dose vial of freeze-dried vaccine. It should be reconstituted with 5 ml of diluent (water for injections).

Its storage: at 2-8oC (36-46oF).

It is preferable to use MMR vaccine immediately after reconstitution. If reconstituted vaccine is not used within 8hours it must be discarded.

MMR vaccine is available at Vacsera company.

Group2:

Patients are subjected to intralesional injection of 0.3 ml saline in the target wart at 3-weeks interval until clearance or for a maximum of 3 treatments.

In both groups, the warts were injected using a built in insulin syringe. Immediate and late side effects were evaluated after each treatment session. Patients were examined before each injection noting the number and surface area of warts.

Follow up of patients was done every month for six months for clinical assessment of results and to any recurrence.

The response was evaluated as follows:

· Complete: disappearance of the wart(s) and appearance of normal skin.
· Partial: 50-99% reduction in size.
· No response: 0-49% reduction in size.

Resolution of distant untreated warts was also assessed.

Statistical analysis of the data

The clinical and laboratory results obtained are statistically analyzed using SPSS/PC* (Statistical package for social science for personal computers).

Results

We found no statistically significant difference in response according to age and sex of patients. The cure rate was better in patients with a shorter duration of the disease and multiple lesions.

Clinical response:

On comparing the treatment responses in the target wart, a significant difference was found between MMR- treated group compared with the control group, showing higher rates of complete response (82% versus 0% respectively), but as regard partial response it was (6% versus 30%) and as regard no response it was (12% versus 70%) (Tabl. I), (Fig. 1).

On comparing different treatment responses in distant wart in both groups, it was found a significantly higher rates in MMR-treated group compared with the control group (complete response: 88.9% versus 0% respectively, partial response: 11.1 % versus 0% respectively, no response: 0% versus100% respectively) by using chi-square test (Tabl. II), (Fig, 2-4).

	Cases (n = 50)		Control (n = 50)		p
	No.	%	No.	%	
Response to treatment					
No response	6	12.0	35	70.0	<0.001*
Partial response	3	6.0	15	30.0	
Complete response	41	82.0	0	0.0	

Table I. Comparison between the MMR- treated group and the control group as regard the response of target wart

p: p value for Monte Carlo test for comparing between the two studied group

***: Statistically significant at p ≤ 0.05**

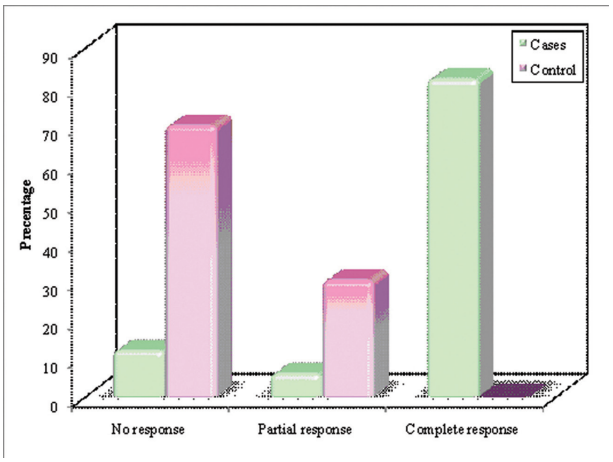

Figure 1. Comparison between the two studied groups according to response to treatment.

	Cases (n = 25)		Control (n = 25)		p
	No.	%	No.	%	
Response to treatment					
No	0	0.0	25	100.0	<0.001*
Partial	3	13.1	0	0.0	
Complete	22	86.9	0	0.0	

Table II. Comparison between the two studied groups according to response to treatment at distant lesions

p: p value for Monte Carlo test for comparing between the two studied group

***: Statistically significant at p ≤ 0.05**

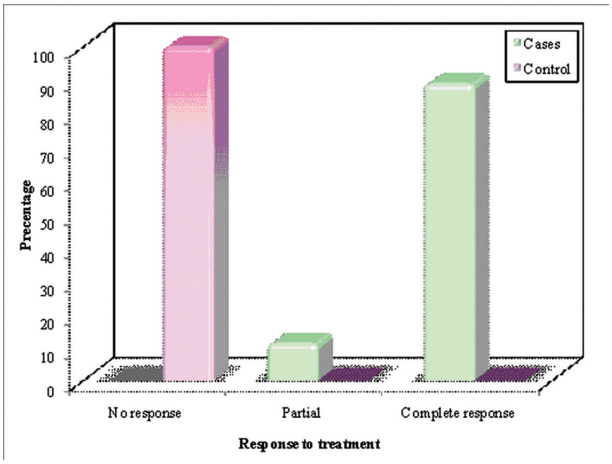

Figure 2. Relation between distant lesions and response to treatment.

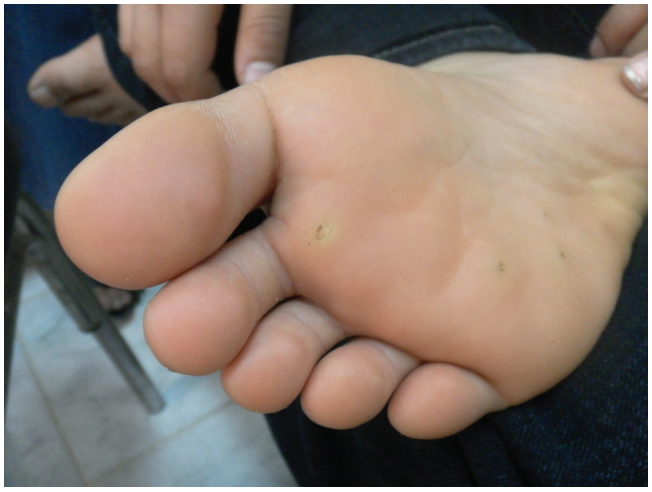

Figure 3. A case of multiple plantar warts before MMR injection.

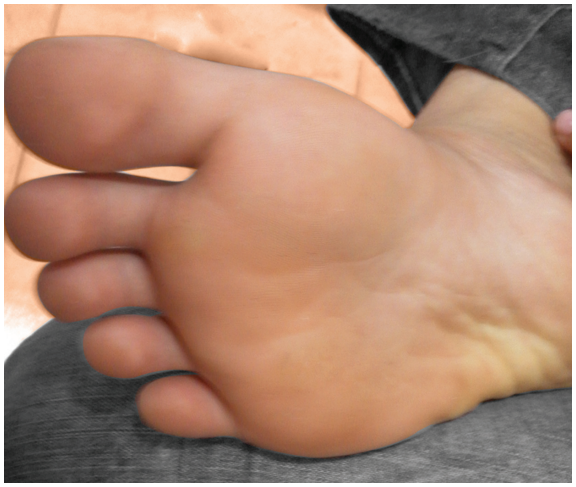

Figure 4. Complete cure of the plantar warts after MMR injection.

Discussion

Plantar warts are common dermatological problem caused by the human papillomavirus (HPV) [1,2].

Papilloma viruses are epitheliotropic non-enveloped small double stranded DNA viruses whose replication is strictly dependent on the terminally differentiating tissue of the epidermis [12].

Immune mechanisms have been suggested to explain the spontaneous resolution of warts. If this immunity could be enhanced, wart resolution could be long lasting. The stimulated immune system would destroy all warts in the body, saving the patients the local treatment for each individual wart [13]. It has been reported that untreated warts resolve after injection of only one wart with intralesional immunotherapy that induces HPV-directed immunity [14]. Antigens used for intralesional immunotherapy include tuberculin [15]; BCG [16]; mumps, candida and trichophyton [17] and MMR [18].

We aimed in this work to evaluate the effectiveness of intralesional injection of MMR vaccine (mumps, measles, rubella) for the treatment of plantar warts.

As regard the response of the target wart, MMR- treated group gave better results compared with the control group, higher rates of complete response (82% versus 0% respectively); but as regards partial response, it was 6% versus 30% respectively and as regards no response, it was 12% versus 70% respectively.

Regarding the response of the distant wart, MMR-treated group showed better results compared with the control group with higher rates of complete response (86.9% versus 0% respectively), partial response (13.1% versus 0% respectively), and no response (0% versus 100% respectively).

The clearance of untreated distant warts strongly indicates the development of a widespread HPV-targeted immunity as a response of antigen injection and represents a major advantage of the intralesional immunotherapy. The total absence of response in the distant warts of the control group confirms the presence of a systemic immune response with MMR treatment.

Our results with MMR-treated group showed a closely similar response rate to those previously reported by Nofal (2010) [18] (his study on the effect of MMR vaccine in the treatment of common warts with complete clearance in 80% of cases and no recurrence was observed during the follow up period), Gamil et al. (2010) [19] (their study on MMR vaccine in treatment of plantar warts with 87% complete clearance in injected warts), Brunk [20] (using candida antigen with 85% clearance) and Gupta et al [21] (using killed *Mycobacterium* W vaccine for the treatment of ano-genital warts with 88.9% clearance), slightly higher than those reported by Phillips et al [13] (using candida antigen injection with72% clearance), Johnson, Roberson, and Horn [22] (using mumps or candida skin test antigens with74% clearance), and Johnson and Horn [14] using combination of skin test antigens with 70.9% clearance), and much higher than those shown by Kus et al [15] (using intralesional tuberculin with 29.4% clearance), Clifton et al [23] (using intralesional mumps or *Candida* antigens with 47% clearance), Signore [24] (using *Candida albican*s intralesional injection immunotherapy of wartswith 51% clearance), and Horn et al [17] (using Intralesional immunotherapy of warts with mumps, candida and trichopyton skin test antigens with 53% clearance).

The relatively higher response in our study as compared to the other related studies which utilize either a single antigen or a combination of antigens may be attributed to the presence of three viral antigens that potentiate each other and could be associated with higher stimulation of the immune system. The differences in the number of the studied patients, the duration and the resistance of warts may also explain this difference.

Although the results of this type of therapy were significantly better than in the control group, a better response might have been obtained if the volume of MMR injected was increased, if more than a wart (not only the target wart) were treated at a time, or if more treatment sessions were used as in Gupta et al. work (2008) [21] showing 88.9% cure 651 ones (>40 years) who showed less immune response.

An important observation in this work was the better cure rate in patients with shorter disease duration. It is quite known that warts typically continue to increase in size and distribution and may become more resistant to treatment over time [23]. So early treatment of warts is mandatory and waiting for spontaneous resolution might sometimes make the condition difficult to treat.

Regarding the number of warts, we found a significant better response in multiple lesions than in single ones.

No serious side effects were reported in patients included in this study. Only reported, tolerable pain during injection was the main side effect.

Flu-like symptoms were reported in two of our patients which resolved within 24 hours, by nonsteroidal anti-inflammatory medications. No swelling, redness, or pruritus at the site of the injection were found.

As regards the benefits to the patients, MMR local injection has significant advantages over other treatments. Most treatment modalities are painful, needing multiple visits (time and money consuming), and are directed to each individual wart. In MMR treatment we have two or three injections, clearance of distant non-injected warts, patients are able to resume normal daily activities and are free of residual scars which was very appreciated by all patients.

The mechanism of action of intralesional immunotherapy is still unclear. It may act through induction of strong nonspecific inflammatory response against the HPV-infected cells [22,23]. It has also been suggested that the trauma itself may cause wart clearance in previously sensitized individuals [15]. Release of cytokines by immune system such as IL-2,IL-4,IL-5,IL-8, IFN-γ and TNF-α stimulate a strong immune response against HPV may be another possible mechanism of action [21]. Horn et al have reported that the response to antigen injection was associated with proliferation of peripheral blood mononuclear cells that promotes Th1 cytokines, including interferon gamma and interleukin 2, which further activate cytotoxic T cells and natural killer cells that eradicate HPV-infected cells [17].

Conclusion

Intralesional immunotherapy by MMR vaccine is a promising modality for the treatment of plantar warts, particularly multiple and recalcitrant warts and those associated with warts at distant locations. It seems to be effective, with good cure rates and excellent safety profile, but how exactly it works to stimulate immunity to cause wart clearance is still unclear.

Recommendation

-Further studies on larger population is recommended.

-Comparing the effect of different types of immunotherapy in the management of plantar warts.

-Comparing the effect of intralesional MMR vaccine in the management of different types of warts.

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GENETIC ANALYSIS OF 5 α REDUCTASE TYPE II ENZYME IN RELATION TO OXIDATIVE STRESS IN CASES OF *ANDROGENETIC ALOPECIA* IN A SAMPLE OF EGYPTIAN POPULATION

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Abstract
Objective: To study the genetic polymorphism of 5-α reductase type II enzyme in relation to oxidative stress in cases of androgenetic alopecia (AGA) in a sample of Egyptian population.
Materials and Methods: This study was conducted on 45 patients with different grades of AGA,and 45 healthy subjects as control group. Laboratory tests included DNA extraction from blood, amplification of the 5-α reductase type II by PCR and V89L mutation analysis by restriction endonuclease enzyme RsaI, and estimation of the levels of plasma catalase and erythrocyte lysate superoxide dismutase (SOD) enzymes by colorimetric methods.
Results: The studied subjects carrying the homozygote(LL) and the heterozygote (VL) genotypes were of no risk of developing AGA.(OR=0). Regarding the leucine allele, the studied subjects carrying the (L) allele were at about 3.7 higher risk of AGA .(OR=3.692), and the results were statistically significant ($p<0.001$). There was significant increase in the level of SOD and catalase in patients than in control group($p=0.005$),and ($p<0.001$) respectively,plasma catalase is significantly higher in patients with LLvariant than inVL variant ($p=0.020$). Asignificant relations was found between the severity of the disease and age and family history ($p=0.037$), and (0.036) respectively, there was no significant correlation between the level of catalase enzyme and SOD in one hand and the severity of the disease among patients.
Conclusions: There is a possible association between AGA and V89L genetic polymorphism of 5-alpha reductase type II enzyme, patients carrying the mutant leucine (L) allele have a risk for developing AGA. Also there is possible association between AGA with oxidative stress.

Key words: androgenetic alopecia; 5-α reductase type II; oxidative stress

Cite this article:
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Introduction

Androgenetic alopecia (AGA), the most common type of baldness in both males and females, it is a hereditary thinning of the hair induced by androgen in genetically susceptible individuals that has its onset in late adolescence. AGA is found to be a stressful condition affecting the psychological functioning of an individual [1-3]. About 50% of male population shows some degree of AGA around 50 years of age, and about 12% of women by the age of thirty and up to 41% of women by the age of seventy. The global incidence varies among the different ethnic groups [4-6].

The most important etiological factor for AGA is genetic predisposition; The suspicion of polygenic inheritance is under investigation [7-9]. The 5-α reductase enzyme is responsible for the chemical reaction that converts the hormone testosterone in to the more potent Dihydrotestosterone (DHT) hormone. There are two isoenzymes of the enzyme, steroid 5-α reductase, type 1 and type II [10–13]. Cases with androgenic alopecia have higher levels of 5-α reductase which is present predominantly in the scalp,increased sensitivity of hair follicles to Dihydrotestosterone (DHT), which in turn causes miniaturization of the hair follicles [7,10].

Environmental factors play a role in the development of AGA by causing oxidative stress, which is a disturbance in the normal redox (oxidation–reduction) state of cells that can cause toxic effects that damage all components of the cell [14,15].

Superoxid dismutase and catalase are enzymes which are an important antioxidant defense in nearly all cells exposed to oxygen. The decrease in their levels or activities can cause an oxidative stress status of the cells of the body including hair keratinocyets [14,16].

Aim

The aim of the work is to study the genetic polymorphism of 5-α reductase type II enzyme in relation to oxidative stress in cases of androgenetic alopecia in a sample of Egyptian population.

Materials and Methods

This study enrolled 90 candidates, divided into two groups, (group I) including 45 patients with different grades of androgenetic alopecia. (group II) as control group,including 45 individual who were not suffering from androgenetic alopecia. Age ranged from 20 to 60 years in both groups. Individuals suffering from increased steroid hormones activity were excluded from the study.

The patients were selected from the dermatology outpatient clinic of the main university hospitals, faculty of medicine, university of Alexandria. After obtaining the approval of ethical committee, both patients and control subjects were subjected to full history taking, dermatological examination, assessment grades of AGA using Hamilton-Norwood's classification in males and Ludwig Classification of Female Hair Loss,and laboratory investigations.

1. Molecular analysis:

Genomic DNA was extracted from peripheral blood anticoagulated with EDTA, using a spin column protocol [GeneJET™ Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific Inc. http://www.thermoscientific.com/fermentas)]. The total DNA yield was determined by spectrophotometer through absorbance at 260nm (A260) using Tris-EDTA (TE) buffer as a blank. The quality of DNA was assessed as well by measuring the absorbance at both 260nm and 280nm (A260/A280 ratio) [17].

Polymorphism of 5-α reductase enzyme type II is analysed by PCR-restriction fragment length polymorphism (RFLP). RsaI RFLP was determined by amplification of a 349bp fragment of exon 1 using forward primer 5'-CGCCTGGTTCCTGCAGGAGCT-3'and reverse primer 5'GTGAAGGCGGCGTCTGTG-3' (Thermo Fisher Scientific Inc. http://www.thermoscientific.com/fermentas). PCR amplification of genomic DNA was carried out using 25µl of PCR master mix, 0.5 µM of forward primer, 0.5 µM of reverse primer,50 nanogram of extracted genomic DNA. The volume is completed to 50µl with deionized water. The thermal conditions required for the reaction were

Initial denaturation at 95°C for 10 minutes. Followed by 35 cycles of 95°C for 1 min, 60°C for 1 min, 72°C for 30 s, followed by a final extension at 72°C for 10 min. The products were then digested with 5 unites of RsaI (Thermo Fisher Scientific Inc. http://www.thermoscientific.com/fermentas). Digested products or the restriction fragments were separated by electrophoresis on 2% agarose gels containing ethidium bromide and visualized by UV illumination [Biometra. http://www.biometra.com] [18].

2. Estimation of SOD in erythrocyte lysate by a colorimetric method [19].

This assay relies on the ability of the enzyme to inhibit the phenazine methosulphate-mediated reduction of nitroblue tetrazolium dye. The lysate was diluted with distilled water so that the % inhibition falls between 30% and 60%. Measurement of the increase in absorbance was performed at 560 nm for 5 minutes for control (Δ Acontrol) and for sample (Δ Asample) at 25°C. Where: (Δ Acontrol) = the change in absorbance at 560 nm over 5 minutes following the addition of PMS to the reaction mixture in the absence of sample (Δ A sample) = the change in absorbance at 560nm over 5 minutes following the addition of PMS to the reaction mixture in the presence of sample.

$$\text{Percent inhibition} = \frac{\Delta \text{ A control} - \Delta \text{ A sample}}{\Delta \text{ A control}} \times 100$$

SOD Activity U/ ml = % inhibition × 3.75.

3. Determination of plasma catalase level by a colorimetric method [20].

Catalase reacts with a known quality of H2O2. The reaction is stopped after exactly one minute with catalase inhibitor. In the presence of peroxidase (HRP), the remaining H2O2 react with 3,5-dichloro-2-hydroxybezene sulfonic acid (DHBS) and 4-aminophenazone(AAP) to form a chromophore. It was read at 510nm and the color intensity is inversely proportional to the amount of catalase in the original sample.Samples were read against a sample blank (Asample), and a standard was read against a standard blank (Astandard) at 510nm.

$$\text{Catalase activity in plasma (U/L)} = \frac{\text{A standard - A sample}}{\text{Astandard}} \times 1000.$$

Results

Clinical characteristics of patients and controls were illustrated in Table I. The severity of AGA in male patients was determined according to the Hamilton Norwood classification, 7 (25.9%) patients were of grade III, 2 (7.4%) patients were of grade IV, 6 (22.2%) patients were of grade V and 12 (44.4%) patients were of grade VI. For the female patients, the severity was determined according to the Ludwig classification of female hair loss:7 (38.9%) patients were of grade I,10 (55.6%) patients were of grade II, and 1 (5.6%) patient was of grade III.

Genotyping was performed in AGA patients and control subjects for the 5 α reductase type II enzyme gene polymorphism using RFLP-PCR and gel analysis. There are three possible genotype for the type II 5-α reductase; a normal homozygote for valine residue (VV), a mutant homozygote for leucine residue (LL), a polymorphic heterozygote which has both valine and leucine (VL). The homozygote (VV) genotype produces 2 bands at 93 bp and 256 bp, while the homozygote (LL) genotype produces 2 bands at 93bp and 236 bp, and the heterozygote (VL) genotype produces 3 bands at 93bp, 236bp and 256bp (Fig. 1).

The frequency of the three genotypes is illustrated in Table II. Based on chi-square, Fisher Exact and odd ratio tests, the studied subjects carrying the homozygote (LL) and the heterozygote (VL) genotypes were of no risk of developing AGA. (OR=0). Regarding the leucine allele, the studied subjects carrying the (L) allele were at about 3.7 higher risk of AGA. (OR=3.692), and the results were statistically significant ($p<0.001$). These results are presented in Table III. The relation between genotype with sex and family history of androgenetic alopecia is illustrated in Table IV.

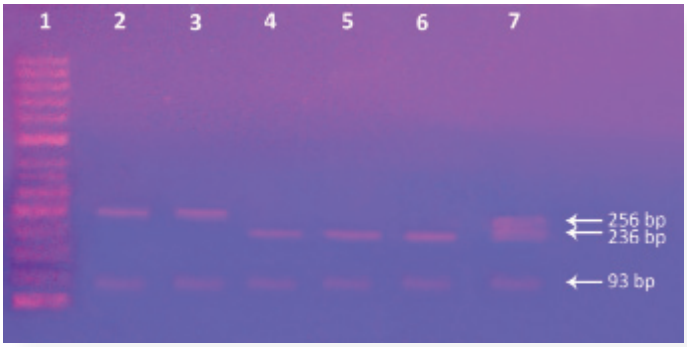

Figure 1. The V89L genetic polymorphism of 5 alpha reductase type II enzyme on agarose gel after digestion by RsaI enzyme. Lanes 2 and 3 showing 2 bands at 93 and 256 bp representing the homozygote (VV) genotype. Lanes 4,5,and 6 showing 2 bands at 93 and 236 bp representing the homozygote (LL) genotype. Lanes 7 showing 3 bands at 93,236 and 256 bp representing the heterozygote (VL) genotype. Lane 1 represents Gene rulerTM Ultra Low Range DNA Ladder, fermentas, Canada.

	Patients		Control		Test of sig.
	No.	%	No.	%	
Sex					
Male	27	60.0	14	31.1	χ^2p = 0.006*
Female	18	40.0	31	68.9	
Age					
<30	10	22.2	23	51.1	
30 – 50	19	42.2	20	44.4	χ^2p <0.001*
>50	16	35.6	2	4.4	
Mean ± SD	43.47 ± 12.86		31.71 ± 10.50		^{t}p <0.001*
Duration of AGA					
Mean ± SD	13.37 ± 9.03				
Family history of AGA	No		%		
-ve	13		28.9		
+ve	32		71.1		

Table I. Clinical characteristics of patients with androgenetc alopecia (AGA) and controls.

p: p value for comparing between the two studied group; * significant at p ≤ 0.05; χ^2: Chi square test; t: t-test

	Patients (n=45)		Control (n=45)		Test of sig.
	No.	%	No.	%	
Genotype					
VV	0	0.0	9	20.0	^{FE}p = 0.003*
VL	26	57.8	36	80.0	χ^2p = 0.023*
LL	19	42.2	0	0.0	χ^2p <0.001*
P	<0.001*				
Allele frequency					
V	26	28.9	54	60.0	χ^2p <0.001*
L	64	71.1	36	40.0	

Table II. Comparison between the two studied groups according to the genotype and alleles frequency.

p: p value for comparing between the two studied group; * significant at p ≤ 0.05; χ^2: Chi square test; MC: Monte Carlo test; FE: Fisher Exact test

	Patients (n=45)		Control (n=45)		Test of sig.	OR	95% CI (LL-UL)
	No.	%	No.	%			
Genotype							
VV	0	0.0	9	20.0	$^{FE}p = 0.003$*		
VL	26	57.8	36	80.0	$\chi^2p = 0.023$*	-	-
LL	19	42.2	0	0.0	$\chi^2p < 0.001$*	-	-
MCp	<0.001*						
Allele frequency							
V ®	26	28.9	54	60.0	$\chi^2p < 0.001$*		
L	64	71.1	36	40.0		3.692	1.984 – 6.870

Table III. The risk of having V89L polymorphism and the leucine allele in relation to androgenetic alopecia.

p: p value for comparing between the two studied group; * significant at p ≤ 0.05; χ^2: Chi square test; MC: Monte Carlo test; FE: Fisher Exact test

	Genotype							
	Patients (n=45)				Control (n=45)			
	LL		VL		VL		VV	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	12	63.2	15	57.7	13	36.1	1	11.1
Female	7	36.8	11	42.3	23	63.9	8	88.9
Test of sig	$\chi^2(p) = 0.137$ (0.712)				$^{FE}p = 0.236$			
Family history								
-ve	7	36.8	6	23.1				
+ve	12	63.2	20	76.9				
Test of sig	0.341							

Table IV. Relation between genotype with sex and family history of androgenetic alopecia.

p: p value for Chi square test for comparing between the two studied group; * significant at p ≤ 0.05; χ^2: Chi square test; FE: Fisher Exact test

Regarding the level of lysate SOD,and plasma catalase,there was significant increase in the level of SOD and catalase in patients than in control group (p=0.005), and (p<0.001) respectively Table V. The relation between plasma catalase enzyme and erythrocyte lysate SOD% and sex, family history and smoking in patients group is illustrated in Table VI. The relation between antioxidant markers and genotype is presented in Table VII, regarding catalase, there was a statistically significant difference between the homozygote (LL) genotype and the heterozygote (VL) genotype, where p = 0.020. While in SOD enzyme, non statistically significant difference was found between the homozygote (LL) genotype and the heterozygote (VL) genotype, where p = 0.530.

Relations between the severity of androgenetic alopecia with genotypes, age, smoking, and family history of androgenetic alopecia in patients group is presented in Table VIII.

	Patients	Control	p
Catalase (U/L)			0.005*
Min. – Max.	15.60 – 384.0	173.0 – 391.0	
Mean ± SD	243.19 ± 88.35	288.33 ± 57.93	
SOD (%)			<0.001*
Min. – Max.	38.0 – 90.0	72.0 – 99.0	
Mean ± SD	67.60 ± 12.49	85.60 ± 6.60	

Table V. Comparison between the two studied groups according to plasma catalase enzyme and erythrocyte lysate SOD enzymes.

p: p value for comparing between the two studied group; * significant at p ≤ 0.05

Catalase					
Sex		Family history		Smoking	
Male	Female	-ve	+ve	No	Yes
238.76 ± 97.83	249.83 ± 74.09	265.08 ± 71.23	234.30 ± 93.99	243.24 ± 83.25	243.13 ± 96.56
P = 0.685		P = 0.295		P = 0.997	
SOD%					
Sex		Family history		Smoking	
Male	Female	-ve	+ve	No	Yes
66.59 ± 13.63	69.11 ± 10.75	66.38 ± 12.70	68.09 ± 12.58	67.60 ± 12.63	67.60 ± 12.65
P = 0.514		P = 0.682		P =1.000	

Table VI. Relation between plasma catalase enzyme and erythrocyte lysate SOD with sex, family history and smoking in patients group.

p: p value for comparing between the two studied group; * significant at p ≤ 0.05

	Genotype	
	Patients	
	LL	VL
Catalase (U/L)		
Min. – Max.	161.0 – 358.0	15.60 – 384.0
Mean ± SD	275.63 ± 48.22	219.48 ± 103.35
P	0.020*	
SOD%		
Min. – Max.	49.0 – 85.0	38.0 – 90.0
Mean ± SD	66.21 ± 12.64	68.62 ± 12.53
P	0.530	

Table VII. The relation between plasma catalase and erythrocyte lysate SOD with the genotype of patients with androgenetic alopecia.

p: p value for comparing between the two studied group; * significant at p ≤ 0.05

Regarding the correlation between the severity (grading) of AGA with catalase enzyme, there was no significant correlation between the level of catalase enzyme and the severity of the disease among patients, where p= 0.107 and 0.668, and r= 0.125 and 0.066 in male and female patients respectively. Also there was no significant correlation between the level of SOD enzyme and the severity of the disease among patients, where p= 0.123 and 0.500 and r= 0.072 and -0.239 in male and female patients respectively.

Discussion

A relationship between the V89L genetic polymorphism of 5-α reductase enzyme and androgenetic alopecia (AGA) has been suggested. In our work we assumed that the genetic polymorphism of the 5-α reductase type II enzyme, would be in close proximity to the etiologic genetic mutations that cause AGA.

In this work, there was a statistically significant difference between the two studied groups regarding the frequency of the three genotypes, where the patients group had a higher frequency of the abnormal mutant polymorphic (LL) genotypes than the control subjects, while the control group had a higher frequency of the normal (VV) genotypes and polymorphic heterozygote (VL) type than the patients group.

Regarding the individual valine and leucine alleles, there was also a statistically significant difference between the two groups. The frequency of (V) allele was higher in the control group, while the frequency of allele (L) was higher in the patients group.We also found that the studied subjects carrying the (L) allele, which was higher in patients group, were at about 3.7 higher risk of developing AGA.

This work also revealed no statistically significant difference between the different genotypes of 5-α reductase type II enzyme, with either the sex, or the family history of AGA. Regarding the severity of AGA, we found that there was no statistically significant difference between the different grades of AGA in relation to the genotypes carried by the patients group.

As AGA being an androgen dependant condition, a relation between the increase of androgens levels, and theV89L genetic polymorphism of the 5-α reductase type II enzyme has been suggested. In 1997, Vilchis et al [21] revealed that the V89L polymorphism of type II 5α reductase gene represents a silent polymorphism which does not alter the phenotypical development among a sample of Mexican population.

	Grading (severity) of AGA													
	Male								Female					
	III (n = 7)		IV (n = 2)		V (n = 6)		VI (n = 12)		I (n = 7)		II (n = 10)		III (n = 1)	
	No	%	No	%	No	%	No	%	No	%	No	%	No.	%
Genotype														
VV	5	71.4	1	50.0	3	50.0	3	25.0	4	57.1	3	30.0	0	0.0
LL	2	28.6	1	50.0	3	50.0	9	75.0	3	42.9	7	70.0	1	100.0
VL	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
MCp	0.225								0.463					
Age														
20 – 30	2	28.6	0	0.0	0	0.0	1	8.3	5	71.4	1	10.0	1	100.0
31 – 40	3	42.9	1	50.0	2	33.3	0	0.0	0	0.0	3	30.0	0	0.0
41 – 50	1	14.3	0	0.0	1	16.7	1	8.3	2	28.6	5	50.0	0	0.0
51 – 60	1	14.3	1	50.0	3	50.0	10	83.3	0	0.0	1	10.0	0	0.0
MCp	0.037*								0.075					
Smoking														
No	2	28.6	1	50.0	2	33.3	2	16.7	7	100.0	10	100.0	1	100.0
Yes	5	71.4	1	50.0	4	66.7	10	83.3	0	0.0	0	0.0	0	0.0
MCp	0.624								-					
Family history														
-ve	3	42.9	0	0.0	0	0.0	0	0.0	5	71.4	5	50.0	0	0.0
+ve	4	57.1	2	100.0	6	100.0	12	100.0	2	28.6	5	50.0	1	100.0
MCp	0.036*								0.466					

Table VIII. Relations between the severity of androgenetic alopecia with genotypes, age, smoking, and family history of androgenetic alopecia in patients group.

MC: Monte Carlo test; p: p value for Kruskal Wallis test; * significant at p ≤ 0.05

In 2001 Allen et al [22] stated that the 5-α reductase type II enzyme V89L polymorphism is not a strong determinant of serum androgens concentrations in Caucasian men.However, In 2010, Jiang et al [23] found that there was an association between the 5-α reductase V89L variants and the increase of the concentration of serum androgens in Chinese elderly men.

There was a study by Ellis et al [24] which revealed that polymorphic amino acid substitution of the 5-alpha reductase enzyme was shown to influence the activity and pharmacogenetic variation of the enzyme encoded by the mutants of 5-alpha reductase enzyme gene, however, it did not show a significant differences between cases and controls in allele, genotype, or haplotype frequencies, the findings in this study showed that there was no association between AGA with the 5-α reductase genetic polymorphism.Similar results were found by Seog-Jun et al [18] who were not been able to discover that association as well.

A relationship between oxidative stress and AGA has been suggested. SOD and catalase are enzymes which are an important antioxidant defense in nearly all cells exposed to oxygen, thus, the decrease in their levels or activities can cause an oxidative stress status of all body cells including hair keratinocyets,which may respond to oxidative stress from irritants, pollutants, and UV irradiation, by producing nitric oxide, and by releasing intracellularly stored IL-1α. This pro-inflammatory cytokine by itself has been shown to inhibit the growth of isolated hair follicles in culture [25].

In this work, the mean of both erythrocyte lysate SOD and plasma catalase levels were significantly lower in patients group than those in control group.We also found that the mean of SOD enzyme was lower in patients carrying the mutant (LL) genotype, than in those carrying the (VL) genotype, but the difference was not statistically significant between the two genotypes.

On the contrary, the mean of plasma catalase enzyme was higher in patients who are carrying the homozygote (LL) genotype, than those who are carrying the heterozygote (VL) genotypes, and there was a statistically significant difference between both groups.

A study performed by Bahta et al, using cultured dermal hair papilla cells (DPC) from balding and non-balding scalp, demonstrated that balding DPCs grow slower in vitro than non-balding DPCs. Loss of proliferative capacity of balding DPCs was associated with changes in cell morphology, and nuclear expression of markers of oxidative stress including catalase and SOD enzyme [26].

There was another study by Upton et al [27] demonstrated that oxidative stress may exacerbate the onset of androgenic alopecia by affecting TGF-β secretion, which is a known inhibitor of hair follicle growth and an inducer of catagen phase.Another study by Naziroglu et al [28] provided some evidence for a potential role of increased lipid peroxidation and decreased antioxidants in alopecia.

In this work there was a positive correlation between the severity of AGA and the positive family history of male patients,but the correlation was non significant in female.

In 1999, Tosti et al [29] revealed that family history predisposes to the early development and rapid progression of AGA. In 2004, Chumlea et al [30] found that men with fathers who had hair loss, were twice as likely to have hair loss than men whose fathers had no history of hair loss.

In 2009, Harvard medical school released a publication which stated that the risk of AGA rises with age, and it's higher in women with a history of hair loss on either side of the family [31]. In 2010, Fatemi et al [32] mentioned that family history is considered one of the important criteria which are needed for the diagnosis of AGA.

In short, our study provides support for the possibility of an association of androgenetic alopecia with the V89L genetic polymorphism of type II 5-α reductase enzyme, also supported the correlation between AGA and oxidative stress, and there was a significant difference between the two studied groups regarding the levels of the antioxidant enzymes.

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GENETIC ANALYSIS OF 5 α REDUCTASE TYPE II ENZYME IN RELATION TO OXIDATIVE STRESS IN CASES OF *ANDROGENETIC ALOPECIA* IN A SAMPLE OF EGYPTIAN POPULATION

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I would like to thank Omar and colleagues for drawing our attention to genetics of androgenetic alopecia (AGA). Although it is one of the most common dermatological problems, current treatment strategies are limited and their effectiveness remains modest at best.

In V89L polymorphism, leucin is inserted in the 5 alpha reductase enzyme type II instead of valine amino acid. Carrying leucine allele predicts about 3,7 higher risk of having AGA according to the study. The statistically significant positive family history of AGA in patients confirms this association. In addition, it should have been better to see the difference in family history of AGA as well as in controls.

Superoxide dismutase (SOD) and catalase enzymes are important antioxidant mechanisms in the body. They function cooperatively. Superoxide dismutase converted superoxide into hydrogen peroxide and oxygen. To complete the antioxidant process this hydrogen peroxide must be converted to water and oxygen by catalase. The authors found higher levels of lysate SOD and plasma catalase in patients than controls. The significantly difference of age between patients and controls may also contribute to this result in the study.

Regarding to catalase, there was a statistically significant difference between the homozygote (LL) genotype and the heterozygote (VL) genotype. On the contrary, the mean of SOD enzyme was lower in patients carrying the mutant (LL) genotype than those who are carrying the heterozygote (VL) genotypes, but the difference was statistically insignificant.

Mutations do not always cause the lack of expressing or translating related protein as we have seen in V89L polymorphism. Like this non-synonymous mutation, amino acid can be replaced by another amino acid. Although valine and leucine are physically and chemically similar, the effect on the enzyme activity of this polymorphism is still not known properly. The association between this polymorphism and antioxidant enzymes mentioned in the study may be one of these effects.

Further studies are needed to reveal the clinical and therapeutic implications of genetic polymorphisms in androgenetic alopecia.

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CYCLO-OXYGENASE 2 IS PRESENT IN THE MAJORITY OF LESIONAL SKIN FROM PATIENTS WITH AUTOINMUNE BLISTERING DISEASES

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Abstract
Introduction: The in situ immune response within skin biopsies from patients affected by autoimmune skin blistering diseases (ABDs) is not well characterized.
Aim: Based on the fact that the ABD immune response is considered an adaptive immune response, both an innate immune response and inflammation would be expected in these diseases. Our investigation investigates the presence of cyclo-oxygenase-2 (COX-2), since this enzyme is commonly involved in innate immune responses.
Methods: We utilized immunohistochemistry (IHC) to evaluate the presence of COX-2 in lesional skin biopsies of patients affected by ABDs. We tested 30 patients with endemic pemphigus foliaceus (EPF), 15 controls from the endemic area, and 15 biopsies from healthy controls from the USA. We also tested archival biopsies from patients with selected ABDs, including 20 patients with bullous pemphigoid, 20 with pemphigus vulgaris, 8 with pemphigus foliaceus and 12 with dermatitis herpetiformis.
Results: Most ABD biopsies stained positive for COX-2 in the lesional blister and/or the dermal inflammatory infiltrate, accentuated in the upper neurovascular plexus. In BP and EPF, the COX-2 staining was also seen in the sweat glands. All controls were negative.
Conclusions: We document that COX-2 is expressed in lesional skin of patients with ABDs.

Key words: Cyclo-oxygenase 2; autoimmune skin diseases; endemic pemphigus foliaceus

Abbreviations and acronyms: Bullous pemphigoid (BP), immunohistochemistry (IHC), direct and indirect immunofluorescence (DIF and IIF), hematoxylin and eosin (H&E), basement membrane zone (BMZ), intercellular staining between keratinocytes (ICS), pemphigus vulgaris (PV), cicatricial pemphigoid (CP), autoimmune blistering skin diseases (ABDs), fogo selvagem (FS), endemic pemphigus foliaceus in El-Bagre, Colombia (El Bagre-EPF).

Cite this article:
Ana Maria Abreu Velez, Juliana Calle Isaza, Michael S. Howard: Cyclo-oxygenase 2 is present in the majority of lesional skin from patients with autoinmune blistering diseases. Our Dermatol Online. 2013; 4(4):476-478.

Highlights:

What is known:
B lineage lymphocytes and complement play an important role in ABDs, by producing antibodies that are deposited in lesional skin and possibly leading to blister formation.

What does the current study add?
Immune system markers such cyclo-oxygenase-2 seem to be expressed in the majority of lesional skin of patients with ABDs, and may represent a consistent feature of the inflammation commonly present in these diseases.

Introduction

Multiple therapies have been utilized for the treatment of cutaneous autoimmune blistering skin diseases (ABDs). Steroids represent a commonly utilized therapy, because many autoimmune disorders are B-lymphocyte mediated processes depositing autoantibodies and complement deposits in the skin. Well documented correlations exist between titers of autoantibodies and the clinical severity of the diseases [1-3].

The present investigation aims to study an inducible marker of the innate immune response, specifically the presence of cyclo-oxygenase 2 (COX-2); this enzyme generates inflammatory prostanoids, and inflammation is a hallmark of multiple ABDs. Thus, we studied the in situ immune response by performing immunohistochemistry (IHC) stains on lesional skin biopsies for COX-2.

Materials and Methods

Subjects of study:

We tested 30 biopsies from patients affected by EPF in El Bagre, Colombia, South America (El Bagre-EPF) and 15 normal controls from the endemic area [4-8]. We also utilized 15 control skin biopsies from cosmetic reduction plastic surgery patients in the USA, taken from the chest and/or abdomen. Biopsies were fixed in 10% buffered formalin, then embedded in paraffin and cut at 4 micron thicknesses. The tissue was then submitted for hematoxylin and eosin (H&E) and IHC staining. In addition, we also tested biopsies from the archival files of two private laboratories led by board certified dermatopathologists in the USA; these patients underwent initial diagnostic biopsies, and therefore were likely not taking immunosuppressive medications at the time of biopsy. We evaluated 20 biopsies from bullous pemphigoid (BP) patients, 20 from patients with pemphigus vulgaris (PV), 8 patient biopsies with pemphigus foliaceus (PF) and 12 from patients with dermatitis herpetiformis (DH). For all of the El Bagre area patients and controls, we obtained written consents as well as Institutional Review Board permission from the local hospital. The archival biopsies were IRB exempt due to the lack of patient identifiers. In both dermatopathology laboratories, each biopsy also was sent for direct immunofluorescence as previous described [3], for correlation with the H&E diagnoses.

Quantitative digital morphometry and IHC staining:

The staining intensity of the antibodies was also evaluated in a semiquantitative mode by an automated computer image analysis system, designed to quantify IHC staining in hematoxylin-counterstained histologic sections. Slides were scanned with a ScanScope CS system, utilizing brightfield imaging. IHC staining was performed as previously described. For IHC, we utilized a Dako monoclonal mouse anti-human COX-2 antibody, clone CX-294; staining was performed as previously described [4-7].

Statistical analysis:

For statistical analysis, the non-parametric Mann–Whitney U-test was used to calculate significant levels for all measurements. Values of $p<0.05$ were considered statistically significant.

Result

We noted that 26/30 patients with EPF were positive in the epidermis in spot areas of the corneal layers, around the neurovascular areas of eccrine and hair follicles. Only 2 controls from the endemic area showed some corneal reactivity ($p<0.05$). Further, 17/20 biopsies from BP patients were positive for COX-2 in the sweat glands, under the blisters and along the bases of the blisters. Some reactivity was seen in the corneal layers ($p<0.05$). Reactivity was seen in the upper neurovascular plexus of the dermis, and in some type of junction between endothelial cells and the extracellular dermal matrix (Fig. 1). In patients with PV, 16/20 biopsies were positive in the upper dermal inflammatory infiltrate, and around the epidermal blisters ($p<0.05$). In patient biopsies with PF, 5/8 were positive in the epidermis in spotty areas of the corneal layers, and around the neurovascular supplies of eccrine glands and hair follicles. In 9/12 patients with DH, positive staining was noted, mostly under the BMZ ($p<0.05$). In Figure 1, we highlight the most common patterns of positivity found in these patients.

Discussion

Because adaptive immunity has been demonstrated to be play a pathogenic role in ABDs, it is important to note that innate immunity is the first step in an adaptive immune response. Unfortunately, few studies have specifically studied molecules involved in the adaptive immune response in ABDs. Hallmark pathologic events in ABDs include vasodilation of the microcirculation, resulting in increased blood flow to the affected area. The vasodilation is responsible for the heat and redness that occurs at sites of inflammation. In ABDs, we also often see increases in the permeability of upper dermal blood vessels, promoting the movement of fluid and plasma proteins into the interstitial areas [8]. In ABDs, chemotatic neutrophils, monocytes and other white blood cells manifest as an inflammatory infiltrate. Activated complement, another innate immune marker found in pemphigus blister fluids, suggests a pathogenetic role for complement in this disorder [9].

In our study, we investigate the immune response induction marker COX-2, a key enzyme of arachidonic acid metabolism. Cyclooxygenase exists as two distinct isoforms. COX-1 is constitutively expressed in most tissues, whereas COX-2 is inducibly expressed at sites of inflammation. An additional recently documented isoform, COX-3, is produced via alternative splicing of COX-1 and has also been described [10]. COX-2 is also inducibly expressed in neoplastic tissues. Prostanoids are produced by many cell types, and act on target cells through specific G protein-coupled receptors. Although prostanoids have traditionally been considered acute inflammatory mediators, studies using knockout mice show that prostanoids may regulate selected aspects of both innate and adaptive immunity; such a dual role may be the case in ABDs. Each prostanoid, depending on which receptor it acts on, exercises specific effects on immune system cells such as macrophages, dendritic cells, and B and T lymphocytes, often in concert to microbial ligands and cytokines. These cellular actions affect the strength, quality, and duration of immune responses. Prostanoids play a critical role in immunopathology, via inflammation, autoimmunity and cancer pathophysiology [8].

We found limited specific information regarding autoimmune diseases and the expression of COX-2. In oral lichen planus, increased levels of COX-2 have been reported [11]. In experimental autoimmune encephalomyelitis, celecoxib (a new generation COX-2 inhibitor) retards inflammation [12]. Since our study utilized archival biopsies, the requisition forms did not contain specific information regarding administration of immunosuppressive agents. The precise role of this enzyme in ABDs requires further investigation since this was a pilot study. We thus recommend larger studies, utilizing only patients known to have no immunosuppressive therapy to study the role of this molecule in ABDs.

We found no specific studies regarding the presence of COX-2 in ABDs. For this reason and because our study has a small sample size, we recommend larger studies to further define the role of COX-2 in these disorders.

Conclusion

We suggest that molecules such as complement and COX-2 are present in the majority of skin lesional biopsies from patients with ABDs; further, it is possible that COX-2 may consistently contribute to the inflammation seen in these diseases. Recent data has also demonstrated that prostanoids regulate selected aspects of both innate and adaptive immunity, and this may also be the case in ABDs.

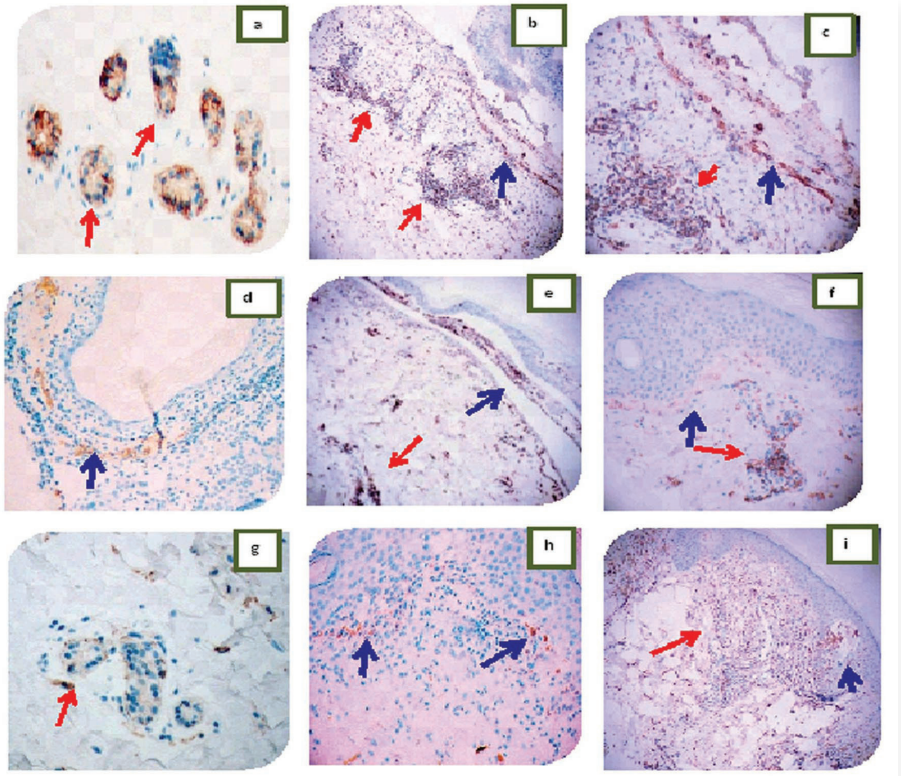

Figure 1. a. COX-2 positive IHC staining in the eccrine sweat glands of a BP patient (brown staining; red arrows). **b and c.** Positive COX-2 IHC staining in a linear manner in the base of the blister in a BP patient (brown staining; dark blue arrows), as well as along the upper dermal neurovascular plexus (brown staining; red arrows; 200X and 400X, respectively). **d.** A representative PV case, showing positive IHC staining with COX-2 at the separation plane of a suprabasilar blister (brown staining, dark blue arrow). **e.** COX-2 positive IHC staining (brown staining) in a second case of PV. The red arrow shows positivity at the upper dermal inflammatory infiltrate, and the dark blue arrow within the blister. **f.** A DH case with positive COX-2 IHC staining (brown staining); some weak linear staining is noted under the basement membrane zone (BMZ) (red arrow) but also around upper dermal blood vessels (blue arrow). **g.** COX-2 positive IHC staining within eccrine sweat gland ducts of a PV patient (brown staining; red arrow). **h.** Positive linear IHC staining with COX-2 in a DH biopsy (brown staining; dark blue arrows). **i.** COX-2 positive IHC staining inside the epidermal blister in a PV case (brown staining, dark blue arrow), and also strong positivity in the upper dermal inflammatory infiltrate (red arrow).

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LA PELLAGRE: ASPECTS EPIDEMIOLOGIQUES ET CLINIQUES DANS LA REGION OUEST DU BURKINA FASO

PELLAGRA: EPIDEMIOLOGICAL AND CLINICAL FEATURES IN THE WESTERN REGION OF BURKINA FASO

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Résumé
Introduction: La pellagre est une carence en vitamine PP qui regroupe l'acide nicotinique ou niacine et le nicotinamide. Elle est encore fréquente dans notre pays. Le but de cette étude était de décrire les aspects épidémiologiques et cliniques de la pellagre dans la région Ouest du Burkina Faso.
Patients et Méthodes: Il s'est agi d'une étude rétrospective, descriptive à partir des dossiers des patients ayant consulté ou ayant été hospitalisés dans les services de dermatologie-vénéréologie et de psychiatrie à Bobo-Dioulasso, de 2005 à 2012.
Résultats: Durant la période, 223 cas de pellagre ont été enregistrés. L'âge moyen des patients était de 37,7+17,2 ans avec des extrêmes de 6 et 85 ans et un sex-ratio de 1/3. Ces cas ont été observés dans les zones aussi bien rurales qu'urbaines de l'Ouest du Burkina Faso. Les femmes étaient les plus atteintes (76,7%), particulièrement les femmes au foyer (47,1%). Les formes ulcéreuses représentaient 6,3% des cas, les atteintes neurologiques 62% et la diarrhée chronique (6,5%). Trois patients sont décédés (1,3%).
Conclusion: La pellagre est une affection fréquente chez les femmes dans l'Ouest du Burkina Faso où le maïs constitue la céréale de base dans l'alimentation des populations. Les formes ulcéreuses pouvaient égarer le diagnostic. Une sensibilisation de la population est indispensable pour prévenir cette affection.

Abstract
Introduction: Pellagra is a deficiency of vitamin PP which include nicotinic acid or niacine and nicotinamide. It is yet frequent in our country. The purpose of this study was to describe the epidemiological and clinical features of pellagra in the Western region of Burkina Faso.
Patients and Methods: It was a retrospective, descriptive survey led through patients admitted in dermatology and psychiatry departments of Bobo-Dioulasso, from 2005 to 2012.
Results: During this period, pellagra was diagnosed in 223 patients with a mean age of 37.7 + 17.2 years (range: six to 85 years) and a sex-ratio of 1/3. The cases were registered in rural as well as urban areas of the western region of Burkina Faso. It concerned mainly women (76.7%), especially the house-wife (47.1%). Cutaneous, ulcerous forms represented 6.3% of the cases, neurologic signs were 62% and chronic diarrhea was 6.5%. Three patients died (1.3%).
Conclusion: This survey showed that pellagra is frequent, affecting mainly women of western region of Burkina Faso where the maize constitutes the basic cereal in the people's diet. Ulcerous forms could cause mistake in the diagnosis. Sensibilization of the population is essential to prevent this affection.

Mots-clé: Pellagre; vitamine B3; ulcérations; femmes; Bobo-Dioulasso
Key words: Pellagra; vitamin B3; ulcerations; women; Bobo-Dioulasso

Cite this article:
Fatou Barro/Traoré, Boukary Diallo, Patrice Tapsoba, Jean-Baptiste Andonaba, Moussa Kéré, Pascal Niamba, Adama Traoré: La pellagre: aspects épidémiologiques et cliniques dans la Région Ouest du Burkina Faso. [Pellagra: epidemiological and clinical features in the western region of Burkina Faso]. Our Dermatol Online. 2013; 4(4): 479-483.

Introduction

La pellagre résulte d'une carence en vitamine PP (Pellagra Preventing factor) ou vitamine B3 qui regroupe l'acide nicotinique ou niacine et le nicotinamide. Cette maladie devenue rare dans les pays occidentaux, demeure de nos jours endémique dans certaines zones d'Afrique et d'Asie où l'alimentation est basée sur le maïs et le millet [1]. L'avitaminose PP peut survenir en cas de déficit en tryptophane (acide aminé essentiel), lors de certaines pathologies interférant avec le métabolisme de la niacine ou au cours d'un traitement par l'isoniazide, le pyrazinamide, l'éthionamide, le 6-mercaptopurine et le 5-fluorouracil [2-4]. La localisation prépondérante des lésions cutanées sur les zones photo-exposées du corps classe la pellagre dans les photodermatoses par photosensibilisation endogène, bien que la cause de la sensibilisation à la lumière reste mal élucidée [5]. Aucune étude n'a été réalisée sur la pellagre au Burkina Faso à notre connaissance. Le constat d'une recrudescence des cas de pellagre dans la région des Hauts Bassins (Ouest du Burkina Faso), et de quelques particularités cliniques chez nos patients, ont justifié cette étude qui avait pour but de décrire les aspects épidémiologiques et cliniques.

Patients et méthodes

Il s'agissait d'une étude rétrospective, descriptive, réalisée par analyse de dossiers de patients reçus en consultation externe ou admis en hospitalisation dans les services de Dermatologie et de Psychiatrie du Centre Hospitalier Universitaire Sanou Sourô (CHUSS) et dans le service de Dermatologie et de lutte contre la lèpre de la direction régionale de la santé (DRS) de Bobo-Dioulasso, du 1er janvier 2005 au 31 décembre 2012, soit une période de 8 ans. Bobo-Dioulasso est la 2ème ville du Burkina Faso, située à l'Ouest, dans la « Région des Hauts Bassins ». Les services de Dermatologie du CHUSS et de la DRS sont les seuls services de la Région où exercent des médecins dermatologistes, si bien que tous les cas de dermatoses, nécessitant un avis du dermatologue, y sont référés. A partir d'une fiche d'enquête, les données sociodémographiques ont été recueillies (âge, sexe, profession, lieu de provenance du patient, les habitudes alimentaires), ainsi que les antécédents de pellagre et d'autres antécédents médicaux personnels, les signes cliniques dermatologiques, digestifs, neurologiques et psychiatriques, le traitement et l'évolution pendant une période d'un mois. Le diagnostic de pellagre était clinique, basé sur les signes cutanéo-muqueux, neuropsychiatriques et digestifs ; le plateau technique étant limité dans notre contexte de travail, nous ne pouvions pas doser la vitamine PP et les patients n'avaient pas les moyens financiers pour que nous puissions envoyer les prélèvements en Europe ou ailleurs. L'atteinte digestive était retenue devant une dysphagie et/ou des douleurs abdominales ou une diarrhée, associée aux signes cutanés et neuropsychiatriques. L'analyse de l'évolution a porté uniquement sur les patients qui ont pu respecter les rendez-vous de contrôle pendant au moins un mois. Etaient exclus les doubles notifications, les dossiers incomplets et les patients perdus de vue avant que leur suivi n'ait atteint un mois (un mois de traitement). La saisie des données a été faite sur le logiciel EPIDATA 3.1 et leur analyse par EPI INFO 6.0.

Résultats

Aspects sociodémographiques

Du 1er janvier 2005 au 31 décembre 2012, 223 cas de pellagre ont été enregistrés dont 4 cas en 2005, 24 cas en 2006, 47 cas en 2007, 27 cas en 2008, 36 cas en 2009, 27 cas en 2010, 24 cas en 2011 et 34 cas en 2012. L'âge moyen des patients était de 37,7+17,2 ans avec des extrêmes de 6 ans et 85 ans. Les enfants de moins de 15 ans étaient au nombre de 10. Cent soixante onze cas (76,7%) étaient de sexe féminin. Les femmes au foyer constituaient 105 cas (47,1%) suivies des agriculteurs et éleveurs avec 31 cas (13,9%), des élèves et étudiants avec 18 cas (8,1%), puis des commerçants et artisans avec 11cas (4,9%) et enfin les fonctionnaires et assimilés avec 4 cas (1,8%). Les patients provenaient du milieu rural dans 98 cas sur les 223 (soit 44%) contre 125 cas (56%) en milieu urbain.

Aspects cliniques

La durée d'évolution de la maladie avant la consultation était de 1 à 36 mois. Il existait un antécédent de pellagre chez 33 patients (15,2%) parmi lesquels 12 étaient à leur 2ème rechute et 21 à leur 4ème. La pellagre était associée à l'alcoolisme dans 2 cas, à 5 cas d'infection par le virus de l'immunodéficience humaine, à une tuberculose dans 2 cas, à un lichen plan muqueux dans 2 cas, à une lèpre dans 1 cas.

Les signes cutanés étaient présents dans 100% des cas. Ils ont été répertoriés dans le tableau I. Les lésions cutanées réalisaient, classiquement, des plaques érythémato-squameuses, hyperchromiques du visage, des bras, des avant-bras et du décolleté en « collier de Casal » (Fig. 1), bien limitées (Fig. 2a, 2b), du dos des pieds et des chevilles. Ces lésions cutanées évoluaient parfois vers de véritables ulcérations (Fig. 3), associées à un œdème du membre, confinant le patient au lit. Les atteintes muqueuses étaient notées dans 102 cas (46%) dominées par les ulcérations buccales (34,6%) et par les chéilites (17,8%). Des symptômes digestifs étaient présents chez 80 sur les 223 patients (35,8 %), notamment des douleurs abdominales (24,2%), l'anorexie (14,7%), la diarrhée chronique (6,5%) et la dysphagie (3,6%).

Nos patients ont présenté différents signes neurologiques et/ou psychiatriques qui ont été répertoriés dans le tableau II. Concernant les patients atteints de neuropathies périphériques, 15,21% avaient d'importantes difficultés à la marche, les rendant invalides. Parmi nos 223 patients, 11% ont consulté d'abord en psychiatrie d'où ils ont été référés en Dermatologie. Parmi ces patients, 93% présentaient un délire, 6 % avaient une agitation psychomotrice et 46% une dépression (un même patient avait parfois plusieurs signes psychiatriques).

Vingt neuf patients (13%) avaient une forme grave de pellagre (ulcérations cutanées avec œdème, signes neurologiques sévères et diarrhée de plus de six selles par jour).

Le traitement a consisté essentiellement en la supplémentation en vitamine PP, en des soins locaux et en des conseils hygiéno-diététiques (l'encouragement à consommer d'autres céréales en plus du maïs, des protéines animales (lait, œufs, poisson, viande) et des légumineuses comme le haricot). Les signes psychiatriques ont été traités par des sédatifs, des neuroleptiques ou des antidépresseurs selon le cas.

Les perdus de vue après la première visite constituaient 46,4%. A la fin d'un mois de traitement, chez les patients étant revenus pour le contrôle médical, 90% des lésions cutanéo-muqueuses étaient guéries; les signes neuropsychiatriques avaient disparu dans 88% des cas, ainsi que 59% des douleurs abdominales. Nous avons enregistré trois cas de décès (1,3%); il s'agissait de formes graves.

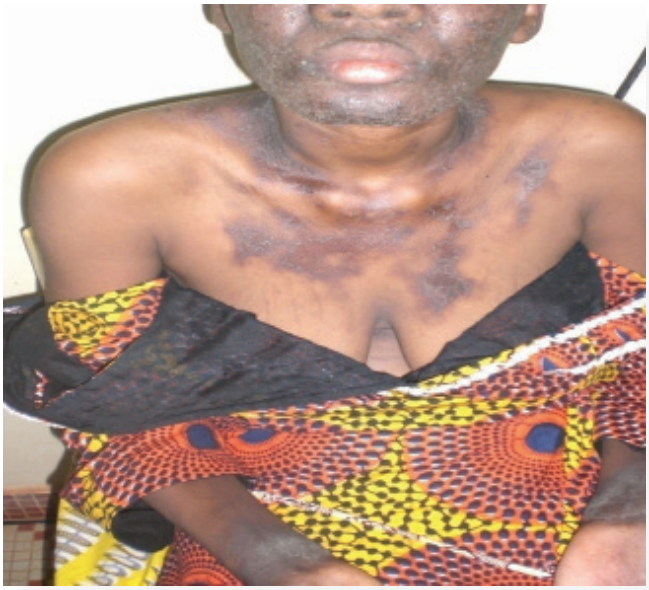
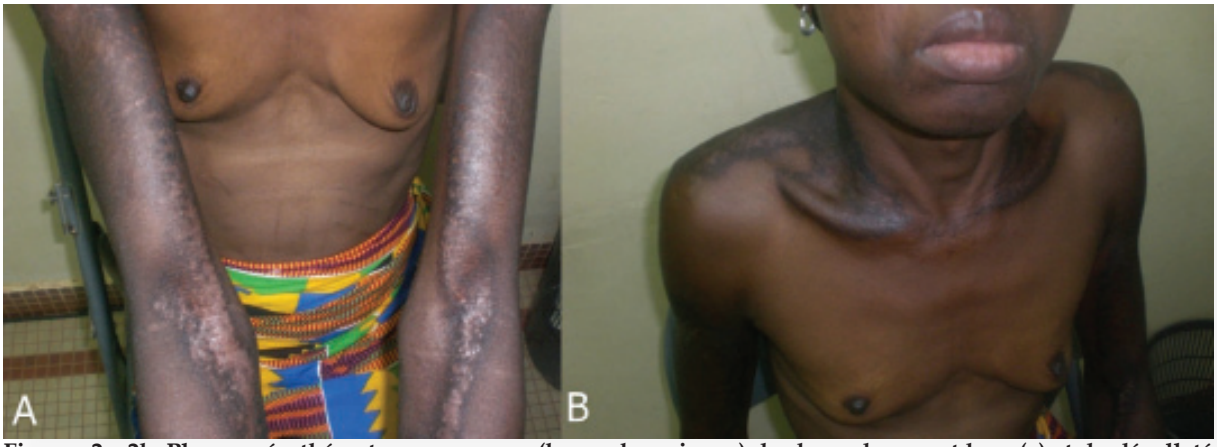


Figure 1. Plaques érythémato-squameuses (hyperchromiques) du visage, des avant bras et du décolleté en « collier de Casal ».

Figure 1. Erythemato-squamous (hyperchromic) plaques on the face, the forearms and the low-necked in "Casal's necklace".



Figures 2a, 2b. Plaques érythémato-squameuses (hyperchromiques) des bras, des avant bras (a) et du décolleté en « collier de Casal » avec cheilite (b) chez la même patiente.

Figures 2a, 2b. erythemato-squamous (hyperchromic) plaques on the arms, the forearms (a) and the low-necked in "Casal's necklace" with cheilitis affecting (b) the same patient.

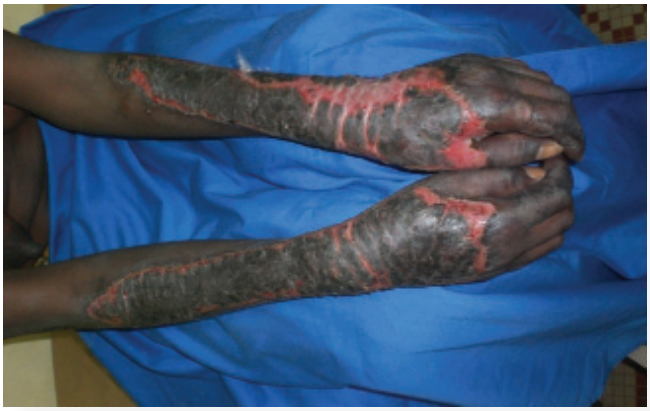


Figure 3. Lésions ulcéreuses à limites nettes avec œdème des mains en voie de cicatrisation.

Figure 3. Ulcerous lesions well limited with edema of the hands which is healing.

Signes	Nombre de cas	Pourcentage (%)
Plaques érythémato-squameuses	177	79,4
Erythème simple (hyperpigmentation cutanée)	53	22,7
Prurit	27	12,1
Ulcérations	14	6,3
Erosions /fissures	13	5,8
Œdème des membres	10	4,5
Vésicules +/-bulles	5	2,2

Tableau I. Répartition des signes cutanés chez nos patients atteints de pellagre.
Table I. Repartition of cutaneous signs affecting our patients suffering from pellagra.

N.B. 1: un même patient pouvait avoir 2 ou 3 signes cutanés.

N.B. 1: one same patient could have 2 or 3 cutaneous signs.

Signes	Nombre de cas	Pourcentage (%)
Neuropathies périphériques	85	61,59
Insomnie	28	20,28
Ralentissement psychomoteur	24	17,39
Délire	14	10,14
Agitation psychomotrice	9	6,52
Dépression	7	5,07
Anxiété	7	5,07
Hallucination	6	4,34
Syndrome confusionnel	4	2,89
Démence	3	2,17

Tableau II. Répartition des signes neuropsychiatriques identifiés chez nos patients atteints de pellagre.
Table II. Repartition of neuropsychiatric signs identified at our patients suffering from pellagra.

Discussion

Comme toutes les études rétrospectives, notre étude avaient quelques limites; nous n'avons pas pu réaliser le dosage sérique du nicotinamide ni des métabolites de la niacine dans les urines du fait de notre plateau technique limité; les données permettant la détermination du statut socio-économique des patients étaient insuffisantes. Néanmoins, nous avons enregistré 223 cas en 8 ans; cela n'est qu'une partie de l'iceberg car l'étude n'a concerné que les patients ayant consulté dans nos services. Les patients venant de toute la région Ouest, les problèmes financiers et d'accès géographique sont un handicap pour certains.

Sur le plan épidémiologique, les particularités de notre étude résidaient en l'augmentation des cas de pellagre à l'Ouest du Burkina Faso depuis 2005 et de la forte fréquence des femmes au foyer. Cet accroissement pourrait être en partie dû au renchérissement des denrées importées qui a obligé les populations à se rabattre sur les céréales locales avec une surconsommation de maïs. L'origine de la maladie est multifactorielle mais la pellagre est due principalement à une carence nutritionnelle en niacine, soit par consommation quasi-exclusive de maïs (car la niacine contenue dans le maïs est sous forme liée, non bio-disponible) [3], soit par carence en protéines animales responsable d'un déficit en tryptophane, un acide aminé indispensable à la synthèse endogène de niacine. L'alcoolisme, une cause classique de la pellagre [3,6,7], a été très rarement noté chez nos patients mais il n'est pas souvent avoué par nos populations. La survenue de la pellagre chez nos deux cas de tuberculose pourrait s'expliquer par la prise d'isoniazide, de pyrazinamide, d'éthionamide. Nous avons constaté une forte fréquence des femmes (76,7%) ; nos résultats étaient supérieurs à ceux de Seal et col. [8] qui en ont enregistrées 72% et de Pitché et col. [9] qui ont colligé 59 femmes pour 49 hommes. La prévalence des femmes au foyer s'expliquerait par le fait qu'ayant un faible pouvoir économique, elles se contenteraient du repas familial, souvent à base de farine de maïs, alors que les hommes, chez nous, ont plus d'opportunités de s'offrir des aliments plus diversifiés et plus riches en protéines en dehors du foyer. Selon l'enquête sur les conditions de vie de la population, en 2007, l'indice de pauvreté dans la région Ouest du Burkina Faso (Hauts Bassins) était passé de 33,1% en 1998 à 34,8% en 2003. Cette situation décrivait une accentuation croissante de la pauvreté. Celle-ci touchait particulièrement les femmes, les enfants et les handicapés (Source: plan d'action triennal de la direction régionale de la santé des Hauts Bassins du Burkina Faso). Frank et col. [10] considéraient la pellagre comme une maladie non transmissible de la pauvreté.

Une sensibilisation de la population pour varier l'alimentation, en y associant des protéines, est indispensable pour prévenir cette maladie.

Nos patients provenaient aussi bien de la ville que de la campagne ; en effet, les repas à base de farine de maïs avec peu de protéines animales est une habitude alimentaire très répandue dans les milieux défavorisés de ces deux populations. Dans toutes les zones où elle a été constatée, la pellagre est apparue lorsque le maïs est devenu l'aliment de base de gens pauvres ne pouvant s'offrir d'autres aliments en complément [1].

Le délai de consultation souvent long serait dû au fait que dans notre pays, en cas de maladie, certains patients se décident à consulter lorsqu'une rechute ou une aggravation survient. En Afrique subsaharienne, les déficits en vitamine PP sont souvent dus aux carences nutritionnelles par insuffisance d'apport en viandes et/ou en poissons [3]. Les rémissions temporaires constatées chez des patients pourraient s'expliquer par une plus grande disponibilité de produits laitiers, d'œufs, du poisson et de fruits en certaines périodes de l'année, notamment la saison pluvieuse. Les particularités cliniques observées chez nos patients résidaient en:

- la présence de véritables ulcérations cutanées, confinant le patient au lit. Ces cas ont fait parfois égarer le diagnostic vers une affection chirurgicale ; ils ont alors été orientés en Chirurgie d'où ils ont été adressés en Dermatologie, souvent après un échec des soins locaux seuls sans supplémentation en vitamine PP.
- L'existence de formes graves d'atteintes neurologiques avec invalidité (15,2% de nos patients avaient des difficultés à la marche), troubles qui se sont améliorés lentement après l'institution du traitement. Ces formes s'expliqueraient par le retard à la consultation, fréquent dans notre pays. Concernant les patients admis en premier lieu en psychiatrie, nos résultats étaient comparables aux données de la littérature [11].
- La diarrhée chronique, signe digestif le plus fréquent dans la pellagre [3], a été rarement mentionnée chez nos patients (6,5% des cas), remplacée par d'autres manifestations digestives, ce qui pouvait égarer le diagnostic.

Le traitement de la pellagre est classiquement efficace [1,3,11,12]. Chez nous, les patients ne reviennent pas souvent au contrôle médical en cas d'évolution favorable d'une maladie; cela expliquerait nos perdus de vue. Nous avons noté 3,1% de décès. Selon Wan et col. [13], la pellagre est la seule photosensibilité où le décès est considérée comme un signe cardinal de l'aspect clinique (les 4D: dermatose, diarrhée, démence et décès) si elle n'est pas traitée.

Conclusion

La pellagre est encore fréquente dans les zones rurales comme urbaines de la région Ouest du Burkina Faso où le maïs constitue la céréale de base dans l'alimentation des populations. Elle atteint en majorité les femmes et des formes graves sont enregistrées. Une étude prospective d'une plus grande envergure est envisagée pour rechercher les facteurs socio-économiques, nutritionnels et pathologiques liés à cette maladie, pour en connaître la prévalence réelle au Burkina Faso et proposer des mesures de prévention.

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NASZA DERMATOLOGIA Online
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NEUTROPHILIC MYOSITIS ASSOCIATED WITH *PYODERMA GANGRENOSUM* IN A BREAK-DANCER

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Competing Interests: None

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Abstract
Neutrophilic myositis is an extremely rare condition, cases of which have been reported in association with neutrophilic dermatosis, inflammatory bowel disease and malignant hematological disease. The disorder is histologically characterized by a sterile infiltration of neutrophils throughout muscle, with necrosis of muscle fibres. We here report the case of a young male who also had associated pyoderma gangrenosum, and who presented with necrotizing fasciitis-like manifestations. In this case, although there were no other underlying disorders, compulsive exertional stress due to break-dancing was thought to be a precipitant. Debridement of the necrotic tissues combined with oral corticosteroid treatment was effective.

Key words: neutrophilic myositis; pyoderma gangrenosum; hard exercise

Cite this article:
Hisashi Tamiya, Hiromi Kobayashi, Kaori Hoshi, Yui Horiguchi, Kurooka Sadahiro, Akiko Naruse, Shigeto Yanagihara, Daisuke Tsuruta: Neutrophilic myositis associated with pyoderma gangrenosum in a break-dancer. Our Dermatol Online. 2013; 4(4): 484-486.

Introduction

Neutrophilic myositis, which is extremely rare, is characterized by a histologically sterile infiltration of neutrophils throughout the muscle accompanied by disruption of the muscle architecture and numerous areas of muscle fiber necrosis [1]. This condition has been reported as an extracutaneous manifestation of neutrophilic dermatosis, and also been associated with inflammatory bowel disease and with hematological malignancies [1-6]. Here, we report a young male with neutrophilic myositis of the lateral aspect of the knee, accompanied by pyoderma gangrenosum. A clinical characteristic of our case was that exercise-induced stress on the knee brought on by compulsive break-dancing was thought to be a trigger of the onset.

Case Report

A 27-year-old man came to our hospital with a complaint of a one-month history of intractable pain and swelling of his right knee. He had experienced prior, similar ‚phlegmonous' swelling of his right knee, with three episodes over the past three years. Previously, oral or intravenous antibiotics relieved his symptoms, but this time, his eruption failed to respond to treatment with several courses of oral antibiotics that included cephems, new-generation quinolones, and tetracycline. When asked about his habits, he disclosed that he had started to break-dance at the age of nineteen, and that in the past the symptoms that affected his right knee consistently appeared after straining his knees during vigorous dancing. At his visit, his right knee was remarkably swollen with marked black cutaneous necrosis and skin ulcers (Fig. 1a). Body temperature was elevated to 38.8oC. Laboratory examination showed the following: white blood cell count, 16,800/μl (neutrophils: 77.6%, lymphocytes: 14.5%, eosinophils: 1.6%); C-reactive protein, 10.49 mg/dl; creatine phosphokinase, 560 IU/L; procalcitonin negative. Other tests, such as liver and renal function, quantitative serum immunoglobulins, blood cultures, urinalysis, and viral serology (cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus), rheumatoid factor, antinuclear antibodies, anticardiolipin and antiphospholipid antibodies, and antineutrophil cytoplasmic antibodies were all normal or negative. Magnetic resonance imaging showed that inflammation involved not only the subcutaneous tissues but also the right musculus quadriceps femoris. We considered this condition as necrotizing fasciitis. We therefore performed emergency debridement of the necrotic tissue including the skin and muscles. Histological study of the debrided tissues revealed marked inflammatory infiltrates, composed predominantly of neutrophils that extended throughout all layers of the skin and involved muscle fibers, accompanied by disruption of the muscle architecture and numerous areas of muscle fiber necrosis (Fig. 2a, b).

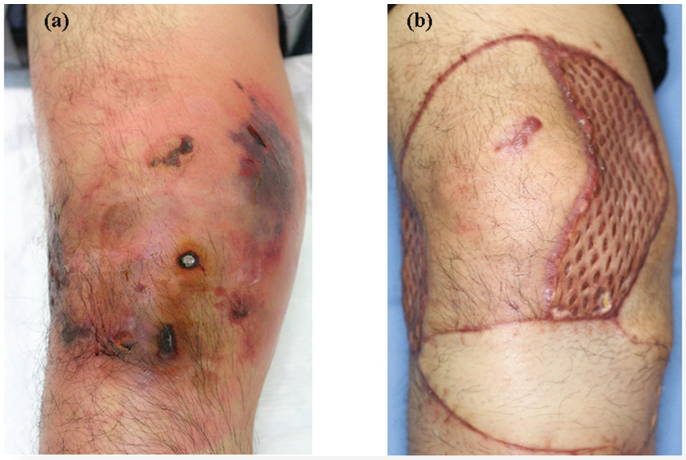

Figure 1. Clinical appearance (a) before, and (b) six months after treatment with debridement and oral steroid. (a) The right knee demonstrates remarkable swelling with marked, black cutaneous necrosis and skin ulcers. (b) After debridement and administration of oral steroids, the ulcerative lesion on the right knee healed with good granulation tissue, and could then be managed successfully with a skin graft and pedicle skin flap, without reactivation.

However, tissue cultures for bacteria, fungi, acid-fast microorganisms and parasitic amoebae were all negative. On the basis of these findings we made a final diagnosis of neutrophilic myositis associated with pyoderma gangrenosum. Investigation for an underlying illness, such as inflammatory bowel disease or a myeloproliferative disorder, (respectively by fibreoptic colonoscopy and bone marrow aspiration) revealed no abnormal findings. After debridement, we started treatment with oral methylprednisolone at a dosage of 40mg per day. His postoperative wound subsequently healed with good granulation tissue and, after one month, we performed a two-stage operation to address the residual ulcer successfully with the combination of a skin graft and pedicle-based skin flap. The dose of oral steroid could be tapered to 10mg per day for about six months, and there has been no exacerbation (Fig. 1b).

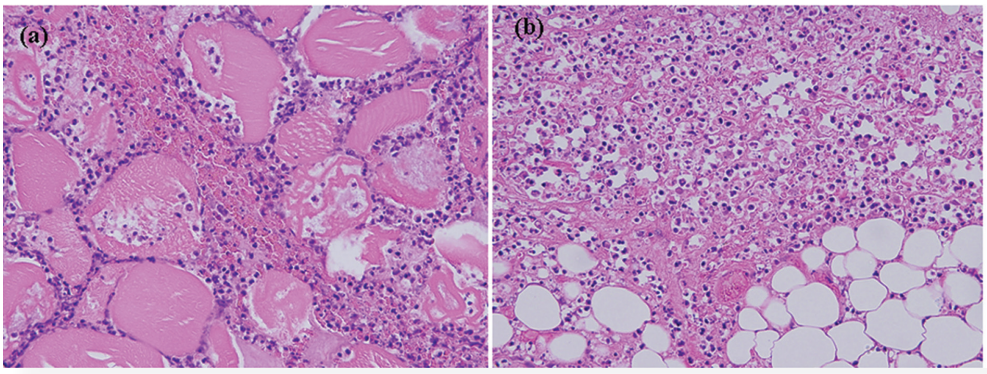

Figure 2. Histological study of the debrided tissues demonstrates severe inflammatory infiltrates, composed predominantly of neutrophils that extend throughout both the right musculus quadriceps femoris (a) and the skin of the same lesion (b). The muscle lesion was accompanied by disruption of the muscle architecture and numerous areas of muscle fiber necrosis. (Haematoxylin and Eosin stain, original magnification x400).

Discussion

Neutrophilic myositis is an extremely rare condition. To the best of our knowledge, only six cases have been reported, apart from ours [1-6]. The cases of neutrophilic myositis are summarized in Table I. The ratio of males to females is 5: 2, and the favorite involved sites were extremities. Three cases were associated with a neutrophilic dermatosis such as pyoderma gangrenosum [1] or Sweet's syndrome [2,3], and all of these cases coexisted with underlying leukaemia. The other cases had no cutaneous involvement, but were accompanied by underlying diseases, such as inflammatory bowel disease [4,5] or a myeloproliferative disorder [6]. Although coexistent pyoderma gangrenosum was seen in our case, there was no other underlying illness, in contrast to the reported cases [1-3]. We should however be vigilant for the later occurrence of such a disorder, particularly inflammatory bowel disease or a myeloproliferative disorder.

The diagnosis of neutrophilic myositis must be based on both histological demonstrations of intense neutrophilic infiltration throughout the affected muscles, with necrosis of muscle fibers, and exclusion of other muscle diseases, for example, polymyositis, dermatomyositis, inclusion body myositis, and pyomyositis [1].

Authors(s) [Ref.]	Sex	Age (years)	Coexisting disease	Involved site of myositis	Treatment	Prognosis
Marie I et al. [1]	Male	65	pyoderma gangrenosum acute myelogeneous leukemia	bilateral lower, upper limbs	Methylpredniso1one chemotherapy	death
Melinkeri SR et al. [2]	Female	6	acute myeloid leukemia	left thigh	Methylpredniso1one chemotherapy	death
Attias D et al. [3]	Female	60	Sweet's syndrome myeloblastic leukemia	bilateral thighs, left shoulder	Methylpredniso1one chemotherapy	death
Alawneh K et al. [4]	Male	42	celiac disease	right thigh, left lowe-re limb	Methylpredniso1one	remission
Qureshi JA et al. [5]	Male	36	ulcerative colitis	right shoulder, lower extremities	Methylpredniso1one	remission
Kim MK at al. [6]	Male	35	acute myeloid leukemia	upper arm	Methylpredniso1one	remission
our case	Male	27	pyoderma gangrenosum	right thigh	Methylpredniso1one debridement	remission

Table I. Summary of past cases of neutrophilic myositis.

Our case could finally be diagnosed as neutrophilic myositis related to pyoderma gangrenosum for the following reasons: the simultaneous onset of both neutrophilic myositis and pyoderma gangrenosum; negative stains and bacterial cultures of muscle and skin biopsy specimens; extensive, negative investigation for other causes of myositis such as infectious and connective tissue disorders; the efficacy of systemic steroids; and the ineffectiveness of broad-spectrum antibiotic therapy.

The etiology of neutrophilic myositis remains unclear. Heterogeneous factors, such as allergy to pathogenic organisms, traumatic injury and immunological abnormality due to co-existing disorders may be associated, as well as pyoderma gangrenosum [7]. The present case is the first in which compulsive exercise-induced stress on the knee due to break-dancing was a potentially causative trigger. This observation suggests that damage to or degeneration of muscle tissue induced by compulsive exercise may induce an abnormal, neutrophilic inflammatory reaction without any underlying immunological imbalance.

Finally, therapy for neutrophilic myositis has not been established. Based on the cases described, including our case, systemic treatment with moderate-to-high dose steroids seems effective [1-6]. Furthermore, a coexisting myeloproliferative disorder seems to indicate a poor prognosis [1-3, 6].

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NEUTROPHILIC MYOSITIS ASSOCIATED WITH *PYODERMA GANGRENOSUM* IN A BREAK-DANCER

by Hisashi Tamiya, Hiromi Kobayashi, Kaori Hoshi, Yui Horiguchi, Kurooka Sadahiro, Akiko Naruse, Shigeto Yanagihara, Daisuke Tsuruta

comment:

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Małgorzata Sokołowska-Wojdyło: comment: Neutrophilic myositis associated with pyoderma gangrenosum in a break-dancer. Our Dermatol Online. 2013; 4(4): 487.

The article is extremely interesting because has touched on the problem of neutrophilic dermatoses.

Pyoderma gangrenosum has revealed as uncommon (ex. 1: 100000 person a year in United States), ulcerative cutaneous condition of uncertain etiology with known pathergic phenomenon. Slight female predominance is observed. The disease occurs mostly in 40-50 years of age. Patients with pyoderma gangrenosum may have involvement of other organ systems that manifests as sterile neutrophilic infiltrates: pulmonary infiltrates (the most common), the heart, the central nervous system, the gastrointestinal tract, the eyes, the liver, the spleen, the bones, and the lymph nodes. The cases with joint destructions were also described. The treatment procedures related to systemic involvements and the specific therapy is not really established. Anyway – surgery should be avoided, if possible, because of the mentioned pathergic phenomenon that may occur with surgical manipulation or grafting, resulting in wound enlargement.

The authors have described the man (27) with muscle involvement treated with success with methylprednisolone and skin graft and pedicle-based skin flap.

So – the patient is quite young for his illness. The muscle has been involved, what was observed only in coexistence with Crohn disease and arthritis [1], with leukaemia [2] or as the extraintestinal manifestation of colitis ulcerosa or celiakia (neutrophilic myositis without pyoderma gangrenosum) [3,4]. These diseases have not been found in the case.

Also the performed surgical procedure does not belong to the canon of therapeutic methods of the illness. It did not release the pathergic phenomenon in this case, probably because of steroids treatment before the surgery (two months) and lack of triggering factor (the break-dance) during the treatment.

The question remains - was the muscle involved here by continuity due to the extent of the huge cutaneous lesion or was it separate, uninfluenced entity? In both cases – the patient have to be observed carefully (repeated blood tests, chest radiography, colonoscopy when any intestinal symptoms will appear) because of possible relapses and to diagnose in time the potentially developing systemic disease.

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NASZA DERMATOLOGIA Online
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ERUPTIVE PIGMENTED PATCHES IN A PATIENT WITH *HIV INFECTION* UNDER HAART

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Source of Support:
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Abstract
Introduction: Highly active antiretroviral therapy (HAART) is a standard treatment for HIV-infected patients. It has been reported that emtricitabine rarely induces skin pigmentation in the palms and soles. We herein report a Japanese case which presented a number of small pigmented patches on the acral sites.
Main observation: A 58-year-old Japanese man complained about multiple brownish skin pigmentations on his both palms and soles after 2 months of HAART therapy. Dermatoscopic observation showed a homogeneous light brown pattern. In spite of continuance of HAART, these lesions spontaneously regressed within 11 months.
Conclusion: We should know about the eruptive pigmented patches as an adverse effect under HAART with HIV infected patients.

Key words: HIV; HAART; emtricitabine; skin pigmentation; adverse effect

Cite this article:
Taeko Nakamura-Wakatsuki, Toshiyuki Yamamoto: Eruptive pigmented patches in a patient with HIV infection under HAART. Our Dermatol Online. 2013; 4(4): 488-489.

Introduction

Highly active antiretroviral therapy (HAART) is a standard treatment for HIV-infected patients. It has been reported that emtricitabine rarely induces skin pigmentation in the palms and soles. We herein report a Japanese case which presented a number of small pigmented patches on the acral sites.

Case Report

A 58-year-old Japanese man complained of multiple skin pigmentations on his palms and soles. He had been under treatment for HIV infection with HAART of emtricitabine and lopinavir/ritonavir for 2 months. A physical examination revealed a number of small light-brownish patches on his bilateral palms and soles (Fig. 1 a, b). Dermatoscopic observation showed a homogeneous light brown pattern without any network that support melanin deposition rather than melanocystic lesion (Fig. 2). Laboratory investigations revealed severe pancytopenia (WBC: 1700 cells/μl; RBC: 3.14×10^6 cells/μl; platelet: 8.7×10^4 cells/μl). CD4 cells count was 20.4 cells/μl in particular. A HIV-viral load was 3.4×10^6 copies/ml. He was diagnosed with emtricitabine-associated skin pigmentation. In spite of continuance of HAART, many of those pigmentations spontaneously disappeared or turned pale 11 months later.

Discussion

Skin pigmentations are sometimes seen among HIV-infected patients under treatment with HAART. There was an ethnic difference in the occurrence ratio between non-Caucasian and Caucasian (African-American: 8%, Asian: 4%, Hispanic: 3% v.s. Caucasian: less than 1%). The skin pigmentation appeared at a median 124 days (range: 7-259 days) and a median number of skin pigmentations was 6.5 (range: 1 to over 50). Generally, the outcome of the pigmentations was mild and disappeared at a median 112 days (range: 28-315). Histopathological findings of the skin pigmentation show increasing of melanin in the basal layer of epidermis similar to lentigo solaris. In the previous report, emtricitabine-associated skin pigmentation occurred 3.9% of Japanese patients [1], however, very few case reports have been seen. Of note, our case showed more than fifty pigmented macules on his palms and soles, many of which regressed spontaneously or turned pale within 11 months. Unfortunately, skin biopsies were not carried out. Interestingly, Namakoola et al [2] described that nail and oral pigmentation are associated with low CD4 count (<200 cells/μl) among HIV-infected individuals under antiretroviral therapy, which may link eruptive skin pigmentation and immunosuppression. Although the pathogenesis of skin pigmentations induced by nucleoside reverse transcriptase inhibitors is still unclear, there might be some common mechanisms which promote melanin pigmentation in the basal layer. Further studies will be necessary to determine the pathomechanisms of emtricitabine-induced eruptive pigmented lesions.

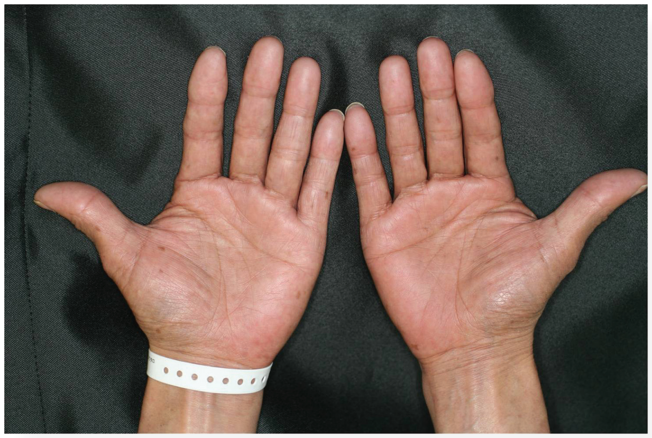

Figure 1a. Small light-brownish pigmentations on the palms.

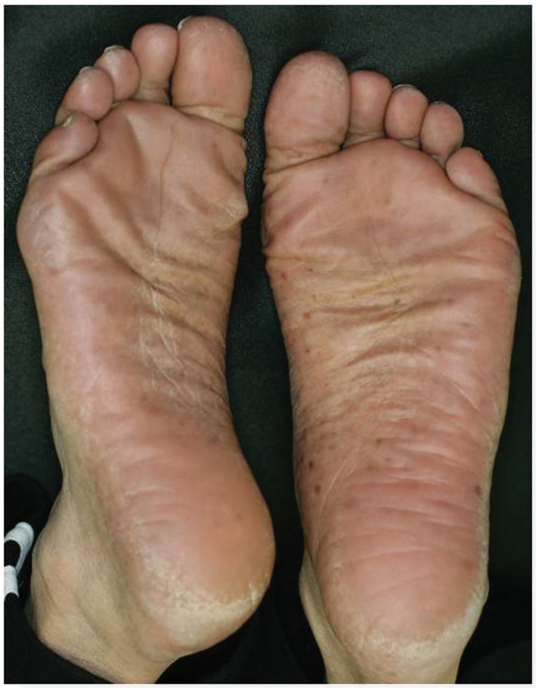

Figure 1b. Small light-brownish pigmentations on the soles.

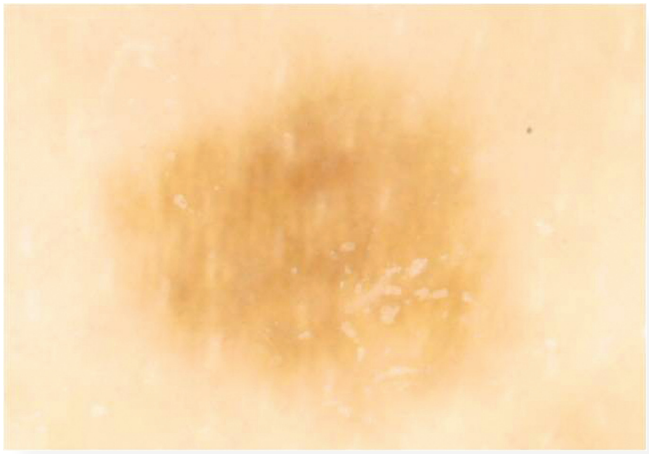

Figure 2. Dermatoscopic examination showed homogenous pattern without pigment network.

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WERNER SYNDROME: A NEW CASE REPORT

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Abstract
"Werner's syndrome" or premature aging syndrome is a rare autosomal recessive genetic disease. It is responsible of several complications related to age, including atherosclerosis and association with cancer. We report the case of a 36 year-old-patient, admitted to department of Internal Medicine of the military hospital of Tunis for suspicion of systemic sclerosis. The patient had all the major signs of Werner syndrome (bilateral cataract, sclerotic skin, "bird face", baldness, small size, parental consanguinity) and 4 minor signs (type 2 diabetes, hypogonadism, squeaky voice, and flat feet). She has also a brother with the same morphotype died at the age of 32 by a myocardial infarction. The current follow-up time is 9 years.

Key words: Werner syndrome; adult progeria; malignancy

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Introduction

Werner's syndrome (WS) is a disease causing premature aging. Its clinical manifestations include several signs usually associated with age, such as prematurely gray hair, alopecia, cataract, atherosclerosis, arteriosclerosis, osteoporosis, and a high incidence of some types of cancer [1]. Werner's syndrome is typically transmitted as an autosomal recessive disease, but atypical forms such as autosomal dominant transmission have also been reported. The prognosis depends on the associated diseases: atherosclerosis with its cardiovascular and neurological complications, insulin-resistance and cancer risk. The treatment is still limited to a multidisciplinary management of the diseases that complicate this syndrome [1,2]. In this regard, we report a case of a 36-year-old patient, followed for WS in the department of internal medicine at the military hospital of Tunis.

Case Report

Mrs. NN 36 years old, unmarried, born to consanguineous parents, was admitted to our department for suspicion of systemic sclerosis. Physical examination revealed a total alopecia, depletion of pilosity with signs of hypogonadism, sharp nose, facial skin was tough and tight with some telangiectasia (Fig. 1a, b). Members were slender with obvious atrophy (Fig. 2), her feet were flat with plantar hyperkeratosis (Fig. 3) and she had hyperchromic spots at the trunk and limbs. Moreover, we noted an increase in the volume of the left lobe of the thyroid containing a firm and painless nodule. She weighed 38 kg for a height of 1.50m (BMI = 16.8). She had secondary amenorrhea since the age of 28 and complained from a decline in visual acuity and a changement in her voice that gets squeaky for few months.

Laboratory tests showed hyperglycemia (Fasting glycemia=2.30 g/l) with a high level of glycated hemoglobin (HBA1C=12.9%) and hypertriglyceridemia (TG=3.12 mmol/l). The immunological tests were negative (antinuclear antibodies<0, anti Scl70<0, rheumatoid factor<0, anti-neutrophil cytoplasmic antibodies<0) and complement components C3, C4 and CH50 were normal. Free T4 and Thyroxin Stimulating Hormone have normal rate. Tumor markers' levels (CEA, CA 19-9 and CA-125) were not high. Follicule Stimulating Hormone and Luteining Hormone levels were above 40mU/l suggesting an early menopause. Ophthalmologic examination revealed a bilateral nuclear cataract. Cervical ultrasound showed a large heterogeneous left thyroid nodule with a central and peripheral vascularisation. Pelvic ultrasound showed atrophic ovaries.

The diagnosis of Werner syndrome was strongly suspected seen the particular signs in our patient especially the skin lesions, signs that are usually present in elderly patients, in addition to parental consanguinity as her brother died with the same symptoms prematurely at the age of 32 by a myocardial infarction. In our case, the course was complicated with type 2 diabetes requiring insulin after the failure of antidiabetic drugs combining. The patient underwent a left loboisthmectomy and pathological anatomy of the nodule concluded that it was a micro and macro-vesicular adenoma with no signs of malignancy.

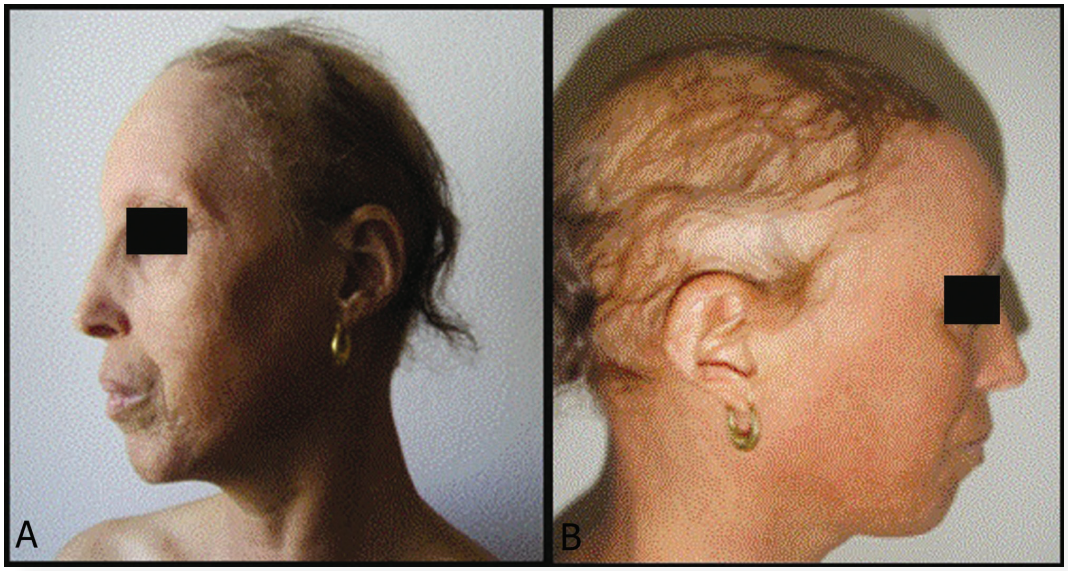

Figure 1a. Sharp nose, tough and tight facial skin with some telangiectasia; 1b. Total alopecia.

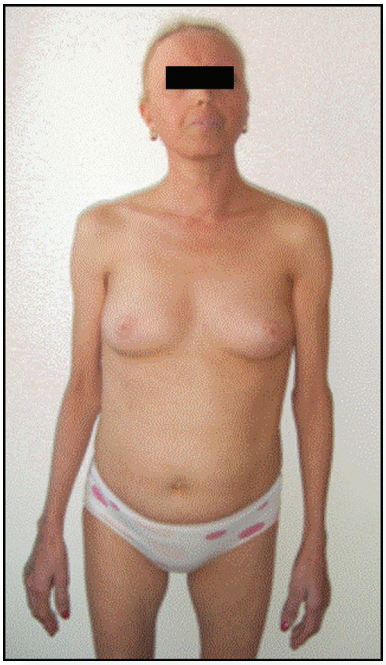
Figure 2. Slender members with obvious atrophy, depletion of pilosity with signs of hypogonadism.

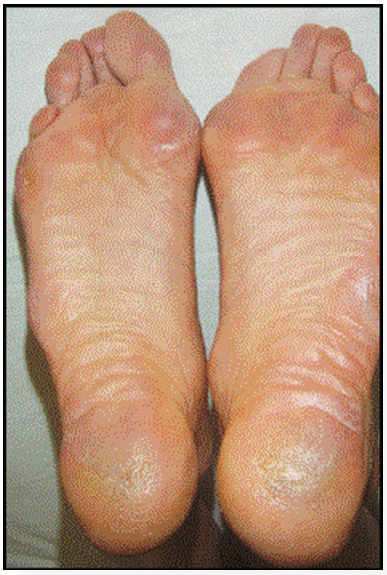
Figure 3. Flat feet with plantar hyperkeratosis.

Discussion

Werner's syndrome (WS) was discovered by Werner in 1904. The diagnosis criteria proposed in 1994 include major signs combining: bilateral cataract, skin changes (thin skin, skin atrophy, pigmentary abnormalities, cutaneous ulcers, hyperkeratosis, subcutaneous atrophy), a characteristic facial appearance "bird face" (tapered nose, decreased subcutaneous tissue), short stature, premature graying of hair or early baldness, parental consanguinity or a first cousin reached by the disease [1]. Minor signs of WS are: type 2 diabetes, hypogonadism (delayed development of secondary sexual characteristics, hypofertility, testicular or ovarian atrophy), osteoporosis, osteosclerosis of distal phalanges of fingers or toe [2], premature atherosclerosis which can cause myocardial infarction, mesenchymal tumors (sarcomas) and unusual sites of melanoma and osteosarcoma. Common carcinomas are also observed [3,4]. Abnormal voice (squeaky, acute) and flat feet are also minor signs of WS [5].

In our patient, the diagnosis of WS was retained seen the presence of all the major signs (bilateral cataract, sclerosis of the skin, "bird face", bald, small size, parental consanguinity) and 4 minor signs (type 2 diabetes, hypogonadism, squeaky voice, flat feet**).**

Werner's syndrome is a genetic disorder transmitted in an autosomal recessive way, its prevalence varies with the rate of inter-marriage in populations. In the Japanese population it is 1/20,000 to 1/40,000 [6]. In the U.S. population prevalence is estimated at 1/20,000.

The percentage of consanguineous marriages in Tunisia is around 30%, raising the prevalence of Werner syndrome which is not known. The pathogenesis of SW has been well studied, a mutation of WRN gene is the only known responsible of Werner Syndrome. This mutation is present in 90% of affected individuals, revealed via a genetic molecular test. It is responsible for the loss of function of the WRN protein leading to early senescence [7].

The severity of the WS is due to its several complications dominated by atherosclerosis. Patients may develop different forms of atherosclerosis, specially that affecting the coronary arteries and leading to myocardial infarction that is the first cause of death in WS, such as the case of our patient's brother. Cancers also threaten patients with Werner syndrome. Our patient had a thyroid nodule which pathological anatomy eliminated thyroid carcinoma. Skin complications are also reported. Giuseppe F. et al [8] published a case of Werner syndrome in a patient whose quality of life was highly affected and in which the main complaint was a painful leg ulcer, relapsing for 9 years.

Prevention of secondary complications through a healthy lifestyle aim to reduce the risk of atherosclerosis: smoking cessation, regular physical activity, weight control. The eviction of trauma, skin care and regular checkups are necessary in the follow-up. WS patients must be monitored with a glucose balance, lipidic profile, and annual eye exam. Monthly monitoring of cutaneous manifestations and regular cancer screening is needed. The mean age of death in WS is about 54 years [9]. In our patient, the current follow-up time is 9 years , the course was complicated with type 2 diabetes and we have no malignancy detected.

Conclusion

In conclusion, the case is presented for the rarity of the syndrome, which should be kept in mind to avoid misdiagnosis, allow preventive measures, and promote adequate periodic screening for dermatological, ophthalmic and cardiovascular complications associated with premature aging, especially malignancies.

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VARIED MALIGNANT PRESENTATIONS IN A SINGLE CASE OF *XERODERMA PIGMENTOS*

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Abstract
Xeroderma pigmentosum is a autosomal recessive genetic disorder in which cutaneous malignancies are very common. We report a rare case where four different varieties of cutaneous malignancies were seen in the same patient.

Key words: Xeroderma Pigmentosa; cutaneous malignancies; squamous cell carcinoma; basal cell carcinoma

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Introduction

Patients with XP are at a high risk for developing skin cancers, such as basal cell carcinoma. Xeroderma pigmentosum, or XP, is an autosomal recessive genetic disorder of DNA repair in which the ability to repair damage caused by ultraviolet (UV) light is deficient [1]. This disease involves both sexes and all races, with an incidence of 1:250,000 and a gene frequency of 1:200.

Metastatic malignant melanoma and squamous cell carcinoma [2] are the two most common causes of death in XP victims.

Case Report

A 19 years of age female patient presented to us with multiple lesions on her face. In addition she had skin pigmentation all over the body, freckles over the face and she complained of photophobia. She had already been diagnosed as a case of Xeroderma pigmentosa. An excision biopsy was done on the ulcerated lesion. Biopsy report of the excised portion revealed basal cell carcinoma. She received 6-7 weeks of radiotherapy for the same. Her younger brother is also affected with the disease. There was no history of consanguineous marriage. Closer examination revealed, a) big lesion (three by three cms) over the left cheek with presence of slough present in the centre, b) Ulcerated nodule of size two cms by two cms over the left forehead with and scab over it, margins were distinct, c) firm nodular swelling of size two cm by one cm over the left inferior border of mandible, d) a nodular swelling of size one cm by one cm over the left cheek just anterior to the previous ulcerated lesion (Fig. 1).

There were small multiple nodular lesions over the right side of face. No significant.

Cervical lymphadenopathy was present. Systemic examinations including neurological function were normal. All investigations with serum biochemistry were within normal limits.

Though the biopsy of one of the lesions showed basal cell carcinoma, a wider margin of one centimeter was taken during excision. Cover was done with intermediate thickness skin graft. Post operative care was uneventful (Fig. 2 - 4). The excised lesions were sent for histopathological examination which revealed four types of cutaneous malignancy, i.e-spindle cell (sarcomatoid) carcinoma and focus of basal cell carcinoma in the cheek lesion, basal cell carcinoma of the forehead lesion, squamous cell carcinoma of the mandibular lesion and a foci of atypical meloncytic hyperplasia,which was not reported as malignant by the pathologist, in the left cheek lesion. All margins were free of tumor.

Discussion

Patients with xeroderma pigmentosa have extreme sensitivity to the sun's ultraviolet rays and should be protected from these rays. Proper protection from the sun and early adequate treatment helps in increasing the longevity of these patients. Unless protected from sunlight, the skin and eyes may be severely damaged [3-5].

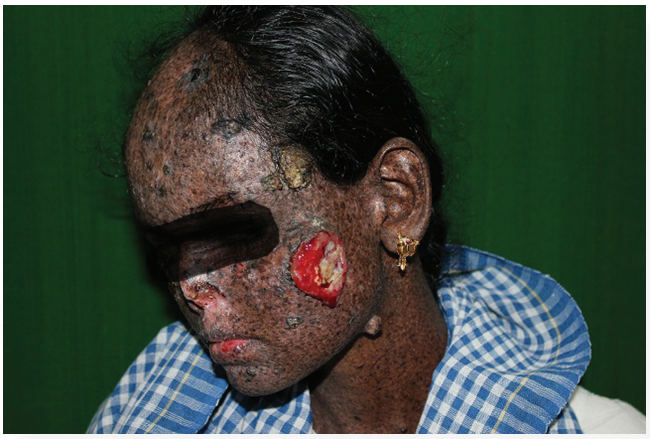

Figure 1. Pre operative picture showing the lesions on the face including a large ulcerated lesion on the cheek.

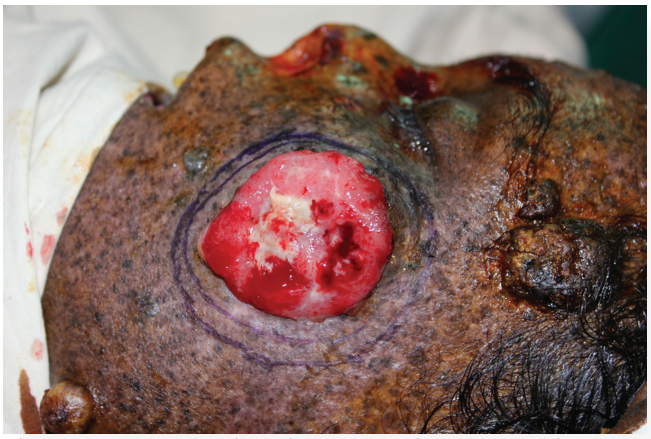

Figure 2. Intra operative picture showing the markings.

Figure 3. Intraoperative picture after a wide local excision was done.

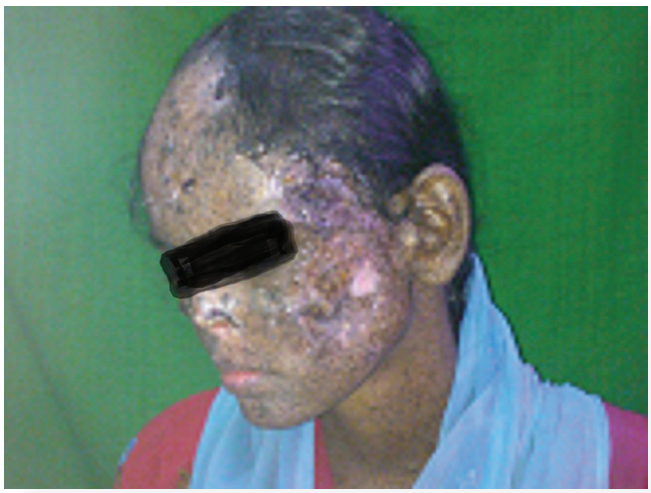

Figure 4. Post operative picture.

Individuals with XP develop multiple cutaneous neoplasms at a young age [6]. Two important causes of mortality are metastatic malignant melanoma and squamous cell carcinoma [7]. Patients younger than 20 years have a 1000-fold increase in the incidence of non melanoma skin cancer and melanoma [8]. The mean patient age for the development of skin cancer is 8 years in the patients with XP compared to 60 years in the healthy population. Actinic damage occurs in the age range of 1-2 years

Variations in the type of malignancies in XP appears to be related to the degree of sun exposure and genetic heterogeneity [9]. The two most common types of cancer found in XP patients are BCC and SCC, mainly occurring on the face, head, and neck. Melanomas occur in one-fourth of cases, and one-third of these occur in the head and neck [10].

A patient presenting with any two of these malignancies is a rare occurrence, with only a few cases reported in the literature; the presence of all the three types of malignancies in one patient is extremely unusual [11]. Early detection of these malignancies is necessary because they are fast growing, metastatize early and lead to an early death. Two important causes of mortality are metastatic melanoma and SCC. Most patients with XP do not live beyond the third decade because of the development of tumors [10]. Cutaneous neoplasms in XP patients cannot be prevented but early protection from UV radiation should be advised, and undertaken.

In our case we have the synchronous occurrence of four different types of cancer which to our knowledge has never been reported before. From a surgeons perspective this holds a lot of importance because of the margin of excsion varies for different types of skin tumors. Usually, since the most common tumor is Basal cell carcinomas, in the absence of preoperative tissue biopsy, one is inclined to treat most lesions as basal cell carcinomas and take a comparatively smaller margin. If the tumor turns out to be squamous cell carcinoma this may result in recurrence. Also in a patient with multiple lesion, when a biopsy is taken only from one tumor, considering it thinking it to be a representative lesion, it may prove wrong ,as illustrated in this patient. It is very important one ensures a complete excision of the tumor in view of the fact that metastatic squamous cell carcinoma and melanoma are the most common cause of mortality in these patients.

Keeping this is mind we propose that in absence of a confirmatory preoperative biopsy it would be advisable to give a considerable margin or plan for frozen section during the surgery so that one can ensure complete clearance. This would be safe and appropriate even if the biopsy turns out to be a SCC.

Conclusion

We present this case wherein four different types of skin tumors were diagnosed on the same patient and in the same anatomical region (face). Synchronous occurrence of multiple cutaneous malignancies in a patient of xeroderma pigmentosa is extremely rare. This underlines the fact that almost any tumor can develop in these patients and hence it becomes imperative that resection with a wide margin is made to ensure total tumor excision.

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AUTOSOMAL RECESSIVE TOTAL CONGENITAL ANONYCHIA, IN A SAUDI FAMILY

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Abstract
The autosomal recessive total congenital anonychia is a rare genetic disorder. In this manuscript we are reporting the occurrence of this trait in a Saudi Arabian family.

Key words: dermatology; genetic; nails

Cite this article:
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Introduction

Total absence of nails since birth, Otherwise called Total Congenital Anonychia; (TCA) is a rare trait.
This rare genetic disorder has been reported in individuals from different countries around the world. Previous report [1], had indicated that it could be found in countries such as, Russia, Great Britain, America, Holland, Iran. Recently, it has been reported in Brazil [2] and Turkey [3].
In this manuscript, we use a Saudi family as a case study.

Case Report

The proband was a 22-year-old boy who had come to hospital for the treatment of acne vulgaris. Complete absence of all nails, had been noticed since birth. His parents are first cousin. One of his sisters have also suffered the same disorder (TCA). Although, she is married to a person from different tribe she has 2 children with normal nails. No other members of the family was affected with nail disorders and no history of the similar condition before in the family.
Family pedigree is shown in Figure 1.The patient had no other obvious case of disorder. However, the parents mentioned that, their affected children always request someone to help scratch their skin whenever they had itchy skin. The parents also noted that the „skin'', in place of the nails (nail bed), get thickened with time.

Physical Examination showed complete absence of all the fingernails, and all toenails. Other examinations, in particular such as hair, teeth, and skeletal system, revealed no abnormality. Skin examination, was also normal and did not show any abnormal pigmentation. Nevertheless, the family declined medical photography and the radiological examination of the hands and feet.
Similarly, his affected sister could not be examined as she lives in another city.

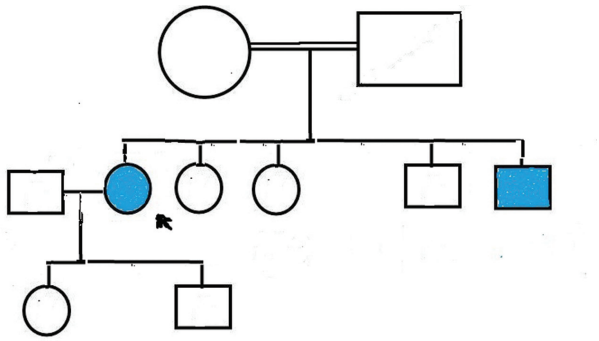

Figure 1. Family pedigree.

Discussion

Genetic disorders are not uncommon in Saudi Arabia. This is because of several factors, and in particular, consanguineous marriages which are very common in Saudi Arabia especially in villages and small towns. The government had launched a pre-marital medical counseling program in order to reduce the burden of genetic disorders especially the genetic blood diseases like sickle cell anemia.

There are several common and rare genetic dermatological disorders reported in families from Saudi Arabia. These include; Kindler syndrome [4], Multiple hereditary trichoepitheliomas [5], Lamellar ichthyosis [6], Hereditary hypotrichosis simplex [7].

Anonychia congenita totalis, had also been reported from Saudi Arabia but in a single patient [8].

Therefore, this is the first report of Total Congenital Anonychia (TCA), in a Saudi family.

Congenital absence of a nail (anonychia) is a rare genetic defect. The first two cases of anonychia were described in 1842 [8].

Anonychia of a single or a few nails can be found in many hereditary disorders and syndromes. For examples in Cooks syndrome which is a combination of anonychia and absence or hypoplasia of distal phalanges [9], also, in Zimmermann-Laband syndrome, which has many features including gingival fibromatosis and hypoplastic or absent nails [10].

However, TCA have been reported with a limited syndromes. A previous review, have listed the following reported associations with TCA:

1. Aplasia or hypoplasia of upper lateral incisor, spaced teeth, loss of some molars.
2. Microcephaly, clinodactyly, single transverse palmar crease, widely spaced teeth.
3. Deafness and onycho-osteodystrophy syndrome, DOOR syndrome (deafness, onycho-osteodystrophy, mental retardation).
4. Glossopalatine ankylosis syndrome (abnormal mouth, tongue being attached to temporomandibular joint).
5. Bizarre flexural pigmentation and hair abnormalies.
6.Dyscephalic mandibulo-oculofacial syndrome and craniofrontal nasal dysplasia.

Nevertheless, TCA can be isolated defect in this family.

TCA is inherited mostly as an autosomal recessive manner like the family in this report. The trait does not affect the life of the affected patients. Yet, patient might be sensitive to touching acidic materials using the tips of their fingers or may feel uncomfortable by scratching the skin with no nails.

It has been found that autosomal recessive form of TCA is caused by loss-of-function mutations in the gene encoding R-spondin 4 (RSPO4), present on chromosome 20p13, which functions in the WNT signaling pathway. This gene plays a crucial role in nail morphogenesis, andacts as a landmark for early nail unit formation [12].

We believe that autosomal recessive TCA is a distinct disorder. However, the affected patients need to be examined thoroughly to exclude systemic or ectodermal defect particularly the teeth.

There is no specific therapeutic procedure for this disorder and the treatment remains masterly inactivity or artificial nails.

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A CASE OF *SUBCUTANEOUS PHAEOHYPHOMYCOSIS* CAUSED BY *EXSEROHILUM SPECIES* IN AN IMMUNOCOMPROMISED PATIENT

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Abstract
Phaeohyphomycoses are rare fungal infections, caused by dematiaceous fungi, manifested as cutaneous and subcutaneous infections, meningitis, sinusitis, keratitis, osteomyelitis and disseminated infection.
This is a case report of a 45year old immuno compromised female on ART (Anti Retroviral therapy) presented with fever and generalized nodular lesions draining pus on face, hands, axilla, groin and labia majora since one month. Biopsy of the subcutaneous nodule on the lateral aspect of the thigh revealed septate fungal hyphae on 10% KOH (10% Potassium Hydroxide) mount. Fungal culture of the biopsy material on SDA (Sabouraud's Dextrose Agar) at 25^0C showed cotton wooly, dark gray to olivaceous black growth with black reverse and identified as dematiaceous fungi belonging to Exserohilum species by microscopy. The patient was put on Itraconazole 200mg BD in combination with Terbinafine 250mg BD for which she responded with healing of pustular lesions in two weeks and complete remission in two months.

Key words: subcutaneous nodules; Exserohilum species; Phaeohyphomycosis

Key message: The increase in the fungal infections may be related to a heightened awareness of these infection in humans and improved diagnostic techniques. Inspite of availability of broad spectrum antifungal agents the fungal infections are causing disasters, it is imperative to investigate and pinpoint the causative agents in all infections to contribute data for further studies which will ultimately give an opportunity for better prevention and care.

Cite this article:
Koppada Rajasekhar, Anaparthy Usharani, Nirupama Padmaja Bondili, Ratna Harika Dusi, Perala Balamurali Krishna: A case of subcutaneous phaeohyphomycosis caused by Exserohilum species in an immunocompromised patient. Our Dermatol Online. 2013; 4(4): 498-500.

Introduction

Very few cases of subcutaneous phaeohyphomycosis caused by Exerohilum species were reported till date. On 17th October 2012 in the journal "Annals of Internal Medicine" there was an article reporting about an outbreak of fulminant meningitis caused by *Exserohilum rostratum* after receiving spinal epidural injections of methylprednisolone contaminated with *Exserohilum rostratum* causing loss of lives in USA [1]. From India very few cases of cutaneous phaeohyphomycosis have been published among which there is a case of cutaneous phaeohyphomycosis caused by *Exserohilum rostratum* in a 40 year old woman that presented to the Department of Biological sciences, Rani Durgavati University, Jabalpur, India in July 1995 with a 3 year history of a cutaneous infection of the upper anterior aspect of the forearm [2].

The phaeoid fungi are a curious group of organisms capable of causing a wide array of clinical pathologies ranging from the superficial to the deep seated infections. As a cosmopolitan disease, phaeohyphomycosis mainly afflicts adults among whom many are immunocompromised. Underlying conditions that contribute to infection by dematiaceous fungi include tuberculosis, diabetes, cancer, tissue transplantation, and use of corticosteroids or other immunosuppressive drugs, surgery, and a number of other conditions including acquired immunodeficiency syndrome (AIDS)due to the human immunodeficiency virus (HIV) [3].
The genus *Exserohilum* was established by Leonard and Suggs. It belongs to the Kingdom: Fungi, Phylum: Ascomycota, Class: Euascomycetes, Order: Pleosporales, Family: Pleosporaceae, Genus: *Exserohilum*.

The three closely related genera Bipolaris, Drechsleria and Exserohilum are distinguished on the basis of such characters as conidial shape and size, hilar morphology, origin of the germ tubes from the basal or other conidial cells, and the location and sequence of the conidial septa. The only *Exserohilum species* known as etiologic agents of phaeohyphomycosis in humans and animals are *E.rostratum*, *E.longirostratum* and *E.meginnisii* [4,5]. An aggressive angioinvasive nature and the ability to grow at 400C indicate their potential to be neurotropic pathogens [1].

Case Report

A 45 year old immunocompromised female from a low socioeconomic background from Vijayawada presented with fever and generalized nodular lesions draining pus on face, hands, axilla , groin and labia majora since one month. No history of arthralgia, decreased sensations or any other systemic manifestations; Figure 1 showing the pustular lesions.

She was on Anti Retroviral Therapy since 4 years with an initial CD4+ count of 50 cells/µl at the time of HIV diagnosis, which has improved to 500 cells/µl at the time of presentation with the present complaints. The symptoms started with fever and upper respiratory infection for which she received antibiotics and after 15 days she developed a generalized pustular eruption for which she was also prescribeded antibiotics irregularly by a local practitioner. The patient did not show improvement and was referred to Government General Hospital, Vijayawada for further care.

On examination there were multiple bilateral generalized erythematous tender nodular lesions draining pus on face, hands, axilla, groin & labia majora. Routine investigations like complete haemogram, LFT (Liver function tests), RPR (Rapid Plasma Reagin) were done and results were within normal limits. FBS -210mg/dl, PPBS -270mg/dl (Fasting blood sugar and Post prandial blood sugar levels are slightly out of range but no history of Diabetes or therapy with hypoglycemic drugs), ESR-46mm, CRP (C- reactive protein) - positive, ASO (Anti steptolysin-O titre) - negative, SSS (Slit skin smears) are negative for Lepra bacilli. Biopsy of subcutaneous nodule on the lateral aspect of the thigh was sent to Department of Microbiology, for mycological diagnosis suspecting phaeohyphomycosis.

Mycological study and diagnosis:

10% KOH mount of the biopsy material revealed the presence of fungal elements showing slightly brown coloured hyphae with septations indicating pheoid fungi.

The biopsy material was inoculated directly onto Sabouraud's Dextrose Agar (SDA) and incubated at 25^0C. After 3 days of incubation cottony white growth appeared which turned to dark grey on further incubation and then turned to olivaceous black with a black reverse. Figure 2 showing the growth of *Exserohilum spp*. on the Sabouraud's Dextrose Agar slant.

Lactophenol Cotton Blue (LPCB) mount of the growth showed phaeoid septate branching hyphae with conidia. Conidia were ellipsoidal, distoseptate and had a protruding and truncate hilum. The fungus was identified as *Exserohilum species* based on the morphology of the conidia. Slide culture was done for further confirmation. Figure 3 showing the conidia of *Exserohilum spp.* in a LPCB mount.

The patient received treatment with Itraconazole 200mg BD in combination with Terbinafine 250mg BD for which she responded with healing of pustular lesions in two weeks. She continued this treatment for 2 months. Patient is on ART with marked improvement in general condition and complete remission of the pustular lesions. Figure 4 showing the healed pustular lesions after the antifungal treatment.

Discussion

Exserohilum may infect both immunocompromised and immunocompetent hosts with variable clinical manifestations, ranging from cutaneous infections to fulminant disseminated disease. During the last decades there has been an increase in the number of reported cases of *Exserohilum* infection. The increase may also be related to a heightened awareness of this infection in humans and improved diagnostic techniques. According to the review of the literature published by Adler A et al., there were 33 cases of *Exserohilum* infection, of which 23 were reported since 1993. Most occurred in regions with hot climates, such as India, Israel, and the Southern USA. Impaired immunity was present in the majority of patients with invasive and skin infections, whereas local trauma and atopy were the predisposing factors in those with corneal infections and allergic fungal sinusitis, respectively. Surgical debridement was the principal mode of therapy for allergic fungal sinusitis. Amphotericin B was the initial single antifungal agent used in all cases of invasive disease. The response rate was low but improved with addition of triazole agents.

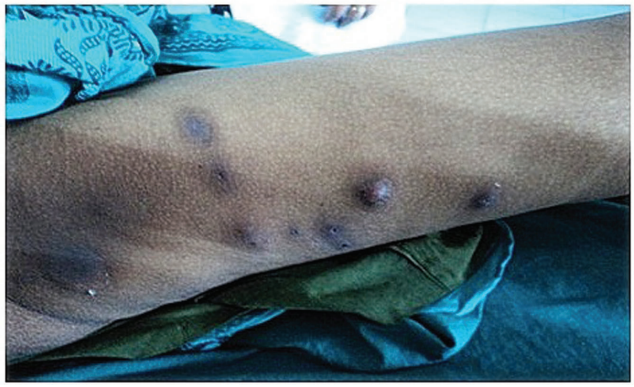

Figure 1. Subcutaneous nodules draining pus.

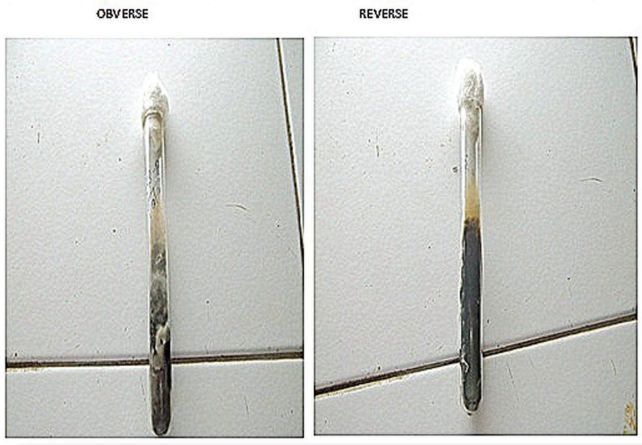

Figure 2. Growth of Exherohilum on SDA slant.

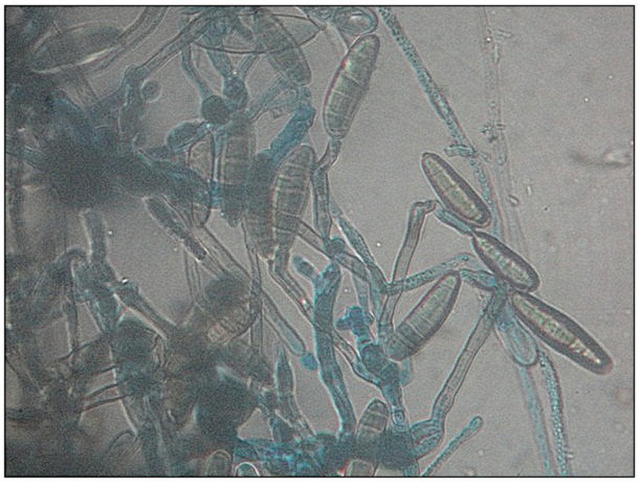

Figure 3. LPCB mount of Exserohilum growth from slide culture showing conidia with protruding hilum.

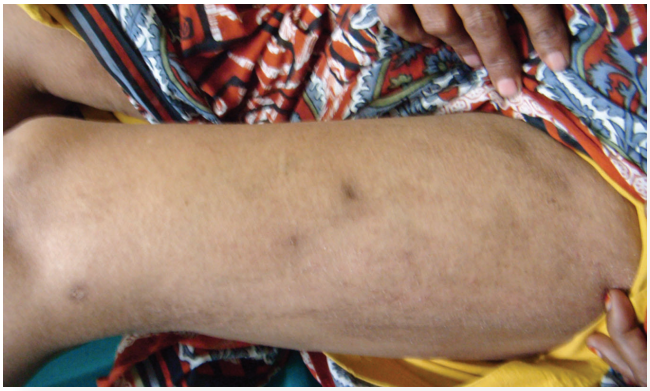

Figure 4. Healed lesions after the treatment.

Outcome appeared to be better than for other mold infections and depended mainly on the underlying diseases [6]. Subcutaneous tissue is a common site for phaeohyphomycosis and is generally thought to occur as a result of traumatic implantation of fungal material from contaminated plants or soil. Corneal infections are due to contamination of traumatic corneal abrasions with asexual fungal spores [3]. A rare case of corneal phaeohyphomycosis due to *Exserohilum rostratum* following organic trauma was reported from Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India in April 1996 [7].

Reports of four cases with two types of skin infection, cutaneous and subcutaneous caused by *Exserohilum rostratum* in immunocompromised men were published by the Department of Dermatology of the National Cheng-Kung University Hospital, Tainan, Taiwan in 1993 [8].

A subcutaneous abscess caused by *Exserohilum rostratum* was diagnosed in 55 year old healthy woman with a subcutaneous abscess and systemic symptoms of nausea, dizziness and chills following minor trauma to her leg [9]. Another case of phaeohyphomycosis of the nasal sinuses caused by a new species of *Exserohilum* was reported in a 27 year old man with a 6 year history of allergies developed nasal polyps that occluded his nose [4].

The pathogen is usually an environmental contaminant. Cases of nosocomial fungal infections linked to contaminated care material, especially cloth tape, adhesive tapes or wooden devices were reported in the literature [7]. It is recommended that when Bipolaris or *Exserohilum species* are isolated from clinical specimens, such isolates should not be carried out simply as contaminants; appropriate studies should be carried out to determine if they play an etiologic role [4].

This is the first diagnosed case of subcutaneous phaeohyphomycosis caused by *Exserohilum* species reported in HIV positive patient in and around Vijayawada.

In all suspected cases of phaeohyphomycosis the relevant specimens should be sent to the Department of Microbiology & Department of Histopathology for identification of the causative etiological agent for better patient care and treatment.

We extend our thanks to the Department of Dermatology for their cooperation.

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IMPORTANCE OF THE TRICHOSCOPY IN *SCALP DYSESTHESIA*

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Abstract
The trichoscopy has been incorporated as a first hand method in patients consulting for scalp problems. Magnifying glass or digital microscope that permit the direct visualization of the hair shaft and the perifolicullar skin are utilized to diagnose cicatricial and non-cicatricial alopecia. A female patient with an alopecia plaque associated with a scalp dysesthesia in which trichoscopy was very useful in its diagnosis is presented.

Key words: trichoscopy; scalp dysesthesia; trichoteiromania

Cite this article:
Maria Bibiana Leroux: Importance of the trichoscopy in scalp dysesthesia. Our Dermatol Online. 2013; 4(4): 501-502.

Introduction

The trichoscopy has been incorporated as a first hand method in patients consulting for scalp problems. Magnifying glass or digital microscope that permit the direct visualization of the hair shaft and the perifolicullar skin are utilized to diagnose cicatricial and non-cicatricial alopecia [1].
The primary psychiatric disorder case bears no skin condition. There are four types of underlying psychopathology. i.e., generalized anxiety, depressive, delusional and obsessive-compulsive disorder. In these cases it can always be observed self-inflicted scalp lesions. No signs of any other disease related to the hair or scalp findings observed are present. Trichotillomania, neurotic scalp excoriations, factitial dermatitis, delusions of parasitosis, scalp dysesthesia and psychogenic pseudo effluvium are among the dermatologic presentations [2].

Case Report

Material and Methods

Female patient, aged 55yr refers extreme sensitivity - burning sensation- in a circumscribed area of the hair scalp close to the top of the head with more than one year evolution. Personal history: depression. Physical examination: 3cm major axis oval alopecia plaque. Negative traction test (Fig. 1). The patient admits that has rubbed the lesion but did not self produce it. There are no other signs or symptoms of dermatological disorders neither in the skin nor in nails or hair.

Results

- A previous scalp biopsy was histological negative.
- Negative medical workup.
- Trichoscopic examination, 70x magnification: plaque peripheral zone preserved - there are no alterations neither of the hair shaft nor of the perifolicullar skin. The lesion images show a great deal of broken hairs, many of them with distal end longitudinally divided in two or three portions, the so called trichoptilopsis (Fig. 2).

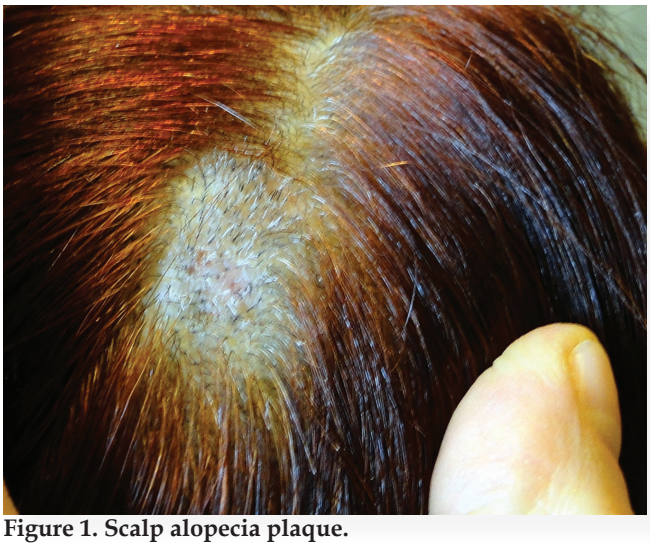

Figure 1. Scalp alopecia plaque.

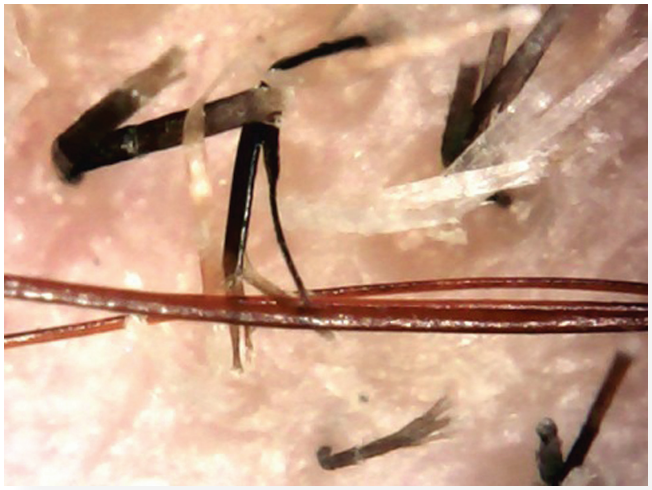

Figure 2. Multiple hair shaft with trichotilopsis, 70 X magnification.

Discussion

Due to the clinical signs and symptoms, the latter referred by the patient, scalp dysesthesia is considered as the probable diagnosis. It represents the manifestation of the coetaneous sensory disorders on the scalp. The role of substance P and others neuropeptides in the pathogenesis of this problem and the relation of such substances to the psyche and emotional stress need further studies. Seventy-six percent of patients show emotional disturbance, mainly depression, compulsive disorders and anxiety. The absence of clinical signs and symptoms permit to rule out temporal arteritis, tension headache or any other scalp pain etiology [2,3].

The dermatologic sign is a consequence of repeated rubbing of the scalp lesion.

- Trichoteiromania - The trichoscopy permits to confirm the self traumatic etiology of the findings and perform a differential diagnosis with other disorders such as tinea capitis or scalp dermatitis [4-6].

Conclusion

The trichoscopy was very useful for the diagnosis and differential diagnosis with others scalp disorders.

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IATROGENIC CUSHING SYNDROME DUE TO TOPICAL GLICOCORTICOSTEROID THERAPY

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None

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Abstract
Topical glicocorticosteroids are the most common drugs to treat acute and chronic inflammatory skin diseases. Prolonged use of them may cause systemic adverse effects including Cushing's syndrome and hypothalamic-pituitary-adrenal axis suppression. We present a case of four year old girl who developed iatrogenic Cushing syndrome and adrenal insufficiency after atopic dermatitis treatment through the misuse of Mometasone treatment without doctor's prescription. We observe a reddness and a moon face, a buffalo hump, central obesity, ginecomasty, subcutaneous hypertrophy, hirsutism, buttocks muscle atrophy and growth retardation. Wrist X-Ray revealed a bone age of two year old child. Laboratory values revealed hypothalamic-pituitary-adrenal axis suppression. The discontinuation of Mometasone treatment and supplement treatment with oral Hydrocotisone three times per day proved successful in this patient.
For this case, the serious side effects of topical glucocorticosteroid treatment should be explained to the family and their long-term therapy should be refrained. Iatrogenic Cushing syndrome in childchood caused by topical treatment is a rare event.

Key words: Cushing syndrome; atopic dermatitis; adrenal insufficiency; mometasone

Cite this article:
Alicja Rustowska, Aleksandra Wilkowska, Roman Nowicki: Iatrogenic Cushing syndrome due to topical glicocorticosteroid therapy. Our Dermatol Online. 2013; 4(4): 503-505.

Introduction

Cushing's syndrome is a group of symptoms due to high levels of glucocorticoids, which can be either endogenous or exogenous. It can be ACTH dependent such as - Cushing's disease, ectopic ACTH – producing tumours or excess ACTH administration or non-dependent such as adrenal adenomas, adrenal carcinomas and excess glucocorticoid administration. Exogenous glucocorticoids are the most common etiological factor [1].
Atopic dermatitis is a chronic, inflammatory disease, an inherited predisposition to eczema, asthma bronchiale or hayfever and atopic individuals may have one or all of these manifestations [2]. The eczema usually begins between the ages of 3 and 12 months, asthma at age 3 and 4 years and the hayfever in the teens. In infancy the eczema may affect the whole body. About fifty percent of such children will also have ichthyosis, in about 90 percent of children the eczema will clear spontaneously by puberty, but in a small minority, it can persist into adult life. A few of these will have very extensive and troublesome eczema all their lives [3]. Prolonged use of glucocorticosteroids may cause systemic adverse effects including Cushing's syndrome and hypothalamic-pituitary-adrenal axis suppression.

Case Report

We present a case of four year old girl who developed iatrogenic Cushing syndrome and adrenal insufficiency after atopic dermatitis treatment through the misuse of Mometasone treatment without doctor's prescription. The girl was admitted to the Dermatological Ward in December 2012 because of erytrodermia due to atopic dermatitis, which she suffers from birth. Skin lesions were localized on a face, hairy scalp, trunk, limbs and flexures. They were erythematous with raised red papules above the surface and had a scaly surface on palms and soles. Lichenification due to continual scratching in the area of antecubital fossae and wrists was observed . The clinical examination showed facial fullness, redness, acne and a moon face, (Fig. 1) hirsutism (Fig. 2), a buffalo hump, central obesity, ginecomasty, subcutaneous hypertrophy (Fig. 3), buttocks muscle atrophy and growth retardation (Fig. 4).
In the admission to the ward: the vital signs showed blood pressure 110/80mmHg, tachycardia 110 beats/min, body weight 1390g, height 89.2cm. The centile chart- under third centile.
The laboratory workup revealed blood cell count with platelets, glucose, electrolytes, total cholesterol, thyroid hormones- tests within normal limits.
Morning cortisol levels at 8.00 am showed value below normal range (cortisol: <22,1; normal range: 101-536nmol/l).
Synacthen test revealed the secondary adrenal insufficiency.
Wrist X-Ray - a bone age of two year old child.
Physiologic dose of oral Hydrocortisone 8,5mg daily was prescribed.

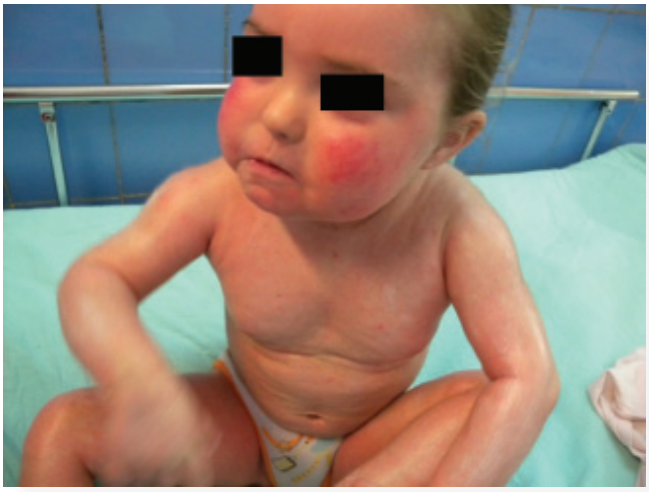

Figure 1. Facial fullness, redness, acne and a moon face.

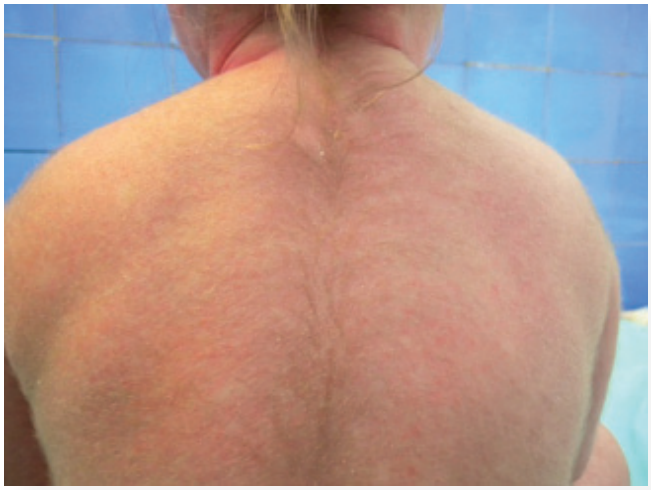

Figure 2. Hirsutism.

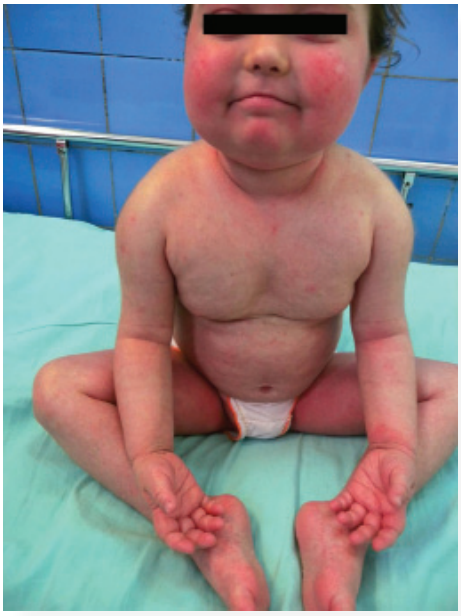

Figure 3. A buffalo hump, central obesity, ginecomasty, subcutaneous hypertrophy.

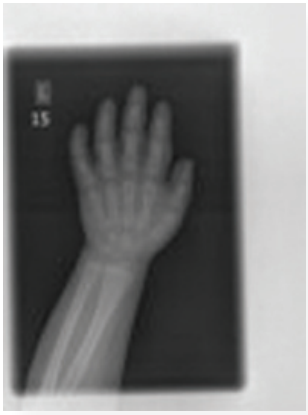

Figure 4. The growth retardation.

After 6 months of treatment laboratory values revealed blood cell count with platelets, electrolytes, total cholesterol, thyroid hormones - tests within normal limits. Morning cortisol level at 8.00 am- 353nmol/l. The Synacthen test – still showed adrenal insufficiency- the continuation of therapy was demanded.

The dose of Hydrocortisone was reduced after 3 months of treatment to 5,5mg daily, then to 3mg daily. The treatment will be discontinued when hypothalamus-pituitary-adrenal axis recovery is confirmed by normal morning cortisol level.

We observed the body proportions (Fig. 5a, b) and the disappearance of hirsutism (Fig. 6a, b). Body weight- 13.7kg, body height- 93.3cm.

Discussion

Topical corticosteroids are the most common drugs to treat acute and chronic inflammatory diseases in dermatology. Adverse effects of these are well known both in localized and systemic adverse effects depending on duration of use and potency of corticosteroid. They can be absorbed through normal skin but more in inflammatory and occlusive skin [4]. Children are more prone to develop systemic reactions to topically applied medication because of their higher ratio of total surface area to body weight [5] and poorly developed skin barrier. Application of agents to large surface areas, occlusion, higher concentrations, increase the risk of side effects of steroids.

There are cases in the literature of iatrogenic Cushing's syndrome and suppression of hypothalamic-pituitary-adrenal axis due to topical corticosteroid therapy. Serap Semiz et al. described two cases of Cushing's syndrome in infants due to overuse of Clobetasol proproniate on the diaper area [5]. Moreover, Therdpong Tempark et al. in case report draws attention to application of Clobetasol proproniate for diaper dermatitis in infants. Among 86% infants with diaper dermatitis and 27% with psoriasis, burn, skin dryness were treated with Clobetasol (82%), Bethamethasone (18%) with the duration of application average about 2.75 months induced typical Cushing's features with suppressed cortisol and ACTH levels [4]. Caroline P. Halverstam et. al presented a Netherton syndrome patient – an 11 year old boy, who had been using excessive amounts of hydrocortisone 1% ointments for more than one year and developed Cushing' syndrome [6].

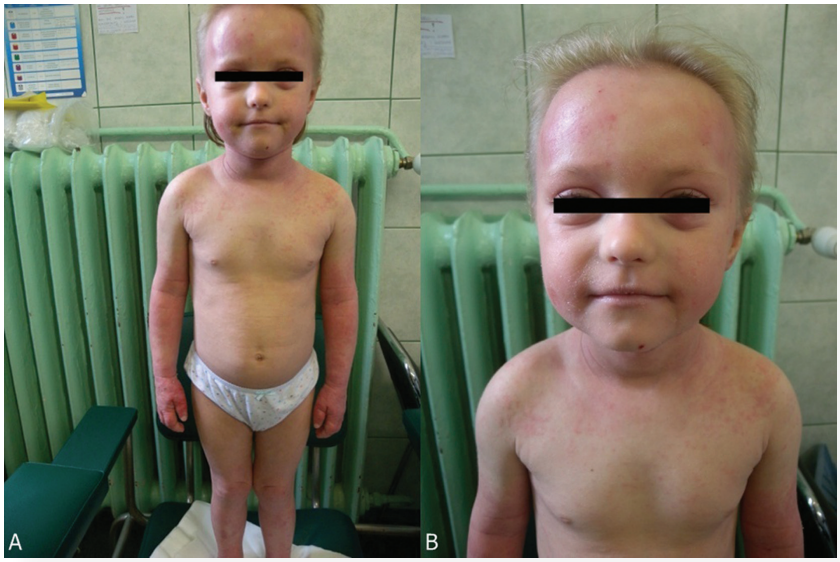

Figure 5a, b. Normalisation of body proportions after 6 months of treatment.

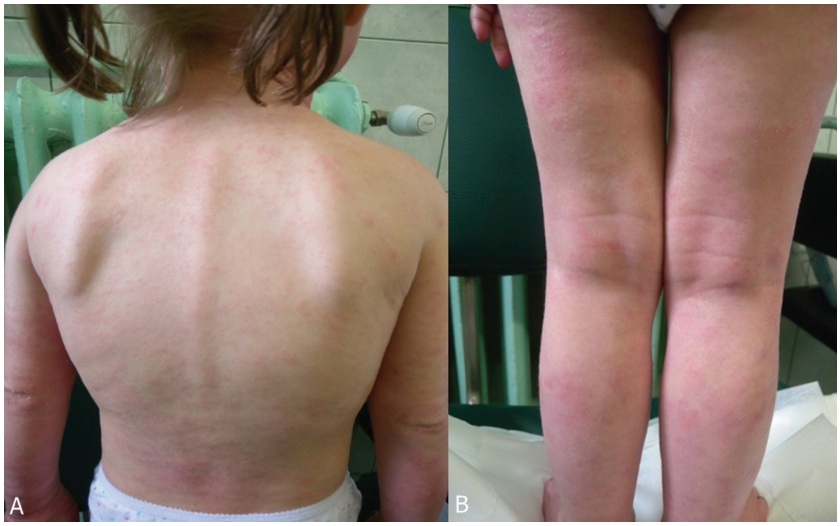

Figure 6a, b. The disappearance of hirsutism after 6 months of treatment.

Iatrogenic CS with hypothalamic-pituitary-adrenal axis suppression through the misuse of topical glicocorticosteroid therapy with Mometasone, is a very rare case. To our knowledge, our patient is the first one with atopic dermatitis who developed Cushing's syndrome after Mometasone application.

Conclusions

In conclusion, the serious side effects of topical glicocortycosteroid treatment should be explained to the family, monitored in young patients, especially the ones with reduced skin barrier function. A long-term therapy should be refrained.

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CUTANEOUS MYXOID CYST ON THE *SCLEROTIC FINGER* IN A PATIENT WITH *DIFFUSE SYSTEMIC SCLEROSIS*

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None

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Abstract
Skin tumors occurring on the scleroderma fingers are rarely seen. Swollen fingers are hallmarks of systemic sclerosis, and mucin deposition in the lesional skin is a constant feature in systemic sclerosis. Here we describe a case of cutaneous myxoid cyst on the flexor aspect of the sclerotic fingers in a patient with severe diffuse cutaneous systemic sclerosis. Cutaneous myxoid cyst is a relatively common benign tumor; however, cases of cutaneous myxoid cysts developing on the scleroderma fingers have not been reported to date. Mucin deposition in the sclerotic skin may be a predisposing factor in the induction of myxoid cyst on the scleroderma finger in our patient.

Key words: systemic sclerosis; myxoid cyst; mucin

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Introduction

Cutaneous myxoid cyst usually occurs in the dorsal aspect of the proximal nail fold, the distal interphalangeal joint, or under the proximal matrix [1]. Histological features show pseudocysts filled with mucoid materials which are overproduced by fibroblasts. Systemic sclerosis (SSc) is a connective tissue disorder characterized by excessive production and deposition of extracellular matrix proteins released from activated fibroblasts. Biopsy specimen reveals mucinous edema in the dermis. Although mucin deposition may be attributable to the activated scleroderma fibroblasts, myxoid cysts are not frequently seen in patients with SSc. We herein report a case of cutaneous myxoid cyst on the flexor aspect of the sclerotic finger in a patient with diffuse SSc.

Case Report

A 45-year-old woman suffering from diffuse cutaneous SSc over several years visited our department, complaining of a symptomless nodule on the finger which appeared 1 year ago. On physical examination, her fingers were swollen, pale and sclerotic, and several digital ulcers were recognized (Fig. 1). A further examination revealed a well-circumscribed, translucent nodule on the flexor aspect of her second finger (Fig. 2). Skin sclerosis involved the forearms, upper arms, chest, and face. Also, she had lung fibrosis, and been treated with prednisolone (5 mg/day) and cyclosporine (NeoralR, 75 mg/day). Laboratory data on blood chemistry including liver and renal function were within the normal range. Antinuclear antibodies (ANA) were detected in the serum (1:1280, homogenous and nuclear). Serum antibodies against Topo-I are elevated to 133.2 U/ml (normal; <10 U/ml), and the anti-U1RNP antibody was slightly elevated to 28.4 U/ml (normal; <15 U/ml). Other antibodies against centromere, DNA, ss-DNA, ds-DNA, SS-A, SS-B, Sm and cardiolipin were all negative or within normal limits. Lung CT showed interstitial fibrosis. Histopathological examination of the skin tumor showed myxomatous spaces in the dermis. The myxoid stroma was positive for alcian blue and colloidal iron staining (Fig. 3). Also, the thickened collagen bundles were observed in the lower dermis. Digital ulcers were treated with topical application of recombinant human basic fibroblast growth factor.

Discussion

Cutaneous myxoid cyst is a translucent cystic nodule, frequently occurring between distal interphalangeal (DIP) joint and the proximal nail fold of the finger. In the majority of cases, myxoid cysts occur on the dorsal aspects, but sometimes on the flexor aspects of the finger [2]. Minor trauma and chronic pressure has been implicated as causative factors. Histological features show myxomatous and ganglion type. In the myxomatous type, fibroblasts are supposed to be a source of overproduction of hyaluronic acid.

In the present case, mucinous nodule occurred in a patient with active diffuse SSc showing prominent sclerosis of the skin. Mucin deposition is observed in scleroderma [3], and scleroderma skin shows mucinous edema at the edematous phase.

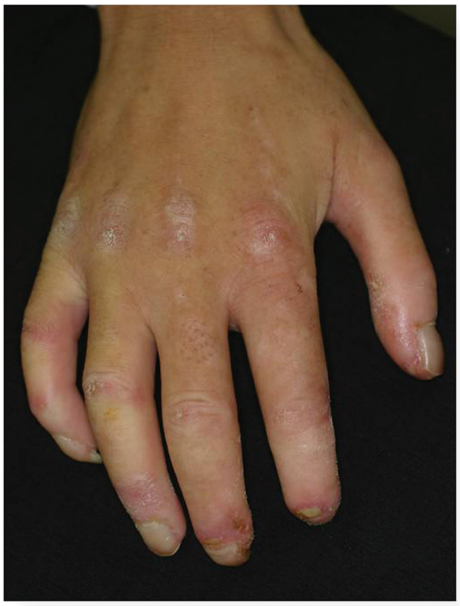

Figure 1. Clinical features showing swollen, pale and sclerotic fingers with several small ulcers.

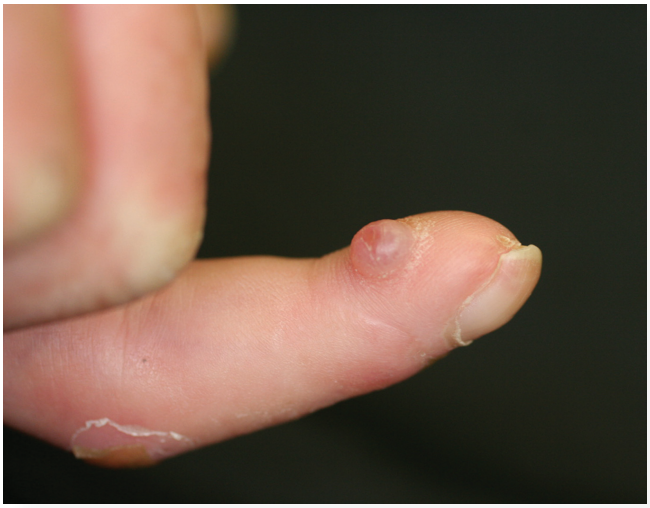

Figure 2. A dome-shaped translucent nodule on the flexor aspect of the finger.

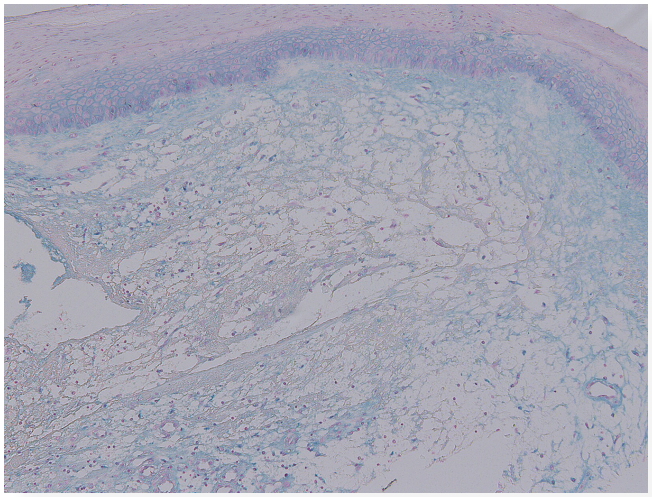

Figure 3. Histological features showing myxoid stroma in the dermis (Colloidal iron stain; x40).

On the other hand, mucinous tumors infrequently occur in patients with SSc, and thus the occurrence of myxoid cyst may be incidental. Mucin deposition is mainly consisted of dermatan sulfate hyaluronic acid [4]. It has been suggested that mucin is produced by fibroblasts stimulated by IL-1 and IL-6. Our case developed myxoid cyst on the finger, suggesting that mechanical stimuli induced inflammatory cytokines such as IL-1 and IL-6 which exerted effects on activated scleroderma fibroblasts.

Further, oxidant stress plays an important role in SSc [5], and low oxygen tension contributes to the increased fibrogenic properties of scleroderma fibroblasts, such as proliferation and collagen production [6,7]. A recent report suggests that hypoxia may play a role in the induction of dermal mucin deposition [8]. Local tissue hypoxia conditions potentially increase fibroblastic biosynthetic activity and dermal hyaluronan production. In addition, roles of CD44 variant 7 are recently reported in the accumulation of chondroitin-4-sulfate [9].

Although the occurrence of myxoid cyst may be coincidental in our case, mucin deposition produced by activated fibroblasts under several stimuli may contribute to the induction of myxoid cyst of the finger.

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NASZA DERMATOLOGIA Online
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DIGITAL ISCHEMIA DUE TO *SYSTEMIC SCLEROSIS* ASSOCIATED WITH *ESSENTIAL THROMBOCYTHEMIA*: A CASE REPORT

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Abstract
Digital ulcers (DU) are a well-known problem in patients with systemic sclerosis. It is an underestimated complication of the disease causing pain and morbidity. Essential thrombocytosis is another cause of DU. The association of theses two diseases increases the risk of ischemic complications and impairment of hand function which are frequently observed in patients with digital ulcers.
This report deals with a 68-year-old patient with rare association of Essential thrombocytosis ,Systemic sclerosis and Raynaud's phenomenon that was refractory to medical treatment of Systemic sclerosis (illoprost,calcium channel blockers) and improved with hydrea[R].

Key words: systemic sclerosis; digital ulcers; essential thrombocythemia

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Introduction

Systemic sclerosis (SSc) is a non-organic specific autoimmune disease that is characterized by fibrosis and excessive laying down of collagen in the skin, gastrointestinal tract and the lungs with an activation of immune system with production of autontibodies and extensive vascular damage. Raynaud's phenomenon (RP) and digital ulcers (DU) represent two faces of the same coin in SSc vasculopathy [1]. Essential thrombocytosis (ET) is another cause of DU. It is a slowly progressive disorder characterized by long asymptomatic periods punctuated by thrombotic or hemorrhagic events [2]. The association of these two diseases increases the risk of ischemic complications and impairment of hand function which are frequently observed in patients with digital ulcers.
We report a rare case of a 68-year-old woman with ET, Systemic sclerosis (Ssc) and Raynaud's phenomenon (RP) that was refractory to medical treatment of Scc (illoprost, calcium channel blockers) and improved with hydrea[R].

Case Report

A 68- year-old woman with no significant past medical history, was presented with a 2-week history of pain and bilateral bluish discoloration of the finger tips and toes. The pain was associated with numbness and tingling with decreased sensation to his fingers and toes and was exacerbated by cold. The patient also reported epigastric pain, post postprandial vomiting, heartburn and dysphagia. Physical examination showed proximal skin sclerosis, thin skin, less hair, bilateral and symmetrical sclerodactily and pulp ulcers of 10 fingers (Fig. 1) and the big toes.
In blood count, Hb was normal on 13.2 g / dl, WBC 12600 elements /mm^3 and platelet count of 634000 elements /mm3. The chest radiography had demonstrated interstitial syndrome, and the X-rays of hands showed resorption of phalangeal tufts of several fingers. The pressure of the lower esophageal sphincter and its peristalsis were reduced in esophageal manometry. Then, the diagnosis of Sytemic sclerosis was confirmed and initial treatment consisted of calcium channel blockers and colchicine. The clinical outcome was marked by the worsening of RP and the extent of digital ulcers.
On the other hand, the thrombocytosis was compounded.

A bone marrow biopsy was done and concluded at a megakaryocytic lineage hyperplasia, and presence of JAK2 mutation in molecular biology which is compatible with the diagnosis of essential thrombocythemia (ET). The patient started a treatment based on hydroxyurea (Hydréa^{R}) with a good clinical evolution of RP after failure of illoprost. On follow-up, she was symptom-free with no evidence of ischemic changes (Fig. 2) and her platelet count was of 219000 elements /mm^3.

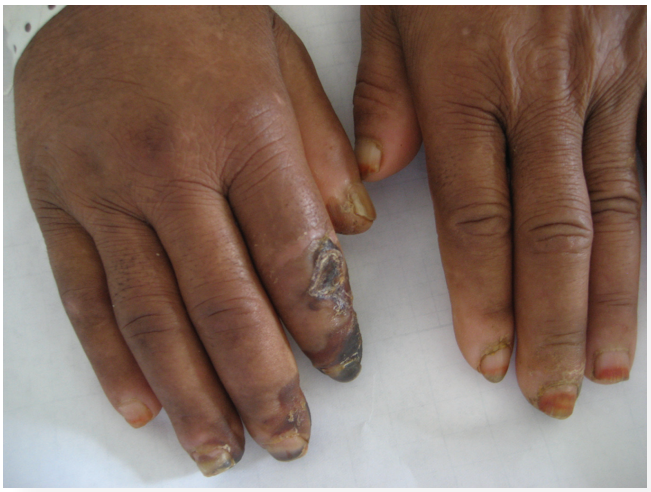

Figure 1. Pulp ulcers of fingers in our patient.

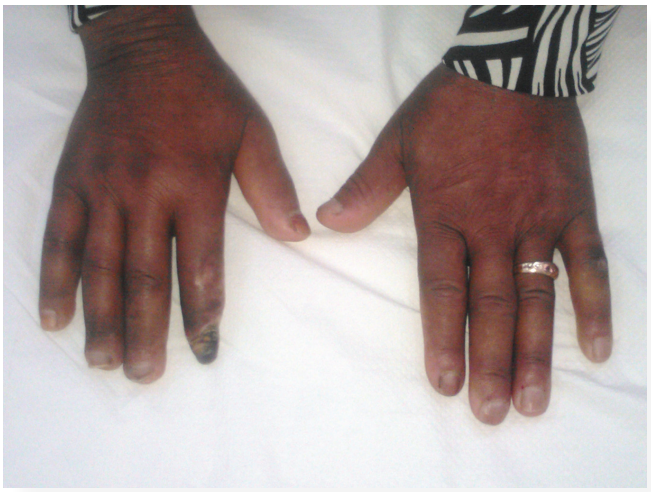

Figure 2. Improvement of the ischemic lesions with hydrea.

Discussion

Acute digital ischemia may be caused by several entities including collagen vascular diseases [3], Raynaud's disease [4], Buerger's disease [5], peripheral atherosclerosis [6], heparin-induced thrombocytopenia with thrombosis syndrome [7], consumption coagulopathy [8] and many others. Although rare, hematologic disorders, however, have to be considered in the differential diagnosis of acute digital ischemia. Essential thrombocytosis is one of them.

It is a slowly progressive disorder characterized by long asymptomatic periods punctuated by thrombotic or hemorrhagic events [9]. The disease usually affects middle-aged to elderly individuals, with an average age at diagnosis of 50 – 60 years [10]. It, however, may also affect children and young adults. The major risk factors for thrombosis are (age older than 60 years and previous thrombotic episode), whereas the advent of thrombosis appears to be unrelated to either the platelet count or hemostasis tests [11].

The most common symptoms in ET at presentation are due to disturbances of the microcirculation, particularly fingers, toes, and central nervous system manifestations including headache, dizziness, and visual and acoustic symptoms [2]. The term erythromelalgia, specific to the myeloproliferative disorders, refers to the occlusion of the microcirculation by platelets and is characterized by redness, congestion, and painful burning sensations of the extremities. Symptoms are characteristically relieved by cold or elevation of the extremity.

In systemic sclerosis, the origin of the ulcers is thought to be multifactorial, including microangiopathy, macrovasculopathy, microtrauma, bacterial infection, fibrosis, and calcinosis. Chronic microangiopathy seems to play an important role in the pathogenesis with endothelial cell damage being most probably the initiating factor [12]. Early diagnosis help to manage this disorder, which is treatable, but not curable. Therapy involves physical therapy as well as the targeting of blood vessel mechanics and fibrosis by colchicine, nifidipine, calcium channel blockers and illoprost [13].

The patient described in this case report was atypical, because she was free of all the aforementioned thrombosis risk factors. We thought initially that her painful acrocyanosis, which progressed to digital gangrene, was probably due to Raynaud's disease related to the SSc rather than to classic essential thrombocythemia, because her extremities were neither warm nor congested. Also, her symptoms were exacerbated by cold and were not relieved by aspirin.

In fact, our patient was managed on admission with aspirin (to reverse the platelet-mediated thrombotic effect) and nifedipine (to reverse the vascular spasm). However, the patient's pain increased, so, we initiate the hydroxyurea with a good clinical course, then we think that DU is in fact due to both: SSc and ET and this makes the originality of our case.

In ET, the high-risk patient population (age >60 years, previous thrombotic episode), however, deserves in fact therapeutic intervention. Cytoreductive therapy with hydroxyurea [14], as our patient, or anagrelide [15] have been effective in preventing additional thrombotic episodes in this population.

When drugs measures fail to limit ischemic phenomena, and there is apparent danger of imminent gangrene, treatment includes urgent therapeutic platelet apheresis which lowers the platelet count, followed by periarterial sympathectomy which provides a valuable adjunctive treatment option in the setting of a normal platelet count to increase the nutitional collateral flow [14].

Discussion

In SSc, the repetitive vasospasm of RP and the structural changes of the digital vessels are the leading contributory causes of the incipient development of ischemic digital ulcers. The association of SSc and ET increases the gravity of DU. The management of RP and DU in this particular case, requires a multimodal approach using a combination of pharmacological and local treatments.

It deserves cytoreductive therapy with hydroxyurea in order to minimize the risk of ischemic digital ulcers and thrombotic episode especially after the non efficiency of the classic treatment of RP.

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A TRANSIENT DRUG INDUCED LUPUS ERYTHEMATOSUS- LIKE ALLERGIC DRUG REACTION WITH MULTIPLE ANTIBODIES

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Abstract
Drug reactions may mimic several dermatoses, including lupus erythematosus. We present an 80 year old female patient on multiple medications, who presented with blisters on her hands and arms for two weeks, which then generalized to the rest of her body. The patient was evaluated by a dermatologist, and biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF) and immunohistochemistry (IHC) were performed. The H&E biopsy examination revealed a mild, superficial, perivascular dermal infiltrate of lymphocytes, histiocytes and abundant eosinophils; neutrophils were rare. No vasculitis was noted. DIF revealed positive basement membrane (BMZ) staining, primarily with patchy Complement/C3c and fibrinogen; in addition, strong reactivity to dermal blood vessel was appreciated. Antibodies to cell junction-like structures were also noted in the epidermis and dermis with these two antibodies. IHC using similar immunoglobulins and complement components showed similar patterns. We observed that contrary to lupus erythematosus, neither IgG nor IgM were positive at the BMZ.

Key words: aspirin; lisinopril; Nexium; hydralazine; Tylenol

Abbreviation: Drug-induced lupus erythematosus (DIL), systemic lupus erythematosus (SLE), basement membrane zone (BMZ), direct immunofluorescence (DIF)

Cite this article:
Ana Maria Abreu Velez, Vickie M. Brown, Michael S. Howard: A transient drug induced lupus erythematosus - like allergic drug reaction with multiple antibodies. Our Dermatol Online. 2013; 4(4): 511-513.

Introduction

Drug-induced lupus erythematosus (DIL) is an autoimmune disorder, caused by chronic use of selected medications. These drugs cause an autoimmune response that can produce a clinical presentation similar to those of systemic lupus erythematosus (SLE). There are multiple known medications that elicit DIL, but three are most strongly associated: hydralazine, procainamide, and isoniazid [1-3].

Case Report

We present an 80 year old female patient, who was using multiple medications and presented blisters on her hands and arms for two weeks. With the rash, the patient described flu-like symptoms. The patient also had a history of chronic leg lymphedema. Physical exam displayed erythematous papules and wheals, with no hyperpigmentation or atrophy. The patient was taking oral simvastatin, aspirin 81 mgs/day, lisinopril, Januvia®, Nexium®, hydralazine, Tylenol, and metropolol tartrate. On physical exam, the lesions were present on the bilateral forearms, hands and wrists, and focally on the face and legs. Skin biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF) and immunohistochemistry (IHC) were performed and processed as previously described [4-7].

Microscopic examination:
Examination of the H&E tissue sections demonstrated a histologically unremarkable epidermis. No subepidermal blistering was noted. Within the dermis, a mild, superficial, perivascular infiltrate of lymphocytes, histiocytes and abundant eosinophils was identified. Neutrophils were rare (Fig. 1).

Direct immunofluorescence (DIF):
DIF was performed, and revealed the following results: IgE (+, focal superficial dermal perivascular); Complement/C1q (-); complement/C3c (+++, shaggy in patches at the basement membrane zone (BMZ), in the dermal blood vessels and directed against some types of cell junctions in the epidermis and the dermis); Complement/C4(+, focal dermal cell junctions); and fibrinogen(patterns and positivity similar to C3c) (Fig. 1).

Fibrinogen and kappa light chain antibodies stained focal subcorneal areas. Epidermal cytoid bodies were observed, and demonstrated positive staining with IgM, fibrinogen, kappa light chains and complement/C3c. Antibodies to Ro/SSA-were positive, predominately with Complement/C3c. Anti-keratin antibodies were seen in the epidermis with IgM (Fig. 2). Immunostochemistry staining revealed similar findings to those seen by DIF, and also reactivity to dermal blood vessels with IgA (Fig. 1).

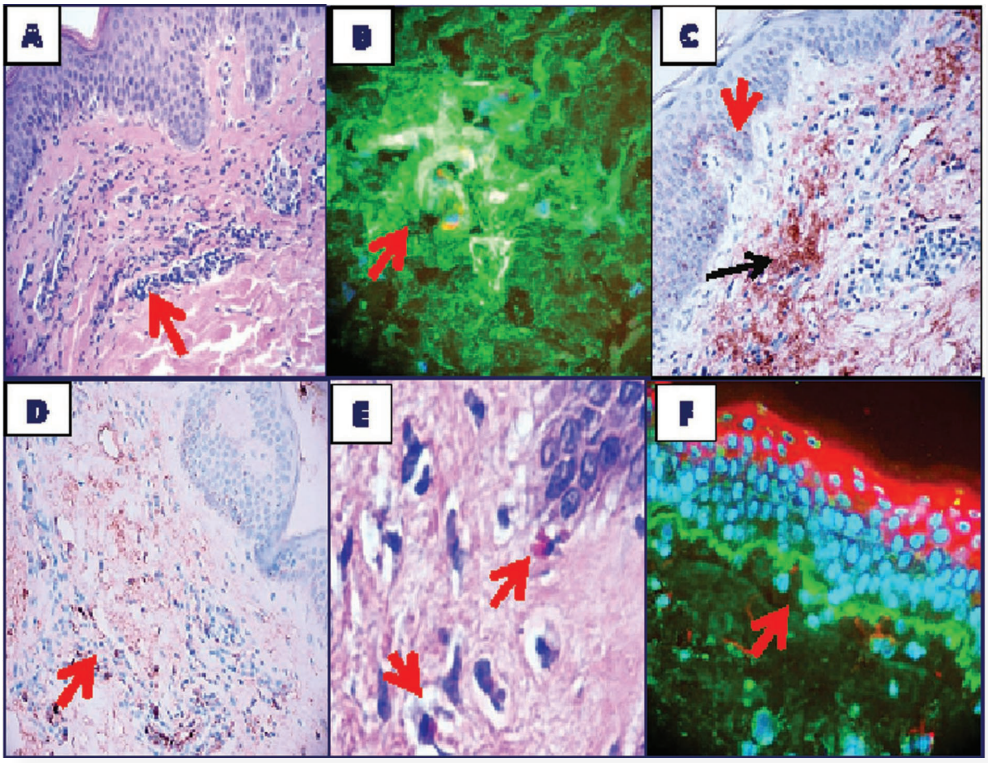

Figure 1. a. H&E staining demonstrates a mild, superficial, perivascular dermal infiltrate (red arrow). **b.** DIF, demonstrating positive staining around dermal blood vessels with FITC conjugated fibrinogen(yellow staining; red arrow). **c.** Positive IHC staining with anti-human Complement/C3c in patches at the basement membrane zone (brown staining; red arrow) as well as around upper dermal blood vessels (brown staining; black arrow). **d.** IHC positive staining with anti-human IgA, around upper dermal blood vessels (brown staining; red arrow). **e.** H&E stain, demonstrating dermal infiltrate eosinophils(red arrows)(400X) **f.** DIF, demonstrating positive staining at the basement membrane zone with FITC conjugated C3c (yellow/green staining; red arrow). Epidermal keratinocyte nuclei were counterstained with Dapi (blue), and the upper layers of the epidermis were stained with rhodamine conjugated Ulex europaeus agglutinin(pink/red staining).

Discussion

Our patient was taking many medications that have been associated with DIL, and thus this diagnosis was favored given our pathologic findings. Clinically, DIL patients often report flu-like and joint discomfort symptoms. Our patient reported a chronic osteoarthalgia, and we could not determine if our DIL diagnosis contributed to this clinical problem. Additional signs and symptoms of DIL include myalgia, fatigue, pericarditis and/or pleuritis; in addition, positive anti-histone antibodies are noted in 95% of cases [1-3]. Our patient was negative for anti-histone antibodies, but positive for antibodies against SS-A/Ro with Complement/C3c.

In DIL, the lesions classically recede after discontinuing use of the eliciting drugs [1-3]. For therapy of our patient, Tacrolimus® 1% cream was prescribed 3 times a day topically, as well as triamcinolone acetonide 0.1% topical cream. In recalcitrant cases of DIL, it may be also necessary to add systemic corticosteroids and/other immunosuppressive agents [3].

Similar to expected findings in lupus erythematosus, we observed cytoid bodies with IgM antibodies. In addition, in our case we noted cytoid body antibodies with Complement/C3c, fibrinogen and subcorneal antibodies that are not classically described in lupus. We observed tissue fixed deposits of immunoglobulin M present in the cytoplasm of epidermal keratynocytes; however, instead of the 3 reported patters described in normal skin [8,9], our reactivity was present throughout the entire epidermis. Also remarkable was the reactivity to some type(s) of likely cell junctions in the epidermis and dermis, best appreciated with anti-Complment/C3c and fibrinogen.

In conclusion, we note differences with classic lupus erythematosus in our case, including lack of an H&E interface dermatitis and the H&E presence of dermal eosinophils. Our case also features immunopathological features that differ from lupus; we noted positive antibodies to Ro/SSA, but with Complement/C3c. Further, in DIF and IHC our case differs from classic lupus due to a lack of linear deposits of IgG or IgM at the basement membrane zone, instead, patchy Complement/C3c and fibrinogen were observed. We also observed significant reactivity to dermal blood vessels, but no vasculitis as noted in selected classic cases of lupus. We also observed reactivity to several likely cell junctions in epidermis and dermis, whose nature remains unknown. Further studies utilizing sera against epidermal and dermal antigens may be helpful in characterizing these putative epitopes.

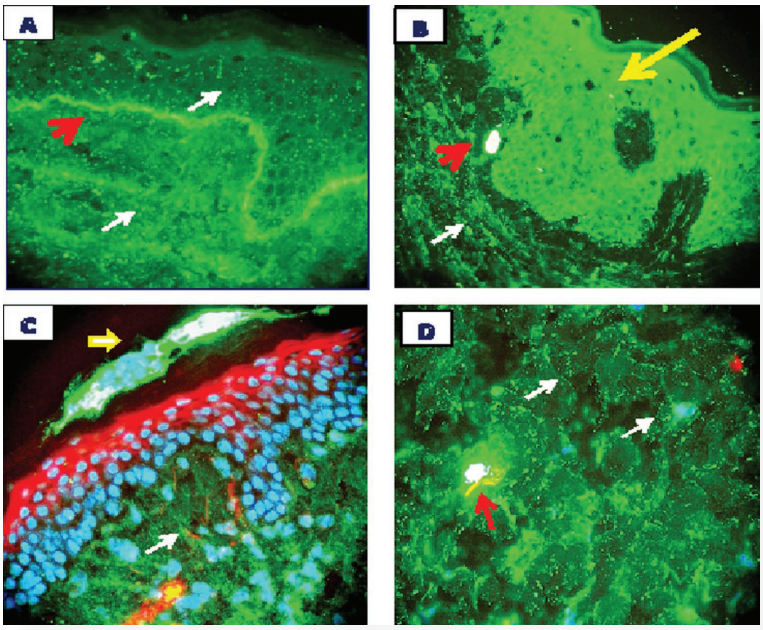

Figure 2. a. DIF, demonstrating positive staining at the basement membrane zone with FITC conjugated Complement/C3c (yellow staining; red arrow); also note the multiple cell junction-like staining, visualized as small dots in the dermis and epidermis (yellow staining; white arrows). **b.** DIF, with positive staining against cytoid bodies with FITC conjugated anti-human IgM (yellow staining; red arrow). Also noted additional staining with this antibody as anti-keratin antibodies in the epidermis (ie, cytoplasmic antigens) (yellow staining; yellow arrow), as well as to some type of cell junction-like structures in the dermis (yellow staining; white arrow). **c.** DIF, showing positive staining within the epidermal stratum corneum with FITC conjugated Complement/C3c(yellow staining; yellow arrow). Epidermal keratinocyte nuclei were counterstained with Dapi (blue), and the upper layers of the epidermis were stained with rhodamine conjugated Ulex europaeus agglutinin. The white arrow highlights additional positive, focal staining against cell junction-like structures in the dermis (yellow staining). **d.** DIF, displaying positive staining with FITC conjugated anti-human fibrinogen, in a dermal perivascular distribution (yellow staining; red arrow); in addition, note the punctuate positive staining against cell junction-like structures in the dermis (yellow staining; white arrows).

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THROMBOMODULIN OVEREXPRESSION SURROUNDING A SUBEPIDERMAL BULLOUS ALLERGIC DRUG ERUPTION

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Abstract
Blistering drug eruptions and drug-induced anaphylaxis and hypersensitivity syndromes are among the most serious types of adverse drug reactions. We report a 69 old female patient who was using multiple medications and presented with a two month history of recurrent blisters, pustules and crusts. The patient was evaluated by a dermatologist, and biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF) and immunohistochemistry (IHC) were performed. The H&E examination revealed a subepidermal blister with numerous luminal eosinophils, as well as a dermal superficial and deep, perivascular infiltrate of lymphocytes, histiocytes and eosinophils. The DIF revealed a linear positive staining on the subepidermal interior of the blister with IgG, IgA, IgM, IgD, Complement/C4, lambda light chains, fibrinogen, and albumin; staining was noted in the basement membrane zone, and also focally present around dermal blood vessels and eccrine glands. The dermal staining colocalized with anti-p0071 (Plakophilin 4). We also observed overexpression of thrombomodulin in adjacent epidermal keratinocytes, as well as in the upper dermal blood vessels; its presence may be linked to mitigation of inflammation. With the increased medications that many patients are taking orally and are using topically, overall drug reaction patterns seem to be more complex than previously described.

Key words: subcorneal blisters; drug reaction; drug-drug interactions

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Ana Maria Abreu Velez, Garin Barth, Michael S. Howard: Thrombomodulin overexpression surrounding a subepidermal bullous allergic drug eruption. Our Dermatol Online. 2013; 4(4): 514-516.

Introduction

Bullous or blistering drug eruptions and drug-induced anaphylaxis and hypersensitivity syndromes are among the most serious types of adverse drug reactions, especially within the senior patient population. Based on the underlying mechanisms, bullous drug eruptions has been previously classified into the following categories: spongiotic or eczematous, acute generalized exanthematous, fixed, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis [1-3].

Case Report

A 66 year old female patient was seen by the dermatologist for a three month history of recurrent healing patches, and focal pain in her foot. The patient also reported itchy blisters, pustules and crusts on her back, extremities and foot dorsum for about two months. This patient was taking several oral medications for hypertension, diabetes, depression, hypercholesterolemia and osteoarthritis. Specific medications she was taking included pioglitazone hydrochloride (antidiabetic, Actos®), atorvastatin calcium (Lipitor®), alprazolam, aspirin 80 mgs / day, tetracycline, clindamycin, and Diovan® HCT (valsartan/ hydrochlorothiazide).

Skin biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF) and immunohistochemistry (IHC) were performed.

Processing of biopsies for H&E examination, DIF and IHC was performed as previously described [4-6]. In addition to DIF antibodies with FITC conjugated markers, we also used an anti-multiepitope cocktail to p0071 from Progen, Germany, with goat anti-mouse Texas red conjugated goat anti-mouse IgG (H & L) as its secondary. Our case was IRB exempt because no patient identifiers were recorded, and no clinical pictures were taken.

Immunohistochemistry (IHC) staining was performed as previously described [4-6], utilizing antibodies obtained from Dako, including monoclonal mouse anti-thrombomodulin. We tested for this molecule based on the fact that it has been implicated in keratinocyte differentiation and wound healing.

In addition, thrombomodulin also acts to create activated protein C, generated from the cleavage of protein C by thrombin coupled to thrombomodulin [7,8].

Examination of the H&E tissue sections demonstrated a subepidermal blistering disorder, with partial re-epithelialization of the blister base. Within the blister lumen, numerous eosinophils were present, with occasional lymphocytes also seen. Neutrophils were rare. Dermal papillary festoons were not observed. Within the dermis, a moderately florid, superficial and deep, perivascular infiltrate of lymphocytes, histiocytes and eosinophils was identified. No evidence of an infectious, or a neoplastic process was seen.

DIF studies demonstrated the following results: IgG (+++, epidermal stratum corneum/acrosyringium and +, linear base membrane zone (BMZ); IgA (+++, epidermal stratum corneum/acrosyringium); IgM (+++, epidermal stratum corneum/acrosyringium); IgD (+++, epidermal stratum corneum/acrosyringium); IgE (+, focal papillary dermal perivascular and perineural); complement/C1q(+++,epidermal stratum corneum/acrosyringium); complement/C3(+++, epidermal stratum corneum and +, papillary dermal perivascular and perieccrine); Complement/C4 (+++, epidermal stratum corneum/acrosyringium); kappa light chains (+++, eccrine acrosyringium and surrounding epidermal stratum corneum); lambda light chains (+++,epidermal stratum corneum/acrosyringium); albumin (+++,epidermal stratum corneum/acrosyringium) and fibrinogen (+, epidermal stratum corneum, linear BMZ and papillary dermal perivascular, perineural and perieccrine) (Fig. 1, 2).

Following workup, the patient was instructed to visit her primary case physician, to try to decrease and/or change the medications she was receiving. In addition, the patient was treated with topical Lidex® (fluocinonide) cream 0.05%, Diprosone (bethamethasone diproprionate) 0.05% cream, and Protopic(tacrolimus) 0.1% ointment, with satisfactory results.

Discussion

Allergic reactions may be serious and potentially life-threatening, and may cause injury to tissues throughout the body. Some people have hypersensitive immune systems that overreact to otherwise minor stimuli such as bee stings, foods, medications, and latex [2,3]. As the number of elderly patient's rises in many countries, drug-related iatrogenic complications are becoming increasingly important, and thus age-related changes in pharmacokinetics and pharmacodynamics of common medications is prevalent [1,4-6].

In drug reactions, significant localized inflammation is often present as well as recruitment of additional leukocytes. Scant investigation has focused on the role of thrombomodulin in allergic drug reactions. Thrombomodulin represents an endothelial cell surface glycoprotein, that inhibits the activities of thrombin and accelerates activation of anticoagulant protein C. Thrombomodulin has been associated with inhibition of leukocyte recruitment during acute inflammation. In our case, we were able to demonstrate the presence of thrombomodulin surrounding the inflammatory process. Thus, we suggest that in our case, the patient immune system is attempting to begin to decrease the in situ inflammation.

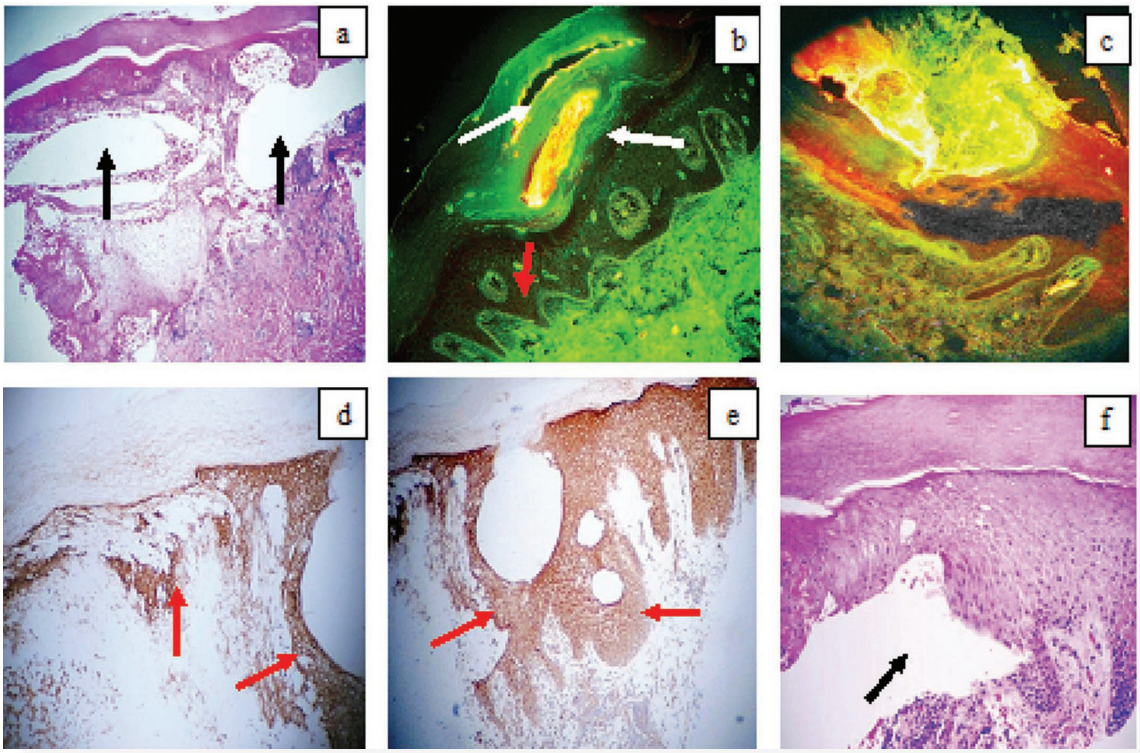

Figure 1. a H&E stain shows the large blisters (black arrows). **b.** DIF positive stain with FITC conjugated IgG demonstates positive staining in a subcorneal blister (yellow staining; white arrows), some stain at the basement membrane zone as well as around the upper dermal blood vessels (green staining; red arrow). **c.** Utilizing DIF double staining with FITC conjugated IgG and rhodamine conjugated anti-IgA, the subcorneal blister was also positive for FITC conjugated IgG (yellow staining) and positive stain with rhodamine conjugated IgA (orange/pink staining). **d and e**. IHC positive staining with anti thrombomodulin demonstrates positive staining in the epidermis around the blister, and in the upper dermal vessels (brown staining; red arrows). **f.** H&E staining shows a subepidermal blister at intermediate magnification (200X)(black arrow).

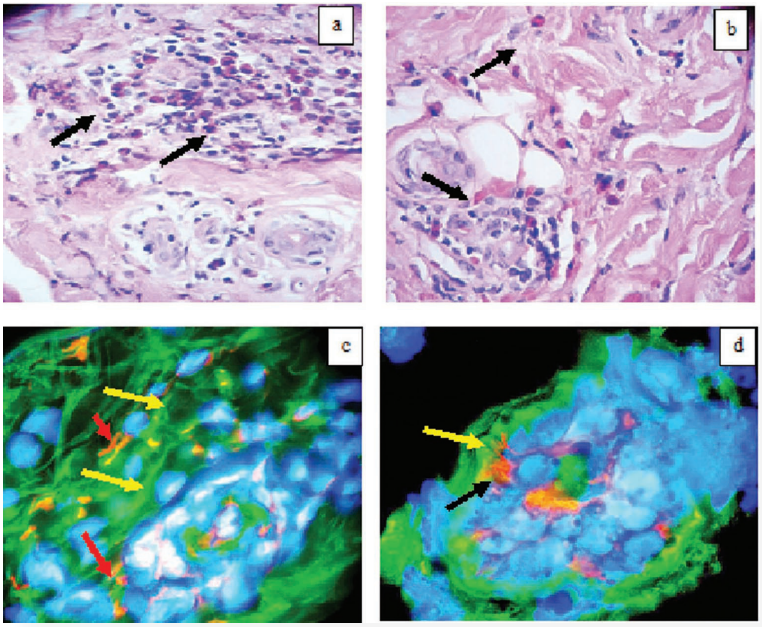

Figure 2. a and b. H&E staining demonstrates an inflammatory infiltrate around dermal blood vessels and eccrine glands respectively, with multiple eosinophils present (black arrows). **c and d.** DIF positive staining around the upper dermal blood vessels using FITC conjugated anti kappa light chains (green staining; yellow arrows). The black arrow highlights an eccrine sweat ductus. We also used the antibody to p0071 conjugated to rhodamine to show colocalization with the blood vessels (red/orange staining, red arrows).

Moreover, thrombomodulin has been shown to be present in normal skin tissue, but appears limited to keratinocytes of the epidermal spinous layer [9]. In our case, thrombomodulin appears to be focally overexpressed; we suggest further study of this molecule and it role in additional allergic drug reaction cases.

All medical providers are thus encouraged to regularly review all medications, taken both systemically and topically, before adding new medications; especially in senior patients, these reviews will help to prevent cutaneous blistering allergic drug reactions [10].

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NECROLISIS EPIDERMICA TOXICA. DESCRIPCION DE DOS CASOS. *ERUPCIÓN CUTÁNEA SEVERA* PRODUCIDA POR FÁRMACOS COMUNES

TOXICAL EPIDERMAL NECROLYSIS. REPORT OF TWO CASES. *SEVERE SKIN RASH* CAUSED BY COMMON DRUGS

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Resumen

Reacción adversa a medicamentos (RAM) es definida por la OMS como cualquier respuesta a un medicamento, que sea nociva e inesperada, que ocurre a dosis normalmente utilizadas en el ser humano para profilaxis, diagnóstico, terapia de enfermedad o para modificación de la función fisiológica. Cuando RAM compromete a la piel se denomina farmacodermia, dermatosis medicamentosa o toxicodermia, la cual ocurre en el 1% de pacientes ambulatorios y 2-5 % de pacientes hospitalizados. La OMS acepta que el 2% de todas las reacciones adversas a fármacos (RAM) son severas (Farmacodermia grave=FG). Son más frecuentes en mujeres, ancianos y pacientes con SIDA. La mayoría de las farmacodermias son leves, pero éstas pueden de inicio ser reacciones severas. 1 de cada 1.000 pacientes hospitalizados sufre una FG, dentro de las cuales se incluyen al síndrome de Stevens Johnson (SSJ) y la Necrolisis Epidérmica Tóxica (NET).

El Síndrome de Stevens Johnson (SSJ) y la Necrolisis Epidérmica Tóxica (NET) son reacciones cutáneas graves, con un potencial de morbilidad y mortalidad elevadas, ocurre en 0.4-2 casos por millón de habitantes por año para el SSJ y para la NET en 1.2-6.0 casos millón de habitantes por año. Se presenta en pacientes de todas las edades, razas y sexo. Estas patologías constituyen una verdadera emergencia dermatológica, donde su cuidado y manejo deben ser multidisciplinarios.

Abstract

Adverse drug reaction (ADR) is defined by WHO as a response to a drug which is noxious and unexpected, which occurs at doses normally used in man for prophylaxis, diagnosis, therapy of disease or for modification of physiological function. When ADR committed to the skin is called farmacodermtoxicoderma, which occurred in 1% of outpatients and 2-5 % of hospitalized patients. WHO accepts that 2% of all adverse drug reactions (ADRs) are severe. They are more common in women, the elderly and AIDS patients. Most toxicodermas are mild, but they can be severe reactions. 1 in 1.000 hospitalized patients suffer a severe toxicoderma (ST), within which are included Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Stevens Johnson's Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe skin reactions with the potential for morbidity and mortality, that occurs in 0.4 to 2 cases per million inhabitants per year for SJS and 1.2 to 6.0 cases per million inhabitants in the year for TEN. It occurs in patients of all ages, races and sex.

These conditions constitute a true emergency dermatology, where the care and management should be multidisciplinary.

Palabras clave: Stevens Johnson; Necrólisis Epidérmica Tóxica; dipirona
Key words: Stevens Johnson; toxic epidermal necrolysis; dipyrone

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Introduccion

El complejo SSJ-NET se observa en todo el mundo y es dos veces más frecuente en las mujeres que en los hombres.

En la actualidad es difícil establecer una frontera definida entre el complejo SSJ-NET y las formas más severas de eritema multiforme.

La extensión máxima del despegamiento epidérmico es el criterio fundamental que permite clasificar a los pacientes en tres grupos: SSJ cuando la afectación de la superficie corporal es menor del 10%, síndrome de superposición SSJ-NET del 10 al 30% y NET cuando es mayor del 30% [1].
Afortunadamente estas reacciones medicamentosas son raras. La mortalidad oscila entre el 30 y 35% en el caso de la NET, entre el 10 y 15 % en los casos de superposición SSJ-NET y aproximadamente el 5% en el SSJ [2].
Los pacientes que tienen mayor riesgo son los inmunocomprometidos, pacientes infectados con HIV (aumenta el riesgo tres veces en comparación a la población general), portadores de enfermedades autoinmunes como lupus eritematoso sistémico (LES) y aquellos con tumores que reciben radioterapia y fármacos antiepilépticos simultáneamente, siendo la principal causa de muerte la sepsis [2].

Descripcion De Los Casos Clinicos

Caso 1

Interrogatorio:
Varón de 17 años, que consulta por ampollas. Tres días antes del ingreso presentó síndrome gripal por lo que se automedicó con dipirona VO, apareciendo horas después de la ingesta de la medicación manchas rojas en la cara. Por tal motivo consulta al Centro de Salud local donde constatan persistencia de fiebre y rash cutáneo medicándolo de nuevo con dipirona, esta vez por vía EV. El cuadro empeora progresivamente hasta generalizarse y 24 horas antes del ingreso se agregan al mismo dificultad respiratoria con lesiones ampollosas y coloración amarillenta de piel y mucosas. Es remitido al Hospital de Clínicas para mejor manejo y tratamiento.
APP: no se conoce portador de patología de base. Niega ingesta anterior de dipirona.

Examen Físico:
Signos vitales: FC: 124/min, FR: 30/min, PA: 110/70.
General: taquicádico, taquipneico, tiraje intercostal bilateral, roncus bilaterales de vértice a base, se palpa hígado a 3 cm. del reborde costal derecho, vigil, lúcido, sin déficit sensitivo ni motor.
Dermatológico: ictericia marcada de piel y mucosas. Ampollas y erosiones múltiples, variadas formas y tamaños de distribución generalizada en piel y mucosas (Fig. 1). Costras hemáticas en borde libre de labios superior e inferior. Signo de Nikolsky +.
Histopatología: NET.
Tratamiento: Inmunoglobulina (Ig) humana a 1 mg/kp/día en 4 dosis.
Evolución: el paciente fue trasladado a UTI del hospital de quemados y fallece por fallo multiorgánico.

Caso 2

Interrogatorio:
Mujer de 46 años de edad que cinco días antes del ingreso presenta ampollas, las cuales aparecen tras la ingesta de carbamazepina (inició el tratamiento con dicha droga 3 semanas antes de la aparición de las lesiones). Dichas lesiones se generalizan rápidamente. Dos días antes del ingreso presenta alteración del sensorio por lo que es remitida a Unidad de Cuidados Intensivos (UTI) del Hospital de Clínicas para tratamiento.
APP: portadora de Artritis reumatoidea (AR) desde hace 8 años en tratamiento con Antiinflamatorios no esteroideos (AINES) en forma regular, sin que los mismos le hayan producido ningún efecto colateral dermatológico.

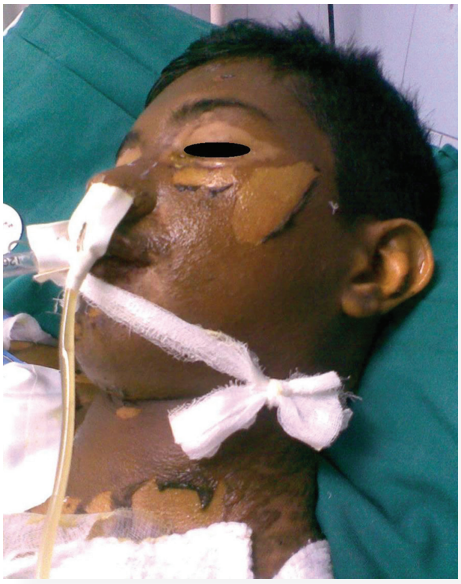

Figura 1. Caso clínico Nº 1. Clínica. Ictericia marcada de piel y mucosas, y ampollas y erosiones múltiples, de distribución generalizada en piel y mucosas.
Figure 1. Case No. 1. Clinic. Marked jaundice of skin and mucous membranes, and multiple blisters and erosions, widespread distribution in skin and mucous membranes.

Examen Físico:
Signos vitales: FC: 110/min, FR: 28/min, PA: 130/80.
General: taquicádica, taquipneica, sin tiraje intercostal, somnolienta, sin déficit motor ni sensitivo.
Dermatológico: ictericia leve de piel y mucosas. Ampollas y erosiones múltiples de distribución generalizada en piel y mucosas. Signo de Nikolsky: + (Fig. 2).
Score pronóstico: 4 (50% riesgo de mortalidad).
Histopatología: NET (Fig. 3).
Tratamiento: Recibe medidas generales como si se tratara de un gran quemado, hidratación, control de medio interno, pero no se instaura tratamiento específico de la NET por lo agudo del cuadro.
Evolución: la paciente fallece al cuarto día de internación por shock hipovolémico.

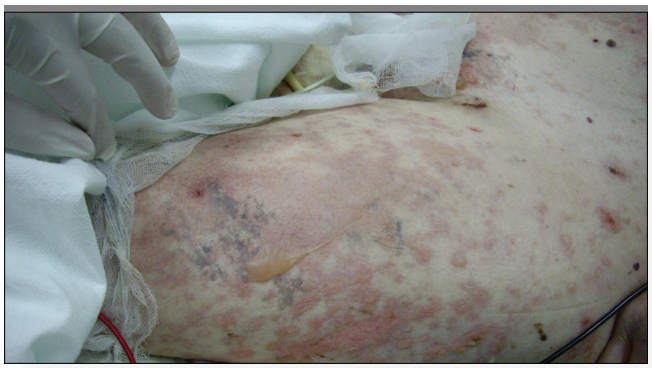

Figura 2. Caso clínico Nº 2. Clínica. Ampollas y erosiones múltiples de distribución generalizada.
Figure 2. Case No. 2. Clinic. Generalized blisters and erosions.

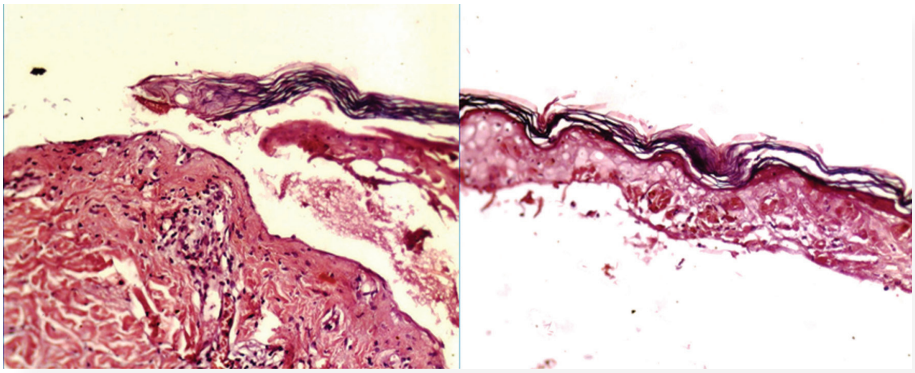

Figura 3. Histopatología. Despegamiento dermo-epidérmico con necrosis epidérmica confluente y escaso infiltrado inflamatorio en dermis superficial (HE 10X).
Figure 3. Histopathology. Dermo-epidermal detachment with confluent epidermal necrosis and pauciinflammatory infiltrate in the superficial dermis (HE 10X).

Comentarios

La continua aparición de nuevos tratamientos farmacológicos obliga a estar preparados para reconocer sus posibles efectos adversos en la piel. Pese a la apariencia inocua de muchos medicamentos, cada vez son más comunes las patologías causadas por sus efectos adversos o colaterales (RAM), que adoptan un amplio espectro de formas clínicas e histopatológicas.

En 1922, Stevens y Johnson describieron dos pacientes con erupciones cutáneas generalizadas, fiebre continua, mucosa oral inflamada y conjuntivitis purulenta grave, cuadro denominado de eritema exudativo multiforme (EEM). En 1950, este cuadro fue dividido en dos categorías: eritema multiforme minor (Von Hebra) y eritema multiforme major (EMM), también conocido como síndrome de Stevens Johnson (SSJ). Desde 1983 el nombre de síndrome de Stevens Johnson pasó a ser usado como sinónimo de EMM. En 1993, Bastuji y Roujeau propusieron que EMM e SSJ son patologías distintas [3,4].

Actualmente se sabe que el SSJ y la NET forman parte de un mismo espectro de enfermedad, están causadas por apoptosis masiva de queratinocitos y se diferencian según el porcentaje de superficie cutánea afecta [5].

Presumiendo que estas patologías tienen un mismo mecanismo fisiopatológico, que consiste en la apoptosis de queratinocitos epidérmicos por la vía del Fas ligando, Ruiz Maldonado y cols. han elaborado una nueva clasificación, en la cual se sustituye la palabra necrosis por apoptosis [6]. En esta se incluyen: el eritema pigmentario fijo, síndrome de Stevens Johnson, casos transicionales o mixtos y el síndrome de Lyell o apoptosis epidérmica tóxica (necrolisis epidérmica tóxica).

Su etiología es muy diversa y puede desarrollarse por causas farmacológicas, infecciosas y tumorales. Los fármacos y las neoplasias son las asociaciones más frecuentes en adultos y en niños son las infecciones [7-9], si bien algunos autores atribuyen únicamente a los medicamentos como causas de estas reacciones cutáneas severas [6].

Clínicamente el SSJ se caracteriza por un cuadro agudo febril, con postración y mal estado general. Las lesiones cutáneas consisten en múltiples máculas eritematosas oscuras, de forma irregular, nunca en blanco de tiro, que no hacen relieve sobre la superficie de la piel y miden de 1 a 5 cm, algunas lesiones permanecen como máculas y otras forman vesículas, la mayoría permanecen individuales, con poca tendencia a unirse con otras. El ataque oral, ocular y a mucosa urogenital es importante, el epitelio se pierde y se forman costras, sobre todo en los labios. El dolor de garganta y la disuria pueden ser síntomas prodrómicos [6].

La NET se inicia con eritema generalizado, disuria, dolor de garganta y fiebre. En pocas horas el eritema se transforma en necrosis masiva de la epidermis que, como una fina tela mojada, cubre grandes áreas del cuerpo y que a la menor presión se desprende, lo que le ha valido el sinónimo de síndrome de la piel quemada. La dermis denudada exuda líquido, que se acumula bajo la epidermis desprendida, formando grandes flictenas flácidas [6]. Las lesiones mucosas son constantes y severas. El esófago, el intestino y la tráquea pueden tener desprendimiento de su epitelio y casi siempre hay alteración de la función hepática.

Las lesiones cutáneas a menudo se hacen confluentes y muestran un signo de Nikolsky positivo [2,7]. Pueden ocurrir en cualquier lugar siendo el rostro, escote y tórax las zonas más afectadas en el SSJ y diseminadas en la NET.

El comienzo de esta dermatosis es repentino con un estado general bastante bueno al inicio, pero pronto aparecen síntomas prodrómicos y el final suele ser fatal en pocos días (en general durante la segunda semana de evolución) y la muerte sobreviene por shock por desequilibrio hidroelectrolítico, septicemia o fallo multiorgánico [10].

Los síntomas sistémicos y el compromiso de órganos internos son frecuentes y a veces severos. La tasa de mortalidad asociada a NET es significativa y puede dejar secuelas secundarias a la cicatrización de mucosas [11].

Existe una escala de valores que se obtiene a partir de parámetros clínicos específicos y nos permiten predecir el porcentaje de mortalidad esperable en un paciente con NET, tal y como se ve en las Tablas I y II [12,13].

La patogénesis básica constituye una reacción de hipersensibilidad tardía a fármacos. Los componentes del complemento e Inmunoglobulinas (IgG) se depositan en la unión dermo-epidérmica y alrededor de los vasos de la dermis. El estado activado del antígeno leucocitario humano (HLA-DR) se expresa en los queratinocitos es reconocida por las células T CD8+ unidas al complejo mayor de histocompatibilidad I (MHC-I) produciendo lesiones cutáneas.

Criterios clínicos Clinical criteria
1. Edad > 40 años 1. Age > 40 yrs
2. Malignidad asociada 2. Associated malignancy
3. Taquicardia > a 120 por minuto 3. Tachycardia > 120 per minute
4. Desprendimiento epidérmico > 10% 4. Epidermal detachment > 10%
5. Uremia > 28 mg/dl 5. Uremia > 28 mg/dl.
6. Glicemia > 252 mg/dl. 6. Glucemia > 252 mg/dl.
7. Bicarbonato < 20 mEq/l. 7. Bicarbonate < 20 mEq/l.

Tabla I.- Criterios clínicos de la NET.

Table I. - TEN clinical criteria.

Score	Probabilidad de muerte. Expected mortality rate
0-1	3%
2	12%
3	35%
4	50%
5-7	90%

Tabla II.- Porcentaje de mortalidad esperable según score.

Table II. - Expected mortality rate according to score.

La deficiencia de glucatión transferasa, presente en el 50% de la población y una deficiencia cualitativa de otras enzimas desempeñan un papel en la patogénesis del SSJ [14].

En cuanto a los métodos auxiliares de diagnóstico no existe ningún test de laboratorio que establezca cual es el fármaco causante, siendo entonces el diagnostico empírico. Los test de provocación no son indicados considerando que la exposición al agente sospechoso puede desencadenar un nuevo episodio grave de SSJ/NET. La biopsia de piel da el diagnóstico definitivo de estas patologías [15]. La misma se caracteriza por necrosis epidérmica confluente con vesiculación subepidérmica y escasa celularidad inflamatoria en dermis [5]

Entre los diagnósticos diferenciales que debemos tener presente son al Síndrome de Hipersensibilidad o eritema inducido por fármacos con eosinofilia, dermatitis exfoliativa por psoriasis, linfoma, exantema viral, sífilis secundaria, gingivo-estomatitis herpética, síndrome de la piel escaldada estafilocócica (SSSS) y vasculitis [16].

En cuanto al tratamiento y manejo de estos pacientes debe ser rápido, debe hacerse un diagnóstico temprano con el reconocimiento y la retirada precoz del agente causal, es decir interrumpir el tratamiento con fármacos potencialmente causales lo cual es esencial para un resultado favorable. La morbilidad y la mortalidad aumentan si el fármaco culpable es retirado tardíamente. En nuestro primer paciente la dipirona fue el agente causal del cuadro, y en el segundo caso, el anticonvulsivante, ya que si bien los AINES se asocian a NET, la paciente los ingirió regularmente por 8 años sin que los mismos le produjeran rash cutáneao alguno y el cuadro se presentó justo al momento de la introducción de la carbamazepina.

El tratamiento de estos pacientes es similar al de los grandes quemados, pueden presentar alteración hidroelectrolítica, bacteriemia, hipercatabolismo y en ocasiones síndrome de distrés respiratorio del adulto.

Los pacientes deben pueden ser ingresados a Unidades de Cuidados Intensivos (UCI) o en Unidades de Quemados lo cual no es obligatorio, salvo en los casos de enfermedad muy extensa o con complicaciones severas.

Los corticoesteroides han sido la piedra fundamental en el tratamiento de SSJ y NET, pero en los últimos años su uso ha sido controversial. Según la mayor parte de autores los corticoesteroides sistémicos constituyen una ventaja no probada en formas tempranas y son claramente deletéreos en formas tardías de SSJ y NET, ya que la cascada se disparó y se produjo la apoptosis masiva de los queratinocitos [17].

El uso de Inmunoglobulina (Ig) es una estrategia prometedora pero no tiene ningún efecto en la progresión del desprendimiento cutáneo ni en la velocidad de renovación epidérmica [16]. Se usa por vía EV a dosis de 0.8-1 mg/kp/día (hasta 3 gr/kp) por 3-5 días [18,19].

En numerosos estudios, la administración temprana de la Ig EV en la necrólisis epidérmica tóxica ha demostrado que puede salvar vidas (nivel de evidencia IIIb, grado de recomendación C) [19]. Aunque el mecanismo de acción no está claro, la administración precoz de altas dosis de Ig se considera que es el tratamiento recomendado cuando hay un caso confirmado de necrólisis epidérmica tóxica, en ausencia de cualquier terapéutica alternativa.

La Ig EV debe ser administrada tan pronto como sea posible después de la confirmación del diagnóstico. El tratamiento con Ig puede ser en monoterapia, además de cuidados intensivos. La administración concomitante de corticoides o inmunosupresores es controversial.

Normalmente solo se requiere un ciclo de tratamiento.

El inicio de la re-epitelización es el mejor parámetro clínico para evaluar la eficacia del tratamiento.

Algunos estudios defienden el beneficio de plamaféresis para el tratamiento del SSJ/NET aunque no modifica la mortalidad ni el tiempo de hospitalización.

Otros esquemas terapéuticos incluyen el uso de la pentoxifilina como factor modulador del Factor de Necrosis Tumoral (TNF), terapias inmunomoduladoras con ciclofosfamida, ciclosporina o anticuerpos monoclonales contra citoquinas, talidomida y anti TNF como el infliximab, siendo necesario el estudio de investigaciones para determinar el valor real de estos fármacos [20-22].

Desde hace ya algunos años se ha postulado el uso de membrana amniótica para cubrir la piel expuesta, pero sin resultados consistentes [23].

Conclusión

El SSJ y la NET son patologías dermatológicas muco-cutáneas agudas y severas poco frecuentes que asocian una importante morbilidad y mortalidad, y que por lo general son desencadenados por fármacos (80 a 95% de los casos de NET y más de 50% de los casos de SSJ) algunos de uso muy común, y en raros casos por infecciones.

Pese a la apariencia inocua de muchos medicamentos, cada vez son más comunes las patologías causadas por sus efectos adversos.

Las farmacodermias graves (FG) son entidades infrecuentes en las que el diagnóstico y la retirada precoz del fármaco desencadenante pueden evitar un desenlace fatal.

Destacamos el rol del dermatólogo en la sospecha clínica de estas entidades y el manejo multidisciplinario de las mismas.

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SEROEPIDEMIOLOGY OF *TOXOPLASMA*, *RUBELLA*, *CYTOMEGALOVIRUS* AND *HERPES SIMPLEX VIRUS -2* IN WOMEN WITH BAD OBSTETRIC HISTORY. PART I: *TOXOPLASMA* AND *RUBELLA* INFECTIONS

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Abstract
Bad obstetric history (BOH) is associated with social and psychological impacts on society worldwide. The causes of BOH may be genetic, hormonal, abnormal maternal immune response, and maternal infection. In women with bad obstetric history (BOH), Toxoplasma (T) IgG high rate has been reported for Nepal (55.2%), while high (42.5%) and lowest (6.97%) active toxoplasma infections has been reported for India. In Arab countries, IgG and IgM higher and lowest seroprevalence rates were for Iraq. The higher susceptibility rates for Rubella in Arab countries excluding Iraq were reported in Morocco (83.4%), Sudan (34.7%), Qatar (25.1%), and Tunisia (20.3%). The lowest susceptibility was reported for Saudi Arabia (6.7%). In Iraq, studies indicate a high susceptibility rates in Thi Qar (98.05%), Kirkuk (91%), Baghdad (79%), and Waset (45.7%). The lowest susceptibility rates were reported for Diyala (0%) in women with previous abortion, and 3.9% in pregnant women without history of BOH.

Key words: TORCH; Toxoplasma; Rubella; CMV; Cytomegalovirus; HSV

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Introduction

Bad obstetric history (BOH) implies previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortions, history of intrauterine fetal death, intrauterine growth retardation, stillbirth, early neonatal death, and/or congenital anomalies [1]. The causes of BOH may be genetic, hormonal, abnormal maternal immune response, and maternal infection [2,3].

TORCH Complex:

The TORCH infections can lead to severe fetal anomalies or even fetal loss. They are a group of viral, bacterial, and protozoan infections that gain access to the fetal bloodstream transplacentally via the chorionic villi. Hematogenous transmission may occur at any time during gestation or occasionally at the time of delivery via maternal-to-fetal transfusion [4]. Primary infections caused by TORCH-*Toxoplasma gondi*i, *Rubella virus*, *cytomegalovirus* (CMV), and *herpes simplex virus* (HSV)-are the major causes of BOH [5]. These infections usually occur before the woman realizes that she is pregnant or seeks medical attention. The primary infection is likely to have a more important effect on fetus than recurrent infection and may cause congenital anomalies, spontaneous abortion, intrauterine fetal death, intrauterine growth retardation, prematurity, stillbirth, and live born infants with the evidence of disease [6].

Most of the TORCH infections cause mild maternal morbidity but have serious fetal consequences [7]. The ability of the fetus to resist infectious organisms is limited and the fetal immune system is unable to prevent the dissemination of infectious organisms to various tissues [8].

TORCH infections in the mother are transmissible to fetus in the womb or during the birth process and cause a cluster of symptomatic birth defects. Many sensitive and specific tests are available for serological diagnosis of TORCH complex [9]; however, ELISA test is more routinely used for its sensitivity. An attempt is being made to find out the correlation of TORCH infection during pregnancy in the Iraqi population. *Toxoplasma gondii* is an obligate intracellular protozoan parasite, which is linked to one of the most prevalent chronic infections affecting one third of the world's human population [10].

The infection is characterized by non-specific symptoms with the consequent formation of cysts that may remain in latent form in many organs [11]. Primary infection is usually subclinical but the infection hazard is its occurrence during pregnancy. There are four groups of individuals in whom the diagnosis of toxoplasmosis is most critical: a) pregnant women who acquire their infection during gestation, b) fetuses, c) newborns who are congenitally infected, immunocompromised patients, and d) those with chorioretinitis [12-14].

Although congenital toxoplasmosis is not a nationally reportable disease in Iraq, it represents a health care problem. Reported studies indicated an estimated 400 to 4,000 cases occur in the U.S. each year [11,15,16]. The overall prevalence and incidence varies in different communities and contributes significantly to heavy morbidity [10]. Congenital toxoplasmosis mainly results from a primary infection acquired during pregnancy [17], but not from the reactivation of a latent infection in immunocompetent pregnant women [18]. However, it is believed that latent toxoplasmosis could reactivate and cause a congenital transmission of the parasite to infants who then become infected in utero [19].

Countries with high disease prevalence have instituted successful secondary prevention programs via widespread maternal serologic screening [20], but universal maternal serologic screening for toxoplasmosis is not currently recommended in most of countries [21-24]. Instead, current practice suggests maternal serological screening when abnormal fetal findings or presence of infertility problem indicate possible infection [22]. ELISA methods is commonly performed in many countries to detect anti-toxoplasma antibodies [25]. ELISA results are generally well accepted by clinicians because of their excellent sensitivities and specificities, the rapid availability of results, and the relatively low costs of the tests. It is important to understand that a single serologic test is not enough for the diagnosis of toxoplasmosis [26]. In worldwide, commercial test kits for Toxoplasma-specific IgG and IgM antibodies are readily available. The presence of IgM antibodies is not always an indication of a recent infection since IgM maybe present for many months [27,28]. Misdiagnosis of recent infections may be as a result of the presence of specific *T. gondii* IgM antibodies in the chronic stage of an infection, or false-positive IgM positivity [17,29]. IgM test results are difficult to interpret and the reliability of test kits is largely dependent upon other factors. A negative IgM with a positive IgG result can indicate infection at least 1 year before. A positive IgM result may indicate more recent infection or may also be a false positive reaction [25].

Currently worldwide, there is no systematic screening of pregnant women to detect seroconversion during gestation and most clinicians make decisions depending on result of single serum sample. This approach is not effective to detect toxoplasma infections during pregnancy, thus monthly serological screening for pregnant women is the recommended approach [30]. The presence of elevated levels of Toxoplasma specific IgG antibodies indicates infection has occurred at some point, but does not distinguish between an infection acquired recently and one acquired in the distant past. In acute infection, IgG and IgM antibodies generally rise within 1 to 2 weeks of infection [31]. Given the potential for false-positive results, the true value of IgM testing is in ruling out the presence of acute infection. In other words, negative IgM results are reassuring, whereas positive results should be interpreted carefully, confirmed in a toxoplasmosis reference laboratory, and followed by serial titers at least 3 weeks apart [12,28,32].

There are different Toxoplasma seropositivity reports from all over the world. The population of Turkish childbearing age women has the seropositivity of *T. gondii* as 1.34% for IgM and 24.6% for IgG [33]. In Maracaibo, Venezuela the overall prevalence of toxoplasmosis was 33%, while 18.2% were positive IgM [34]. In Qatar among 823 women of childbearing age, the *T. gondii* IgG and IgM was 35.1% and 5.2% respectively [35].

Sixty-five studies [3,33,36-97] characterizing the prevalence of maternal infections with *T. gondii* in developing and developed countries and fifty-nine [35,98-155] studies in Arab countries (30 studies reported for Iraq) were identified. The features and results of these studies are summarized in Tables I and II.The majority of studies had small sample sizes, between 0– 4112 subjects. Most of these studies were conducted in antenatal clinics, hospitals, health care facilities or prenatal clinics. The remaining studies (3.3%) were community-based and the study setting was not specified in 7.4% of the studies. The most commonly used test was ELISA, which is the gold standard for T. gondii analysis. The median of IgG Toxoplasma prevalence was 38.5% [64] for Bangladesh. IgG high rate of detection was reported for Brazil [50] (75%, 832 pregnant women), while the lowest rate was for Thailand [38] (5.3%, 831 pregnant women). IgM lowest rate reported for China [49] (0%, 235 pregnant women) and Vietnam [59] (0%, 300 pregnant women), while the highest rate reported for Ghana [87] (76.1%, 159 pregnant women).

In women with bad obstetric history (BOH), IgG high rate was reported for Nepal [62] (55.2%, 345 BOH) and the lowest one was that reported by Natu et al [74] (19.44%, 499 BOH). IgM in BOH high rate was reported for India [36] (42.5%, 200 BOH), while the highest one for India also [91] (6.97%, 86 BOH).

In Arab countries, the median of IgG prevalence was 41.9% which was reported for Sudan [144]. IgG highest rate of detection reported for Iraq [132] (94%, 54 pregnant women) Bahrain [137] (15.8%, 146 Pregnant women), while the corresponding values for IgM were 55.5% (Iraq, 180 pregnant women) [129] and 2.8% (Egypt, 323 pregnant women) [153] respectively. Concerning BOH, IgG ranges between 77.1% (Iraq,122 BOH) [114] and 6.84% (Iraq, 190 BOH) [130], while the range of IgM was between 58% (Iraq, 50 BOH) [127] and 0.97% (Iraq, 310 BOH) [104].

Rubella virus

Rubella is a contagious viral disease caused by a togavirus and usually goes unnoticed. However, maternal infection during pregnancy may result in fetal loss or in congenital rubella syndrome (CRS) [156,157]. Infection in the first eight to ten weeks of pregnancy results in damage in up to 90% of surviving infantswhere multiple defects are common.

The risk of damage declines to about 10 to 20% with infection occurring between 11 and 16 weeks gestation [158]. Fetal damage is rare with infection after 16 weeks of pregnancy, with only deafness being reported following infections up to 20 weeks of pregnancy. Some infected infants may appear normal at birth but perceptive deafness may be detected later [157,158]. Before the introduction of Rubella immunisation, Rubella was commonly prevalent in children, and more than 80% of adults had evidence of previous rubella infection [159].

Article	Location, setting of study	Type, Duration	Population	Results
Wanachiwanawin et al [38]	Thailand, antenatal clinic	Cross sectional , 2 years	831 Pregnant women	5.3% IgG, IgM positive in 4.5% of IgG positive
Lopes et al [39]	Brazil, antenatal clinic	Cross sectional, 7 months	492 Pregnant women	49.2% IgG, IgM 1.2% of IgG positive
Varella et al [40]	Brazil, Hospital	Cross-sectional, 7 years	41112 Pregnant women	0.48% seroprevalence
Khurana et al [41]	India, antenatal clinic	Cross sectional, No information	300 Pregnant women	15.3% IgG, 3% IgM
Vaz et al [42]	Brazil, No information	Cross-sectional, 15 months	20389 Pregnant women	53.3% IgG, 3.26% IgM
Alvarado-Esquivel et al [43]	Mexico, Rural	Community based,	439 Pregnant women	8.2% IgG, 2.3% IgM
Sakikawa M et al [44]	Japan, antenatal clinic	All cases screening, 7.5 years	4466 Pregnant women	10.3% seroprevalence ,0.25% primary infection
Maggi et al [45]	Albania, General outpatient centre	Screening, 6 months	498 Pregnant women	48.6% IgG, IgM 1.3% of IgG positive
Sen MR et al [46]	India, Hospital	Descriptive case control, 2 years	380 pregnant women	19.4% IgM
Sarkar et al [47]	India, antenatal clinic	Descriptive case control, 10 months	105 Pregnant women	49.52% IgG, 21.9% IgM
Barbosa et al [48]	Brazil, Maternity hospital	Cross-sectional, 10 months	190 Pregnant women	66.3% IgG, 0.53% IgM
Liu et al [49]	China, antenatal clinic	Cross-sectional	235 Pregnant women	10.6% IgG, 0% IgM
Ribeiro et al [50]	Brazil, PHC	Cross sectional, 3.5 years	832 Pregnant women	75.1% IgG, 2% IgM
Rosso et al [37]	Colombia, Healthcare facility	Cross-sectional, 5 months	955 Pregnant women	45.8% IgG, 2.8% IgM
Abdi et al [51]	Iran,	Cross-sectional,	553 Pregnant women	44.8% IgG
Mostavi N [52]	Iran, Survey	Cross-sectional, 1 year	217 Child bearing age	47.5% seroprevalence (IgG)
Hajsoleimani [53]	Iran, PHC	Cross-sectional,	500 Pregnant women	37.2% IgG, 1.4% IgM
Ndiaye et al [54]	Senegal, Hospital	Cross-sectional, 1 year	109 Pregnant Women	22% IgG, 3% IgM
Spalding et al [55]	Brazil, PHC	Cross-sectional, 18 months	2128 Pregnant women	71.5% IgG, 3.6% IgM
Castilho-Pelloso et al [56]	Brazil, Public health care	Observational Retrospective, 3 years	290 Pregnant women	1.07% IgM
Sharifi-Mood et al [57]	Iran, Hospital	Cross sectional,	200 Pregnant women	27% serpositive
Ndir et al [58]	Senegal, Health centre	Case control, 6 months	70 Pregnant & 70 Abortion cases	37.1% in pregnant, 40% in abortion
Buchy et al [59]	Vietnam,	Cross-sectional,	300 Pregnant women	11.2% IgG, 0% IgM
Akoijam et al [60]	India, Antenatal clinic	Cross-sectional, 1 year	503 Pregnant women	41.75% seroprevalence
Mahdi et al [61]	Iran, Antenatal clinic	Cross-sectional,	245 Pregnant women	49.2% seroprevalence
Rai et al [62]	Nepal, Antenatal clinic	Cross-sectional, 2 years	345 BOH	55.2% seroprevalence
Chintana et al [63]	Thailand, Antenatal Clinic	Cross-sectional, 6 months	1200 Pregnant women	13.2% IgG
Ashrafunnessa et al [64]	Bangladesh, Antenatal clinic	Cross-sectional	286 Pregnant women	38.5% IgG
Zhang et al [65]	China	Cross-sectional	1250 Pregnant women	7.28% seroprevalence
Sroka et al [66]	Brazil, Hospital	Cohort, 10 weeks	963 Pregnant women	68.6% IgG, 0.5% IgM
Zhang et al [67]	China, antenatal clinic	Cross-sectional	4126 Pregnant women	3.38% IgM
Gonzalez-Morales et al [68]	Cuba, Health centres	Cross-sectional, 2 years	3913 Pregnant women	70.9% seroprevalence
Galvan Ramirez et al [69]	Mexico, Hospital	Case control	350 High risk pregnancy	34.9% IgG, 20.7% IgM
Lelong et al [70]	Madagascar,		599 Pregnant women	83.5% seroprevalence
Sun et al [71]	China, hospital	Cross sectional	1211 Pregnant women	39.14% IgG, 4.21% IgM
Martinez Sanchez et al [72]	Cuba, Community survey	Cross sectional, 6 months	362 Pregnant women	71% seroprevalence
Bari et al [73]	India, antenatal clinic	Cross sectional	302 Pregnant women	46% IgG, 27.7% IgM
Natu et al [74]		Case control	499 BOH	19.44% seroprevalence
Bittencourt [75]	Brazil, Public health services	Cross sectional, 16 months	4022 Pregnant women	59.8% IgG, 1.1% IgM
Shanmugam et al [76]	India, antenatal	Cross sectional	225 Pregnant women	23.6% Seropositive
Reis et al [77]	Brazil, Hospital	Cross sectional, 6 years	10468	61.1% Seroprevalence
Harma et al [78]	Turkey, Prenatal clinic	Cross-sectional,	1149 Pregnant women	60.4% IgG, 3% IgM
Hou et al [79]	China, Hospital	Cross-sectional	347 Pregnant and post partum women	5.5% seroprevalence.
Doehring et al [80]	Tanzania, Hospital	Cross-sectional	849 Pregnant women	35% Seropositive
Soto et al [81]	Venezuela, Hospital	Cross sectional	7969 Pregnant women	53.91% Seroprevalence

Table I. Characteristics and results of studies reporting prevalence of maternal Toxoplasma infection .

Article	Location, setting of study	Type, Duration	Population	Results
Khurana et al [82]	India, Antenatal clinic	Cross-sectional	300 Pregnant women	15.33% IgG, 3% IgM
Ouermi et al [83]	Burkina Faso, Healthcare facility	Cross-sectional 6 months	276 Pregnant women	27.2% IgG, 4.7% IgM
Zemene et al [84]	Ethiopia, Community based	Cross-sectional, 2 months	201 Pregnant women	81.1% IgG, 2.5% IgM
Flatt A & Shetty N [85]	UK, Antenatal clinic	Cohort, 2 years	5000 Pregnant women	17.32 % IgG
Surpam et al [86]	India, Antenatal clinic	Case control,	150 BOH	14.66% IgM
Ayi et al [87]	Ghana, Antenatal clinic	Cross-sectional, 4 months	159 Pregnant women	73.6% IgG, 76.1 IgM
Cvetkovic D et al [88]	Macedonia,	Retrospective, 2 years	235 Pregnant women	20.4% overall seroprevalence
Karabulut A et al [89]	Turkey, Antenatal clinic	Case control, 1 year	1102 Pregnant women	37% IgG, 1.4% IgM
Kumari N et al [1]	Nepal, Hospital	Case control, 4 months	12 BOH	50% seropositive
Nabi SN et al [90]	Bangladesh, Hospital	Case control, 10 months	111 Pregnant women	23.42% IgG, 0.9% IgM
Sadik MS et al [91]	India, Hospital	Case control, 2 years	86 BOH	20.93% IgG, 6.97% IgM
Akyar I [33]	Turkey, Hospital	Cross sectional, 7.5 years	17751 Child bearing age	24.6% IgG, 1.34% IgM
Frischknecht F et al [92]	Switzerland, Hospital	Cross sectional, 1 yr	723 Pregnant women	44.11% serpositive
Inagaki ADM, et al [93]	Brazil, Antenatal clinic	Cross sectional, 1 year	9559 Pregnant women	69.3% IgG, 0.4% IgM
Turbadkar D, et al [3]	India, Antenatal clinic	Case control, 1 year	380 BOH	42.1% IgG, 10.52% IgM
Linguissi LS et al [94]	Burkia Faso,	Cross sectional, 3 years	Pregnant women	20.37% IgG
Chopra S et al [36]	India, Antenatal clinic	Case control, 1 year	200 BOH	42.5% IgM
Koksaldi-Motor et al [95]	Turkey, Hospital	Cross sectional, 1 year	1103 Childbearing age	59.9% IgG
Vilibik-Cavlek T, et al [96]	Croatia, Hospital	Cross sectional, 5 years	Pregnant & non pregnant women	29.1% IgG, 0.25% IgM
Goncalves MA, et al, [97]	Brazil, Hospital	Retrospective, 2 years	574 Pregnant women	62% IgG, 3.4% IgM

Table I. Characteristics and results of studies reporting prevalence of maternal Toxoplasma infection (continued).

Article	Location, setting of study	Type, duration of study	Population	Results
Al-Ani RT [103]	Iraq, Al- Anbar, Hospital	Cross sectional, 6 months	50 Pregnant women	50% IgM
Razzak et al [104]	Iraq, Duhok, Hospital	Case control, 18 months	310 Women with BOH	0.97% IgM
El Mansouri et al [105]	Morocco, Institute National Hygiene	Cross-sectional	2456 Pregnant women	50.6% seroprevalence
Elnahas et al [106]	Sudan, Antenatal clinic	7 months	487 Pregnant women	34.1% IgG, 14.3% IgM
Abdel-Hafez et al [107]	Jordan,	Case control, 1 year	55 Aborted women 46 Pregnant women	58.2% Aborted women, 26.1% Pregnant women
Hammouda et al [108]	Egypt, Hospital	Case control,	100 BOH	65% seroprevalence
Abdulmohaymen N [99]	Iraq (Baghdad), Hospital	Case control, 9 months	119 Aborted women	24.2% IgM recurrent spontaneous abortion 14.7% IgM non recurrent spontaneous abortion. 8.1% IgG recurrent spontaneous abortion 5.9% IgG non recurrent spontaneous abortion
Salih HA [109]	Iraq, Najaf, Hospital	Case control	260 Aborted women	30.76% IgG, 11.92% IgM
Al-Mohammad et al [110]	Saudi Arabia, Maternity Hospital	Cross-sectional, 1 year	554 Pregnant women	51.4% IgG, 8.8 IgM
Jasim et al [100]	Iraq, Waset, Hospital	Case control, 1 year	162 Aborted women	53.9% IgG, 54.8% IgM
Al- Taie et al [101]	Iraq, Mosul, Private laboratory	Case control, 1 year	100 BOH	43% IgM
Al Seadawy MAH [111]	Iraq, Al Muthana, Hospital	Case control, 3 months	81 Aborted women	44.5% IgM
Mousa DA [112]	Libya, Hospital	Case control, 6 months	143 BOH	44.8% IgG, 8.4% IgM
Mahmood SH et al [113]	Iraq, Baghdad, Public Health Central Laboratory	Case control, 8 months	120 Aborted women	39.16% IgG, 17.79% IgM
Aziz & Drueish[114]	Iraq, Baghdad, Hospital	Case control	122 Aborted women	77.1% IgG, 58.1% IgM
Al-Hamdani & Mahdi [115]	Iraq, Basrah, PHC	Case control, 8 months	81 Habitual abortion	18.5% seropositive
Al-Sodany & Saleh [116]	Iraq, Basrah, Hospital	Case control, 8 months	81 Habitual abortion	81.5% seropositive

Table II. Characteristics and results of studies in Arab countries reporting prevalence of maternal Toxoplasmosis infection.

Article	Location, setting of study	Type, duration of study	Population	Results
Majeed AK [117]	Iraq, Baghdad,	Case control, 3 years	260 Aborted women for IgG 259 Aborted women for IgM	21.2% IgG35.1% IgM
Alsaeed et al [118]	Iraq, Al-Hila, Hospital	Case control, 6 months	120 Aborted women	41.66% seropositive
Almishhadani & Aljanabi [119]	Iraq, Al- Anbar, Medical Laboratory	Case control study, 3 years	230 Aborted women	58.3% IgG, 8.3% IgM
Khudair M K [120]	Iraq, Diala, Hospital	Case control, 5 months	50 Aborted women	54% seropositive
Hasan SF [121]	Iraq, Karbala, Immunology Centre	Cross sectional, 3 months	82 Childbearing age women	18.3% IgG
Ali AA [122]	Iraq, Al- Tameem, Hospital	Cross sectional, 1 year	100 Pregnant women 97 BOH	61% Seroprevalence 74.22% BOH non pregnant
Kadir MA et al [123]	Iraq, Kirkuk, Hospital & PHC	Cross sectional, 7 months	319 Pregnant women 121 Aborted women	36.6% seroprevalence LAT, 16.92 IgM ELISA52% LAT, 25.61% IgM ELISA
Alkulabi R [124]	Iraq, Najaf, Hospital	Cross sectional study	137 Pregnant women	60.5% IgG, 43.7% IgM
Yousif JJ et al [125]	Iraq, Najaf, PHC	Cross sectional, 3 months	120 Pregnant women 120 Non pregnant	40% IgG29.2% IgG
Al-khafaji & Mohsen [126]	Iraq, Thi Qar, Hospital	Case control, 10 months	74 Habitual abortion	23% IgG, 31.1% IgM
Alkhashab FMBA, et al [127]	Iraq, Mosul, Hospital	Case control, 16 months	50 Aborted women, 100 Pregnant women	34% IgG, 58% IgM20% IgG, 41% IgM
Alaa Z [128]	Iraq, Tikrit, Hospital	Case control, 15 months	226 BOH	26.1% IgG, 3.1% IgM
Rashid KN [102]	Iraq, Tikrit, Private laboratory	?????	100 Women 15 -45 years age	46% IgG, 32% IgM of IgG positive cases,
Al-Marzoqi AHM, et al [129]	Iraq, Babylon, Hospital	Cross sectional, 6 months	180 Pregnant women	62.2% IgG, 55.5% IgM
Hadi NJ [130]	Iraq, Thi Qar, Hospital	Case control	190 Aborted women	6.84% IgG, 12.63% IgM
Salman YG [131]	Iraq, Kirkuk, Hospital	Case control, 11 months	184 BOH	4.84% Seropositive, 17% IgM
Mossa HAL [132]	Iraq, Baghdad, Hospital	Retrospective, 2 years	54 Pregnant women	94% IgG, 33% IgM
Al- Shimmery MN [133]	Iraq, Diwanya, Hospital	Case control, 5 months	125 Aborted women	45.6% IgG, 29.6% IgM
Bouratbine A, et al [134]	Tunisia, Hospital	Cross sectional	1421 community sample	70% seroprevalence at age of 30 years
Barkat A et al [135]	Morocco, Hospital	Cross sectional, 1 year	368 Pregnant women	44.3% IgG
Bouhamdan SF et al [136]	Lebanon, Hospital & Private laboratories	Retrospective, 1year	3516 Female for IgG 3426 Female for IgM	62.2% IgG6.8% IgM
Tabbara & Saleh [137]	Bahrain, Hospital	Cross-sectional, 46 months	146 Delivering women	15.8% IgG
Ibrahim HM et al [138]	Egypt, Private Clinical Laboratory	Cross sectional,	101 Pregnant women	51.49% seroprevalence
Al-Hindi & Lubbad [139]	Palestine, Hospital	Case control, 6 months	312 Aborted women	17.9% IgG, 12.8% IgM
Abu- Madi MA, et al [35]	Qatar, Hospital	Cross sectional, 3 years	847 Women > 20 yr age	38.2% IgG, 5.1% IgM
Gashout A, et al [140]	Libya, Hospital	Case control, 5 years	692 Aborted women	45% IgG, 17.6% IgM
Al-Qahtani & Hassan [141]	Saudi Arabia, Hospital	Cross sectional, 5 months	75 Adult female	44% seroprevalence
Al-Harithi SA et al [142]	Saudi Arabia, Hospital	Cross sectional, 6 months	197 Pregnant women	29.4% IgG, 5.6% IgM
Elamin MH, et al [143]	Sudan, Hospital	Case control,	94 Pregnant Aborted during study 94 Pregnant with normal outcome	35.1% IgG, 15.2% IgM, 39.4% IgG, 16.2% IgM, Overall 37.2% IgG, 5.9% IgM
Khalil KM, et al [144]	Sudan, Hospital	Case control,	245 Pregnant women 209 Aborted women	35.9% seroprevalence58.3% Seroprevalence
Mohamad K, et al [145]	Sudan, Hospital	Cross sectional,	253 Childbearing age women	73.1% IgG
Al- Nahari AM, et al [146]	Yemen, Central Laboratory	Cross sectional, 2 years	463 Pregnant women	41.9% IgG, 11.88% IgM
Ghazi HO, et al [147]	Saudi Arabia, Hospital	Cross sectional	926 Pregnant women	35.6% IgG
Sellami H, et al [148]	Tunisia, Hospital	Cross sectional, 13 years	40 566 Pregnant women	39.3% seroprevalence, 1.3% acute infection during pregnancy.
Almogren A [149]	Saudi Arabia, Hospital	Retrospective, 1 year	2176 Pregnant women	38% IgG, 0% IgM
Al- Hindi A, et al [150]	Palestine, IVF centre	Retrospective, 6 years	1954 Women with infertility or abortion	7.9% IgM

Table II. Characteristics and results of studies in Arab countries reporting prevalence of maternal Toxoplasmosis infection (continued).

Article	Location, setting of study	Type, duration of study	Population	Results
El-Gozamy BR, et al (151)	Egypt, Hospital	Cross sectional, 17 months		Rural 57.6% seroprevalence, 46.5% Urban
Hussein AH, et al (152)	Egypt, Hospital	Case control,	152 randomly selected individuals, 31 full term pregnant, 38 BOH	IgG- 57.9%, 58.1%, 44.7%IgM – 10.5%, 6.5%, 23.7%
El- Deeb HK, et al (153)	Egypt, Hospital	Cross sectional	323 Pregnant women	67.5% IgG, 2.8% IgM
El- Ridi AM, et al, (154)	Egypt, Hospital	Case control	72 BOH	27.8 % Seropositive
Jumaian NF (98)	Jordan, Antenatal	Cross sectional,17 months	280 Pregnant women	47.1 seropositive,
Mohammed TK (155)	Iraq, Baghdad, Hospital	Cross sectional, 6 months	212 Pregnant women	28.77% IgG, 23.8% IgM

Table II. Characteristics and results of studies in Arab countries reporting prevalence of maternal Toxoplasmosis infection (continued).

Rubella infection of a pregnant woman may have devastating effects on the developing fetus and once congenital infection occurred there is no availability of treatment for the foetus. Thus the mainstay of prevention is the universal immunization of all infants and identification and immunization of women at risk [156].

Fetal infection is acquired hematogenously, and the rate of transmission varies with the gestational age at which maternal infection occurs, with higher frequency in first trimester [160]. Periconceptual maternal infection does not seem to increase the risk of CRS [160]. Maternal immunity, either after vaccination or naturally derived, is generally protective against intrauterine rubella infection [162,163]. However, there have been cases of CRS after maternal reinfection [163]. Therefore, CRS should always be considered in a fetus or neonate with a clinical picture suggestive of congenital infection [162]. It should be noted that no case of CRS has been reported when maternal reinfection occurred after 12 weeks of pregnancy [164].

Fifty- nine studies (Tabl. III) characterizing the epidemiology of maternal rubella were identified mostly for low and middle income countries [1,3,36,89-97,165-211] and 19 studies (Tabl. IV) for Arab countries [35,100,101,129-131,140,150,212-221]. Seven studies were with a retrospective (12.1%) study design and of the total 13 (22.4%) studies deals with women with bad obstetric history (BOH). These studies detected the presence of maternal anti-rubella IgG as a marker of past infection or immunization and mothers who did not possess these antibodies were susceptible to Rubella infection. Maternal IgM was detected in some studies as a marker of recent or current infection, which is associated with an increased risk of vertical transmission. The range of maternal susceptibility to Rubella was 2.1% to 43% in pregnant women [186,189] and 21.1% - 71.04% in women with BOH [91,190]. Higher susceptibility rates were reported [1,91,93,178,209,210] in Nigeria (84.8%), India (71%), Nepal (50%), Brazil (28.4%), Iran (25%), and Sri Lanka (24%).

The higher susceptibility rates for Arab countries excluding Iraq were reported [35,216,220,221] in Morocco (83.4%), Sudan (34.7%), Qatar (25.1%), and Tunisia (20.3%). The lowest susceptibility was reported [217] for Saudi Arabia (6.7%).

In Iraq, reports indicate a high susceptibility rates in Thi Qar (98.05%), Kirkuk (91%), Baghdad (79%), and Waset (45.7%). While the lowest susceptibility rates were reported for Diyala (0%) in women with previous abortion, and 3.9% in pregnant women without history of BOH [215]. The same figures was reported later by another research group in Babylon [213].

Article	Location, setting of study	Type, duration of study	Population	Results
Lin et al, [166]	Taiwan, Hospital	Cross-sectional, 7 yrs	10,089 pregnant women	Seronegativity was 14%
Tamer et al, [167]	Turkey, Antenatal clinic	Cross-sectional,	1972 pregnant women	Anti-rubella IgG 96.1% Anti-rubella IgM 0.2%
Ai & Ee, [168]	Malaysia, Antenatal & hospital	Cross-sectional	500 pregnant women	Seronegativity 11.4%
Majlessi et al, [169]	Iran, PHC	Cross-sectional, 2 yrs	965 Pregnant women	Seronegativity 8.9%
Das et al, [170]	India, hospital	Case control	1115 pregnant BOH	Seropositivity 3.6%
Ocak et al, [171]	Turkey, Antenatal	Retrospective, 23 months	1652 Pregnant women	Anti-rubella IgG 95% Anti-rubella IgM 0.54%
Pehlivan et al, [172]	Turkey, Community based	Cross-sectional, 7 months	824 Women	Anti-rubella IgG 93.8% Anti-rubella IgM 0.6% Negative 5.6%
Tseng et al, [173]	Taiwan, Hospital	Retrospective observational, 4 yrs	5007 pregnant women	13.4% susceptible

Table III. Characteristics and results of studies reporting prevalence of maternal rubella infection.

Article	Location, setting of study	Type, duration of study	Population	Results
Bareto et al, [174]	Mozambique, antenatal	Cross-sectional, 3 months	974 pregnant women	Anti-rubella IgG 95.3%
Corcoran & Hardie, [175]	South Africa, Antenatal clinic	Cross-sectional	1200 serum sample	96.5% immune
Desinor et al, [176]	Haiti, hospital	Cross-sectional, 4 months	495 pregnant women	95.2% seropositive
Weerasekera et al,[177]	Sri Lanka, antenatal	Cross-sectional, 2 yrs	500 pregnant women	82% positive for rubella IgG
Palihawadana et al, [178]	Sri Lanka, antenatal	Cross-sectional,	620 pregnant women	76% seropositive
Ashrafunnessa Khatun, et al [179]	Bangladesh, hospital	Cross-sectional, 11 months	609 pregnant women	14.1% seronegative
Dos Santos et al, [180]	Brazil, antenatal	Cross-sectional, 8 months	1024 pregnant women	77.4% seropositive
Surpam et al [181]	India, Antenatal clinic	Case control,	150 BOH	4.66% IgM
Uyar Y et al [182]	Turkey, Hospital	Cross sectional, 1 year	600 Pregnant women	94.3% IgG, 1.7% IgM
Karabulut A et al [89]	Turkey, Antenatal clinic	Cross sectional, 1 year	1268 Pregnant women	95.1% IgG, 0% IgM
Kumari N et al [1]	Nepal, Hospital	Case control, 4 months	12 BOH	50% Seropositive
Nabi SN et al [90]	Bangladesh, Hospital	Cross sectional, 10 months	111 Pregnant women	81.08% IgG, 6.3% IgM
Sadik MS et al [91]	India, Hospital	Case control, 2 years	86 BOH	29.06% IgG, 4.65% IgM
Fomda BA [183]	Kashmire, Hospital	Case control,	892 Pregnant with BOH1028 Pregnant with previous normal pregnancy	26.12% IgM8.96% IgM
Bamgboye AE et al [184]	Nigeria, Antenatal clinic	Cross sectional,	159 Pregnant women	68.5% IgG
Linguissi LS et al [94]	Burkina Faso,	Cross sectional, 3 years	Pregnant women	77% IgG
Jubaida N, et al [185]	Bangladesh, Outpatient clinic	Cross sections, 6 months	134 Pregnant women	84.33% IgG, 0.75% IgM
Amina MD et al [186]	Nigeria, Antenatal clinic	Cross sectional, 10 months	430 Pregnant women	97.9% IgG
Chopra S et al [36]	India, Antenatal clinic	Case control, 1 year	200 BOH	17.5% IgM
Ogbounnaya EC [187]	Nigeria, Hospital	Cross sectional, 1 year	190 Pregnant women	6.84% IgM
Koksaldi-Motor et al [95]	Turkey, Hospital	Cross sectional, 1 year	1103 women childbearing age	93.6% IgG
Langiano E et al [188]	Italy, Hospital	Cross sectional, 23 months	1242 Child bearing age	77.9% IgG
Onakewhor & Chiwuzie [189]	Nigeria, Hospital	Cross sectional,	270 Pregnant women	57% IgG, 91.3% IgM
Raveendran V et al [190]	India, Hospital	Case control, 1 year	182 BOH	78.9% IgG, 31.58% IgM
Fokunang et al [191]	Cameroon, Hospital	Cross sectional, 4 months	211 Pregnant women	88.6% IgG
Calimeri S et al [192]	Italy, Hospital	Cross sectional, 18 months	500 Pregnant women	85.8% IgG
Corcoran & Hardie [193]	South Africa, Hospital	Cross sectional, 1 year	1200 Pregnant women	95.3% - 98 % IgG
Mora- Garcia GJ et al [194]	Colombia, Hospital	Cross sectional, 1 year	1528 female 10-49 yrs	93% IgG
Uysal A et al [195]	Turkey, Hospital	Cross sectional, 8 years	5959 Pregnant women	97.8% IgG, 0.37% IgM
Combich JJ et al [196]	Kenya, Hospital	Cross sectional, 7 months	470 Pregnant women	92.9% IgG
Kearns MJ et al [197]	Canada, Provincial Public Health Laboratory	Retrospective Observational study, 3.5 years	140 473 Pregnant women	91.2% IgG
Jahromi AS et al [198]	Iran, Hospital	Case control, 8 months	220 Aborted women	91.2% IgG, 10.8% IgM
Ramana BV et al [199]	India, Hospital	Case control,	150 BOH	12.67% IgM
Cheong & Khoo [200]	Malaysia, Hospital	Cross sectional,	500 Pregnant women	11.4% susceptibility
Honarvar B, et al [201]	Iran, Hospital	Cross sectional, 3 months	138 Pregnant women	96% IgG
Nwanegbo et al [202]	USA, Prenatal care clinic	Retrospective Cross sectional, 1 year	642 Pregnant women	6.9% Non rubella immune
Eslamian L [203]	Iran, Hospital	Cross sectional, 10 months	500 Pregnant women	76% IgG
Ozdemir M et al [204]	Turkey, Hospital	Cross sectional, 6 months	249 Pregnant women	95.9% IgG, 0.4% IgM
Adesina OA [205]	Nigeria, Hospital	Cross sectional,	230 Childbearing age women	93.5% IgG
Frischknecht F et al [92]	Switzerland, Hospital	Cross sectional, 1 yr	723 Pregnant women in labor	93.08% seropositive
Ang LW et al [206]	Singapore,	Retrospective	Epidemiological data 1991-2007	84.2% Immune to rubella
Upreti SR et al [207]	Nepal,	Retrospective 2004-2009	2224 Childbearing age	90.8% IgG

Table III. Characteristics and results of studies reporting prevalence of maternal rubella infection (continued).

Article	Location, setting of study	Type, duration of study	Population	Results
Odland JO, et al [208]	Russia, Hospital	Case control, 4 months	182 Pregnant & 127 Aborted women	77.5% versus 59.8% seroprevalence
Goncalves MA, et al, [97]	Brazil, Hospital	Retrospective, 2 years	574 Pregnant women	93.1% IgG, 0.6% IgM
Turbadkar D, et al [3]	India, Antenatal clinic	Case control, 1 year	380 BOH	61.3% IgG, 26.8% IgM
Inagaki ADM, et al [93]	Brazil, Antenatal clinic	Cross sectional, 1 year	9559 Pregnant women	71.6% IgG, 0.1% IgM
Agbede OO, et al [209]	Nigeria, Antenatal clinic	Cross sectional, 3 months	92 Pregnant women	15.2% IgG, 3.3% IgM
Ebadi p, et al [210]	Iran, Hospital	Case control, 3 years	120 Aborted women	75% seropositive
Malarvizhi et al [211]	India, Private hospital	Cross sectional, 2 years	232 Pregnant women	50.9% IgG, 3.4% IgM
Vilibik-Cavlek T, et al [96]	Croatia, Hospital	Cross sectional, 5 years	Pregnant & non pregnant women	94.6% IgG, 0% IgM
Ballal M et al [165]	India, Hospital	Case control,	334 BOH	4.49% IgM

Table III. Characteristics and results of studies reporting prevalence of maternal rubella infection (continued).

Article	Location, setting of study	Type, duration of study	Population	Results
Abdulmohaymen N [99]	Iraq (Baghdad), Hospital	Case control, 9 months	119 Aborted women	4.8% IgM recurrent spontaneous abortion 2.9% IgM non recurrent spontaneous abortion. 6.5% IgG recurrent spontaneous abortion 20.6% IgG non recurrent spontaneous abortion
Jasim et al [100]	Iraq, Waset, Hospital	Case control, 1 year	162 Women with spontaneous abortion	54.3% IgG, 62.3% IgM
Al- Taie et al [101]	Iraq, Mosul, Private laboratory	Case control, 1 year	100 BOH	16% IgM
Hadi NJ [130]	Iraq, Thi Qar, Hospital	Case control	190 Aborted women	1.05% IgG, 4.21% IgM
Salman YG [131]	Iraq, Kirkuk, Hospital	Case control, 11 months	75 BOH	8.88% Seropositive, 6.75% IgM
Abdul-kareem ET, et al [212]	Iraq, Baghdad, Hospital	Case control, 8 months	79 Aborted women	34.2% seropositive
Al-rubaii B, et al [214]	Iraq, Babylon, Hospital	Cross sectional , 14 months	250 Childbearing age women	78.33% Pregnant, 75.71% non- pregnant
Hasan ARS, et al [215]	Iraq, Diyala, PHC	Case control	46 Pregnant - BOH, 52 Pregnant - Non BOH 47 Non pregnant Without Abortion 39 Non pregnant with Abortion	IgG- 76% IgG- 96.1 IgG – 85.1% IgG- 100%
Hammod AM, et al [213]	Iraq, Babylon, Hospital	Case control, 20.5 m0nths	46 Pregnant - BOH, 52 Pregnant - Non BOH 47 Non pregnant Without Abortion 39 Non pregnant with Abortion	IgG- 76% IgG- 96.1 IgG – 85.1% IgG- 100%
Hamdan HZ, et al [216]	Sudan, Hospital	Cross sectional, 2 months	231 Pregnant women	65.3% IgG, 3.4% IgM
Ghazi HO, et al [217]	Saudi Arabia, Hospital	Cross sectional	926 Pregnant women	93.3% IgG
Al-Marzoqi AHM, et al [129]	Iraq, Babylon, Hospital	Cross sectional, 6 months	180 Pregnant women	73.9% IgG, 53.9% IgM
Gashout A, et al [140]	Libya, Hospital	Case control, 5 years	692 Aborted women	89% IgG, 4.3% IgM
Abu- Madi MA, et al [35]	Qatar, Hospital	Cross sectional, 3 years	847 Women > 20 yr age	74.9% IgG
Barah & Chehada [219]	Syria, University Laboratory	Cross sectional, 3 months	90 university female students	85.6% IgG
Caidi H, et al [220]	Morocco, Hospital	Cross sectional, 1 year	967 childbearing age women 15-39 yrs	16.6% IgG
Hannachi N, et al [221]	Tunisia, Hospital	Cross sectional,	404 Pregnant women	79.7% seroprevalence
Al- Hindi A, et al [150]	Palestine, IVF centre	Retrospective, 6 years	1954 Women with infertility or abortion	7% IgM
Nama J et al [218]	Iraq, Najaf, Hospital	Case control, 10 months	300 Aborted women	77% IgG, 4.66% IgM

Table IV. Characteristics and results of studies in Arab countries reporting prevalence of maternal rubella infection.

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SEROEPIDEMIOLOGY OF *TOXOPLASMA*, *RUBELLA*, *CYTOMEGALOVIRUS* AND *HERPES SIMPLEX VIRUS -2* IN WOMEN WITH BAD OBSTETRIC HISTORY. PART II. *CYTOMEGALOVIRUS* AND *HERPES SIMPLEX VIRUS* INFECTIONS

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Abstract
Bad obstetric history (BOH) is reported worldwide and is associated with social and psychological impacts. Cytomegalovirus and herpes simplex virus play an important role in the induction of adverse outcomes of pregnancy. Highest CMV IgG prevalence rate was reported for India (91.05%), while the lowest rate was reported for Iran (14.28%). Unfortunately, six studies in Iraq reported a high prevalence of CMV IgM in non-married, pregnant and women with BOH. The range of recent CMV infection in pregnant women with BOH was from 1.4% in Jordan to 60.2% in Iraq. In women with BOH, the highest HSV 2 prevalence (16.8%) was noted in India, while the lowest rate (1.69%) was reported in India also. In Arab countries, among women with BOH, HSV 2 IgG and IgM seroprevalence higher rates were reported for Iraq. This literature review highlights the high bacterial and viral maternal infection rate in the developing world. Urgent, concerted action is required to reduce the burden of these infections. In addition to raising awareness about the severity of the problem of maternal infections in the developing world, data from this review will be beneficial in guiding public health policy, research interests and donor funding towards achieving improvement in health care delivery.

Key words: TORCH; Toxoplasma; Rubella; CMV; Cytomegalovirus; HSV

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Cytomegalovirus:

Primary *Cytomegalovirus* (CMV) infection during pregnancy is a frequent and serious threat to the fetuses of pregnant women [222]. The rate of susceptibility to CMV during pregnancy is also well established in many global countries [223,224]. Eight European countries (France, Belgium, Spain, Italy, Germany, Austria, Portugal, and the Netherlands) routinely screen the majority of pregnant women serologically for CMV [225,226]. This routine serologic screening occurs without the recommendations or guidelines of any governmental agency, authority, or a professional medical society. In Iraq, such screening program is not followed routinely and pregnant women screening order depends on personal interest of the clinicians. Routine serologic screening for CMV of pregnant women in Europe has yielded very important advances in our understanding of CMV infections among pregnant women [227-230].

The major risk factor for maternal acquisition of CMV during pregnancy is frequent and prolonged contact with a child less than three years of age [231-235]. This occurs among women with a child in the home or among women employed in child care centers or schools [236-241]. Another group of high-risk women are those who are seronegative, young, and poor. Even for this group, contact with a young child is an independent predictor of delivering a CMV congenitally infected infant, as is a history of frequent sexual activity [235]. A recent study suggested that C MV is likely transmitted not only via the oral mucosal route, but also via the vaginal mucosal route [231].

Characteristics and results of studies reporting prevalence of maternal

CMV infection

Forty studies [1,3,36,86,89-93,95,96,167,170,171,182,204, 208,210,242-263] on maternal cytomegalovirus infection prevalence were identified (Tabl. V). The median prevalence of maternal IgG to CMV (calculated from 28 studies that reported this) was 92%, indicating a high proportion of mothers with previous exposure to CMV. Two hospital-based study in India (29.5%) [36] and Iran (28.58%) [262] identified a statistically significant higher prevalence of CMV IgM (indicating active or recent infection) in mothers with Bad Obstetric History (BOH), highlighting a role for maternal CMV infection in adverse pregnancy outcome in this setting. The highest prevalence of IgG in pregnant women was in Turkey [95] (98.9%, 1103 childbearing age women), while the lowest prevalence reported for Ireland [253] (30.4%, 1047 pregnant women). However, in women with BOH, the highest IgG prevalence rate was reported for India [3] (91.05%, 380 BOH), while the lowest rate was reported for Iran [262] (14.28%, 42 Aborted women).

Active or recent infection high prevalence rate in pregnant women was reported for Poland [252] (13%, 1332 Pregnant women), while the lowest rate was reported for Turkey [204] (0%, 249 Pregnant women). In women with BOH the highest prevalence rate of IgM was reported for India [36] and the lowest one was reported for India [91].

In Arab countries, twenty- two studies [35,99-101,108,117-119,129-131,139,147,216,221,264-269] on maternal CMV infection prevalence were identified (Tabl. VI). The median prevalence of maternal IgG to CMV was 77.8% indicating lower proportion of mothers with previous exposure to CMV as compared to global studies. Unfortunately, six studies in Iraq [100,101,117,129,264,266] reported a high prevalence of CMV IgM in non-married, pregnant and women with BOH. The range of active or recent CMV infection in pregnant women was from 2.3% in Jordan [269] to 57.2% in Iraq [129], while the range in women with BOH was from 1.4% in Jordan [269] to 60.2% in Iraq [100]. In pregnant women, maternal IgG to CMV prevalence higher rate was reported in Jordan [269] (88%, 260 pregnant women), while the lowest one was reported for Iraq [129] (77.8%, 180 pregnant women). In addition, in women with BOH, maternal IgG to CMV prevalence higher rate was reported for Jordan [269] (95%, 898 Aborted women), and the lowest one was reported in Iraq [99] (4.8%, 119 Aborted women).

Article	Location, setting of study	Type, duration of study	Population	Results
Tabatabaee et al, [242]	Iran, hospital	Cross-sectional, 7 months	1472 pregnant women	97.68% seropositive, prevalence of active infection 4.35%.
Das et al, 2007 [170]	India, hospital	Cross sectional study	1115 BOH	11% prevalence in BOH, 4% prevalence in normal pregnant women
Ocak et al, [171]	Turkey, hospital	Retrospective observational study, 2 years	1652 pregnant women	94.9%seropositivity for anti-CMV IgG, 0.4%positive for anti-CMV IgM
Picone et al, [243]	France, Hospital	Cross sectional study prospective, 2 years	4287 pregnant women	46.8% IgG
Tamer et al, [167]	Turkey, antenatal Clinics	Cross sectional study,	1972 Pregnant women	97.1% IgG, 2.6% IgM
Surpam et al [86]	India, Antenatal clinic	Case control,	150 BOH	5.33% IgM
Uyar Y et al [182]	Turkey, Hospital	Case control, 1 year	600 Pregnant women	97.3% IgG, 1% IgM
Karabulut A et al [89]	Turkey, Antenatal clinic	Case control, 1 year	1000 Pregnant women	98.7% IgG, 1.2% IgM
Kumari N et al [1]	Nepal, Hospital	Case control, 4 months	12 BOH	8.3% seropositive
Nabi SN et al [90]	Bangladesh, Hospital	Case control, 10 months	111 Pregnant women	95.49% IgG, 0.9% IgM
Baschale MD [244]	Italy, Hospital	Cross sectional, 2 years	2385 Pregnant women	92% IgG, 0.4% IgM
Sadik MS et al [91]	India, Hospital	Case control, 2 years	86 BOH	23.25% IgG, 0% IgM
Chopra S et al [36]	India, Antenatal clinic	Case control, 1 year	200 BOH	29.5% IgM
Koksaldi-Motor et al [95]	Turkey, Hospital	Cross sectional, 1 year	1103 women childbearing age	98.9% IgG
Ozdemir M et al [204]	Turkey, Hospital	Cross sectional, 6 months	249 Pregnant women	98.7% IgG, 0% IgM
Frischknecht F et al [92]	Switzerland, Hospital	Cross sectional, 1 yr	723 Pregnant women in labor	4.7% seropositive
Vilibik-Cavlek T, et al [96]	Croatia, Hospital	Cross sectional, 5 years	Pregnant & non pregnant women	75.3% IgG, 0.09% IgM
Sarawathy TS, et al [245]	Malaysia, Antenatal clinic	Cross sectional, 2 years	125 Pregnant women	84% IgG, 7.2% IgM
Akinbami AA, et al [246]	Nigeria, Hospital	Cross sectional, 2 months	179 Pregnant women	97.2% IgG,
Bagheri L, et al [247]	Iran, Hospital	Cross sectional, 3 months	240 Pregnant women	69.6% IgG, 2.5% IgM
Arabpour M, et al [248]	Iran, Hospital	Cross sectional, 5 years	844 childbearing age women	93% IgG, 5.4% IgM

Table V. Characteristics and results of studies reporting prevalence of maternal CMV infection.

Article	Location, setting of study	Type, duration of study	Population	Results
Canon MJ, et al [249]	Global, Review	Review		45 – 100% seroprevalence
Ahmad RM, et al [250]	Nigeria, Hospital	Cross sectional,	90 Pregnant women	97.8% IgG
Seo S, et al [251]	Korea, Hospital	Cross sectional, 2 months	744 Pregnant women	98.1% IgG, 1.7% IgM
Gaj Z, et al , [252]	Poland, Hospital	Cross sectional, 11 years	1332 Pregnant women	76.7% IgG, 13% IgM
Knowles SJ, et al [253]	Ireland, Hospital	Cross sectional, 1 year	1047 Pregnant women	IgG 30.4% in Irish & 89.7% in non- Irish women [Africa, Asia, E. Europe]
Yamamoto AY, et al [254]	Brazil, Hospital	Cross sectional	985 Pregnant women	97% seroprevalence
Odland JO, et al [208]	Russia, Hospital	Case control, 4 months	182 Pregnant & 127 Aborted women	78% versus 81.1% seroprevalence
Chen MH, et al [255]	Taiwan, Hospital	Cross sectional, 10 months	483 Pregnant mother	91.1% IgG, 3.5% IgM
Gumber S et al [256]	India, Hospital	Cross sectional, 17 months	150 BOH	4.67% IgM
Dollard SC, et al [257]	USA, Hospital	Cross sectional,	6067 Women 12-49 yrs	58% IgG, 3% IgM
Enders G, et al [258]	Germany, Hospital	Retrospective, 15 years	40 324 Pregnant women	42.3% IgG
Correa CB, et al [259]	Cuba, Hospital	Cross sectional, 1 year	1131 Pregnant women	92.6% seropositive, 2.4% active infection
Rajaii & Pourhasan [260]	Azerbaijan, University Lab.	Cross sectional, 4 years	2049 Women 20-35 yrs [of them 75 Pregnant]	88.53% IgG, 8.29% IgM, In Pregnant 66.7%seropositive
Turbadkar D, et al [3]	India, Antenatal clinic	Case control, 1 year	380 BOH	91.05% IgG, 8.42% IgM
Ashrafunnessa et al [261]	Bangladesh, Hospital	Case control, 11 months	420 Pregnant women	68.6% IgG, 5% IgM
Inagaki ADM, et al [93]	Brazil, Antenatal clinic	Cross sectional, 1 year	9559 Pregnant women	76.6% IgG, 0.2% IgM
Falahi S, et al [262]	Iran, Hospital	Case control	42 BOH	14.28% IgG, 28.58% IgM
Ebadi p, et al [210]	Iran, Hospital	Case control, 3 years	120 BOH	78.33% seropositive
Oruc AS, et al [263]	Turkey, Hospital	Cross sectional,5 years	11 360 Pregnant women	98.5% IgG, 0.3% IgM

Table V. Characteristics and results of studies reporting prevalence of maternal CMV infection (continued).

Article	Location, setting of study	Type, duration of study	Population	Results
Hammouda et al [108]	Egypt, Hospital	Case control	100 BOH	51% Seroprevalence
Abdulmohaymen N [99]	Iraq, Baghdad, Hospital	Case control, 9 months	119 Aborted women	17.7% IgM recurrent spontaneous abortion 14.7% IgM non recurrent spontaneous abortion. 4.8% IgG recurrent spontaneous abortion 0% IgG non recurrent spontaneous abortion
Jasim et al [100]	Iraq, Waset, Hospital	Case control, 1 year	162 Aborted women	55.5% IgG, 60.2% IgM
Al- Taie et al [101]	Iraq, Mosul, Private laboratory	Case control, 1 year	100 BOH	24% IgM
Almishhadani & Aljanabi [119]	Iraq, Al- Anbar, Medical Laboratory	Case control study, 3 years	230 Aborted women	90.4% IgG, 6.1% IgM
Majeed AK [117]	Iraq, Baghdad,	Case control, 3 years	135 Aborted women	20.7% IgG45.9% IgM
Alsaeed et al [118]	Iraq, Al-Hila, Hospital	Case control, 6 months	120 Aborted women	79.5% IgG, 18.8% IgM
Hadi NJ [130]	Iraq, Thi Qar, Hospital	Case control	190 Aborted women	16.84% IgG, 9.47% IgM
Salman YG [131]	Iraq, Kirkuk, Hospital	Case control, 11 months	84 BOH	8.02% Seropositive, 7.89% IgM
Al- Azzawi RHM, [264]	Iraq, Baghdad, Hospital	Cross sectional, 8 months	161 Non married women 15-35 yrs	67.1% IgG, 41% IgM
Khalf MS, et al [265]	Iraq, Baghdad, Hospital	Case control, 17 months	108 BOH	15.7% IgM
Hannachi N, et al [221]	Tunisia, Hospital	Cross sectional,	404 Pregnant women	96.3% seroprevalence
Al- Hindi A, et al [139]	Palestine, IVF centre	Retrospective, 6 years	1954 Women with infertility or abortion	6% IgM
Al- Shimmery MN [266]	Iraq, Diwanya, Hospital	Case control, 5 months	125 Aborted women	49.6% IgG, 22.4% IgM

Table VI. Characteristics and results of studies in Arab countries reporting prevalence of maternal CMV infection.

Article	Location, setting of study	Type, duration of study	Population	Results
Al-Khafaji & Al-Zabaidi [38]	Iraq, Thi Qar, Hospital	Case control, 10 months	60 aborted women	85% IgG, 65% IgM
Kafi SK, et al [267]	Sudan, Hospital	Cross sectional, 2 months	100 Pregnant women	95% IgG
Hamdan HZ, et al [216]	Sudan, Hospital	Cross sectional, 2 months	231 Pregnant women	72.2% IgG, 2.5% IgM
Ghazi HO, et al [147]	Saudi Arabia, Hospital	Cross sectional	926 Pregnant women	92.1% IgG
Al-Marzoqi AHM, et al [129]	Iraq, Babylon, Hospital	Cross sectional, 6 months	180 Pregnant women	77.8% IgG, 57.2% IgM
Abu- Madi MA, et al [35]	Qatar, Hospital	Cross sectional, 3 years	847 Women > 20 yr age	96.8% IgG, 2.7% IgM
Barah F [268]	Syria, University Laboratory	Cross sectional, 15 months	316 Female university students	74.5% seropositive
Daboui & Al-Zaben [269]	Jordan, Medical centre	Case control, 2 months	260 Pregnant, 100 Unmarried women, 898 Aborted women	IgM- 2.3% pregnant, 1% unmarried, 1.4% Abortion. IgG- 88% pregnant, 79% unmarried, 95% abortion

Table VI. Characteristics and results of studies in Arab countries reporting prevalence of maternal CMV infection (continued).

Herpes simplex virus

Herpes simplex virus (HSV) is an ubiquitous, enveloped, and double stranded DNA virus, belonging to the family of Herpesviridae transmitted across mucosal membranes and non-intact skin, that migrate to nerve tissues, where they persist in a latent state [270]. HSV-1 predominates in oro-facial lesions, and it is typically found in the trigeminal ganglia, whereas HSV-2 is most commonly found in the lumbo-sacral ganglia [271]. Nevertheless these viruses can infect both oro-facial areas and the genital tract. In some developed countries type 1 has recently emerged as the prominent causative agent in genital lesions [272]. Changes in sexual behaviours of young adults may partly explain its higher incidence [273,274].

Herpes simplex virus (HSV) infections are caused by two strains, HSV-1 and HSV-2. Oro-labial infection is mainly caused by HSV-1, however, this strain is responsible for up to 53% of primary genital herpetic infection [270]. HSV-2 genital infection is much more likely to recur than genital HSV-1 infection, thus the presence of antibody to HSV-2 and a compatible clinical history would be strong presumptive evidence that the disease is recurrent genital herpes [275-277]. In addition to agent factor, genetic may play a role in susceptibility to HSV infection [278]. Primary genital HSV-1 or HSV-2 infection in pregnant women can result in abortion, premature labor and congenital and neonatal herpes [279-281]. HSV-2 infections in the newborn are particularly severe and frequently involve the CNS [282]. Recent changes in HSV-1 and HSV-2 infection epidemiology have been reported, with type incidence changes and sequential genital infections with HSV-1 and HSV-2 [272,283].

Little is known about the risk factors associated with HSV seropositivity in pregnant Iraqi women. Identification of the risk factors may help to improve the control measures of HSV infection. Although there is improve in the diagnosis and treatment of TORCH infections, it still represents a problem in developing countries. Clinical diagnosis of TORCH is difficult, since most of the maternal infections with adverse outcomes are initially asymptomatic. Routine TORCH complex screening during pregnancy is not recommended in Iraq and the extent to which it is performed is unknown.

A first primary infection develops when a susceptible person (lacking of preexisting HSV-1 and HSV-2 antibodies) is exposed to HSV. Indeed, a first non-primary episode occurs when a person with preexisting HSV antibodies (against type 1 or 2) experiences a first episode with the opposite HSV type. Recurrent infection occurs in a person with preexisting antibodies against the same HSV type [271]. Infections during pregnancy may be transmitted to newborns: HSV-1 and HSV-2 may cause eye or skin lesions, meningo-encephalitis, disseminated infections, or foetal malformations.

In recent years, genital herpes has become an increasing common sexually transmitted infection. From the late 1970s, HSV-2 seroprevalence has increased by 30%, resulting that one out of five adults is infected [284,285]. HSV seroprevalence in patients with STD varies from 17% to 40% (6% in the general population and 14% in pregnant women) [286,287]. Age and sex are important risk factors associated with the acquisition of genital HSV-2 infection. In fact, the prevalence of HSV infection rises with age, reaching the maximum around 40 years [284]. This infection appears related to the number of sexual partners, and regarding sex it is more frequent in women than in men [288,289]. In addition, ethnicity, poverty, cocaine abuse, earlier onset of sexual activity, sexual behavior, and bacterial vaginosis can facilitate a woman's risk of infection before pregnancy [290,291].

Regarding pregnant population, there is a high prevalence of genital herpes, however, it is varies from country to others, depending on social and sexual behaviors and activity [289,292-294].

The risk of neonatal infection varies from 30% to 50% for HSV infections that onset in late pregnancy (last trimester), whereas early pregnancy infection carries a risk of about 1% [295-297].

Thirty-one studies [1,3,90,91,96,204,256,298-320] outlining the prevalence of maternal Herpes simplex virus 2 (HSV-2) were identified (Tabl. VII). These studies detected the presence of antibodies to HSV as a marker of maternal infection. Median prevalence of IgG HSV-2 was 18.2% which was reported for Belgium [315,357]. In pregnant women, higher seroprevalences were noted in Germany (82%), Turkey (63.1%), Zimbabwe (51.1%), and Iran (43.75%) [298,299,309,313]. However, the lowest seroprevalences were reported in two studies in Turkey [204,314], which reported a rates of 4.4% and 5%. In women with BOH, the highest prevalence (33.58%) was reported in India [3], while the lowest one (18.6%) was reported in India also [91].

Concerning IgM, the highest prevalence in pregnant women was reported in Turkey (13.8%, 130 pregnant women) [298], while the lowest rate was reported in Turkey (0%, 249 pregnant women) also [204].

In women with BOH, the highest prevalence (16.8%, 450 BOH) was noted in India [320], while the lowest rate (1.69%, 86 BOH) was reported in India also [91].

In Arab countries, nine studies [35,99-101,129,147,268,319,320] outlining the prevalence of maternal HSV-2 were identified (Table VIII). The median IgG seroprevalence was 27.1%, which was noted in Saudi Arabia [147]. A higher (27.1%, 926 pregnant women) IgG maternal seroprevalence in pregnant women was reported in Saudi Arabia [147], while the lower rate (6.5%, 459 pregnant women) was noted in Saudi Arabia also [319]. In women with BOH IgG seroprevalence was 60.6%, which was reported in Iraq [100]. Concerning IgM, the highest prevalence's were reported in Iraq [100,129] for both pregnant women (28.9%, 180 pregnant women) and those with BOH (73.9%, 62 BOH).

Article	Location, setting of study	Type, duration of study	Population	Results
Kurewa et al, [299]	Zimbabwe, peri-urban clinics	Cross sectional, 19 months	691 Pregnant women	51.10% IgG
Yahya-Malima et al, [300]	Tanzania,antenatal clinics (6)	Cross sectional,	1296 Pregnant women	20.7% prevalence of genital herpes
Chen et al, [301]	China, antenatal clinic	Cross sectional, 3 months	502 pregnant women	10.8% seroprevalence
Haddow et al, [302]	Australia, antenatal clinic	Cross sectional, 2 years	535 pregnant women	30% seroprevalence
Joesoef et al, [303]	Indonesia, prenatal clinic	Cross sectional, 15 months	599 pregnant women	9.9% seroprevalence
Surpam et al [86]	India, Antenatal clinic	Case control,	150 BOH	8.66% IgM
Kumari N et al [1]	Nepal, Hospital	Case control, 4 months	12 BOH	33.3% Seropositive
Nabi SN et al [90]	Bangladesh, Hospital	Case control, 10 months	111 Pregnant women	9.91% IgG, 1.8% IgM
Sadik MS et al [91]	India, Hospital	Case control, 2 years	86 BOH	18.6% IgG, 1.69% IgM
Ozdemir M et al [204]	Turkey, Hospital	Cross sectional, 6 months	249 Pregnant women	4.4% IgG, 0% IgM
Xu F et al [304]	USA, Hospital	Cross sectional, 4 years	626 Pregnant women	22% seroprevalence
Kucera P et al [305]	Switzerland, Hospital	Cross sectional,	1030 Pregnant women	21.2% seroprevalence
Patrick MD et al [306]	Canada, antenatal clinic	Cross sectional, 1 year	1215 Pregnant women	17.3 % seroprevalence
Munjoma MW et al [307]	Zimbabwe, Antenatal clinic	Cross sectional, 6 months	354 Pregnant women	49.1% seroprevalence
Diawara S et al [308]	Senegal, Antenatal clinic	Cross sectional, 6 months	260 Pregnant women	22% seropositivity
Sauerbri A et al [309]	Germany, Hospital	Cross sectional, 8 years	200 Pregnant women	82% IgG
Ades AE et al [310]	UK, Hospital	Cross sectional, 2 years	3533 Pregnant women	10.4% IgG
Rathore S et al [311]	Kashmir, Antenatal clinic	Cross sectional, 2 year	200 Pregnant women	7.5% IgG
Duran N [298]	Turkey, Hospital	Cross sectional, 21 months	130 Pregnant women	63.1 % IgG, 13.8% IgM
Biswas D et al [312]	India, Hospital	Cross sectional, 2 years	1640 Pregnant women	8.7% HSV-2 IgG
Shahraki AD et al [313]	Iran, Hospital	Cross sectional,	96 Pregnant women	43.75% HSV-2 IgG
Dolar N et al [314]	Turkey, Hospital	Cross sectional,	300 Pregnant women	5% HSV-2 IgG
Bodeus M, et al [315]	Belgium, Hospital	Cross sectional,	1000 Pregnant women	18.2% HSV-2 IgG
Chen XS et al [301]	China, Hospital	Cross sectional, 3 months	504 Pregnant women	10.8% seroprevalence
Sasadeusz JJ et al [316]	Australia, Antenatal clinic	Cross sectional,	1371 Pregnant women	13.6% seroprevalence
Vilibik-Cavlek T, et al [96]	Croatia, Hospital	Cross sectional, 5 years	Pregnant & non pregnant women	6.8% IgG, 1.2% IgM
Straface G et al [317]	Italy, Review	Retrospective		7.6 – 8.4% seroprevalence Italy22% seroprevalence USA
Kim D et al [318]	Korea, Hospital	Retrospective, 19 months	500 Pregnant women	17% HSV-2 seroprevalence
Gumber S et al [256]	India, Hospital	Cross sectional, 17 months	150 BOH	3.33% IgM
Turbadkar D, et al [3]	India, Antenatal clinic	Case control, 1 year	380 BOH	33.58% IgG, 3.6% IgM
Li et al [319]	China, Hospital	Cross sectional	1740 Pregnant women	23.56% seroprevalence
Haider M, et al [320]	India, Hospital	Case control	450 BOH	16.8% IgM

Table VII. Characteristics and results of studies reporting prevalence of maternal HSV-2 infection.

Article	Location, setting of study	Type, duration of study	Population	Results
Abdulmohaymen N [99]	Iraq, Baghdad, Hospital	Case control, 9 months	119 Women with history of abortion	8.1% IgM recurrent spontaneous abortion 17.4% IgM non recurrent spontaneous abortion.
Jasim et al [100]	Iraq, Waset, Hospital	Case control, 1 year	162 Women with spontaneous abortion	60..6% IgG, 73.9% IgM
Al- Taie et al [101]	Iraq, Mosul, Private laboratory	Case control, 1 year	100 BOH	11% IgM
Alzahrani et al [319]	Saudi Arabia, Hospital	Cross sectional,	459 Pregnant women	6.5% IgG, 0.5% IgM
Obeid EO [320]	Saudi Arabia, Hospital	Cross sectional, 2 years	459 Pregnant women	6.8% IgG
Barah F [317]	Syria, University Laboratory	Cross sectional, 15 months	316 Female university students	52% seropositive
Ghazi HO, et al [192]	Saudi Arabia, Hospital	Cross sectional	926 Pregnant women	27.1% IgG
Al-Marzoqi AHM, et al [174]	Iraq, Babylon, Hospital	Cross sectional, 6 months	180 Pregnant women	22.2% IgG, 28.9% IgM
Abu- Madi MA, et al [87]	Qatar, Hospital	Cross sectional, 3 years	847 Women > 20 yr age	26.3% IgG, 7.6% IgM

Table VIII. Characteristics and results of studies in Arab countries reporting prevalence of maternal HSV-2 infection

Gaps in existing knowledge

In the process of reviewing the subject, we identified several facility-based retrospective studies reporting causes of maternal mortality. Many of these studies attributed a proportion of deaths to infection or sepsis, but were unable to provide microbiological or serological evidence of the specific underlying mortality causes. Our review confirms the suspected high prevalence of parasitic and viral maternal infections in the developing world, as demonstrated by the median prevalence rates calculated for each pathogen studied. Of particular concern are the aetiology of infection. The literature review highlights a gap in existing knowledge on the epidemiology and impact of maternal infection, especially on the aetiology of infectious agents that lead to puerperal sepsis and subsequent mortality. Increased surveillance and diagnostic capabilities in healthcare facilities and in the community is needed to identify the aetiological agents responsible for puerperal sepsis and maternal mortality.
The prevalence of maternal infection reported by the studies identified in this literature review may be an underestimate of actual rates of infection as not all pregnant women in developing countries may have access to or choose to access formalized antenatal care. This could be due to financial constraints, difficulties in accessing these facilities and personal or cultural beliefs. In addition, antenatal care services may not have the capacity to routinely screen for maternal infections, especially those that are asymptomatic and those that require serological tests such as PCR and ELISA to diagnose, due to limited resources or expertise. These infrastructural problems are essential contributors to the persistence of high maternal morbidity and mortality in developing countries and need to be overcome in order to accurately characterize the burden of maternal infections in these countries.

Conclusion

This literature review highlights the high bacterial and viral maternal infection rates in the developing world. Urgent, concerted action is required to reduce the burden of these infections. In addition to raising awareness about the severity of the problem of maternal infections in the developing world, data from this review will be beneficial in guiding public health policy, research interests and donor funding towards achieving improvement in health care delivery.

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A STUDY ON CONTACT DERMATITIS TO HAIR DYE AND HENNA

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Abstract
P- Phenylenediamine is an oxidative chemical that is frequently used as a permanent hair-coloring agent. It is added to henna to increase the intensity and longevity of the tattoo and expedites its drying time. Henna itself is a greenish brown vegetable coloring made from the leaves of Lawsonia inermis and rarely causes allergic contact dermatitis. The addition of PPD causes the contact sensitization to black henna. Serious adverse skin reactions to permanent hair dyes and temporary black tattoos have been reported. As temporary tattoos have become fashionable among adolescents, the risk profile for p-phenylenediamine (PPD) sensitization of the population has changed simultaneously with an increasing use of hair dyes in this age group. With increased popularity of body art such as body piercing and tattooing, an increase in temporary henna tattoos has also occurred. Although the appeal of non-permanence exists for henna tattoos, dermatologists have begun to see numerous cases of allergic contact dermatitis linked with a certain type of henna. We selected 50 patients using hair dye and henna for our study. Patch testing was done in all the patients using Indian standard series of antigens. Regarding to the side effects to hair dye and henna and itching was the commonest symptom seen in 16% patients, erythematous scaly plaques were seen in 10% patients, vesicular reactions were seen in 6% patients, angioneurotic oedema and contact urticaria was seen in 4% patients each and anaphylaxis and keloidal reaction was seen in 2% patients each.

Key words: dermatitis; hair dye; henna; allergic; PPD

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Introduction

Paraphenylenediamine is a chemical substance that is widely used as a permanent hair dye. Henna has been used for centuries in certain cultures as body paint and more recently as a hair coloring agent. It has been noted to be a very low-level sensitizer [1]. At the same time, body tattooing has enjoyed increased acceptance among the youth of many cultures, including those in the West. The active ingredient of henna is lawsone (2-hydroxy-1, 4-naphthoquinone) [2]. It is traditionally used in Islamic and Hindu cultures as a hair coloring and as a dye for decorating the nails or making temporary skin tattoos. Actually, henna has a very low allergic potential. In most cases, allergic reactions not caused by henna, but by the chemical coloring additives that are added to henna mixtures. A recent phenomenon is „temporary tattooing," in which the tattoo colors the stratum corneum and lasts until that layer is shed. Such tattoos are usually referred to as henna tattoos or black henna tattoos. Recently, reports of reaction to these temporary henna tattoos have become common [3]. In the vast majority of such cases, the offending allergen has been found to be PPD. The level of PPD in these products is much higher than that found in hair color [4,5]. Because of PPD's high sensitization potential, the application of PPD to the skin is not an approved use. Since sensitization to PPD from tattoos is likely to be lifelong, we will likely see a population of individuals who will respond adversely to their attempts at hair coloring as they age [6].

Allergy to natural henna is not usual; however the addition of para-phenylenediamine (PPD) to the natural henna increases the risk of allergic contact dermatitis [7,8]. The objectives of the study were to identify the presence and concentration of PPD. PPD is present in concentration higher than that recommended for hair dyes in most of the black henna samples. The presence of PPD in the black henna increases the risk of allergic contact dermatitis among users of black henna [9,10].

In the Arab world and Indian subcontinent henna is used for skin decoration and hair dying during social celebrations, and during marriage ceremonies people celebrate by adorning the bride, and sometimes the groom, with henna. Despite the wide spread use of natural henna, specially, in countries where henna art is traditionally practiced, reports of allergic contact dermatitis to natural henna are very rare in the literature. It can therefore be assumed that natural henna is a very weak skin allergen.

Materials and Methods

We selected 50 patients using hair dye and henna for our study. Patch testing was done in all the patients using Indian standard series of antigens by CODFI (Contact Dermatitis Forum of India). Informed consent was taken from all the patients before the study. Prior approval of hospital ethical was taken. The patients were instructed to stop any oral corticosteroids before the patch testing. The patch testing reading was taken after 48 hours and 72 hours. Various types of reactions were noted and tabulated.

Aims

1. To study the various types of reactions to hair dye and black henna tattooes.
2. To see the patch testing positivity in all the patients.

Results

The data was tabulated and the results were analyzed statistically (Tabl I, II).

Sr no	Side Effects	Number of patients	Percentage
1.	Angioneurotic oedema	2	4
2.	Itching	8	16
3.	Contact urticaria	2	4
4.	Vesicular reactions	3	6
5.	Erythematous scaly plaques	5	10
6.	Anaphylaxis	1	2
7.	Keloidal reaction	2	4

Table I. Side effects.

Sr no	Site	Number of patients	Percentage
1.	eyelids	5	10
2.	ears	2	4
3.	forehead	3	6
4.	neck	2	4
5.	beard	4	8

Table II. Sites of involvement.

Discussion

The mean age group of patients in our study was 36+20 years. Females outnumbered females and female: male was 1.5:1.

The mean age at first hair dyeing was 25 years. Out of all the patients , 4% patients had history of temporary tattoos during the childhood. Regarding to the side effects to hair dye and henna and itching was the commonest symptom seen in 16% patients, erythematous scaly plaques (Fig. 1) were seen in 10% patients, vesicular reactions were seen in 6% patients, angioneurotic oedema and contact urticaria was seen in 4% patients each and anaphylaxis and keloidal reaction (Fig. 2) was seen in 2% patients each. The commonest site of involvement was eyelids seen in 10% patients, beard involvement was seen in 8% patients, forehead in 6% patients and neck and ear involvement was seen in 4% patients each. Ptch testing positivity was seen in 84% patients.

In recent years, attention has been drawn to the use of p-phenylenediamine (PPD) in henna dyes and the potential for this allergenic chemical to cause hyper sensitivity reactions [11]. It is the immediate , partially oxidized state that may cause allergy in sensitive individuals. Fully oxidized PPD is not a sensitizer [12]. Reaction is caused by the use of hair dye in mild cases only involves dermatitis to the upper eyelids or the rims of the ears. In more severe cases, it often extends beyond the scalp to include the forehead, neck, eyelids and face. It manifests as pruritic, oedematous, erythematous scaly patches and plaques and vesicular lesions in some cases. Severe allergy to PPD can result in contact urticaria and rarely anaphylaxis. Dermatitis on the hands is seen in hair dressers. Other skin reactions, such as post inflammatory hyper or hypopigmentation, can also ensue.

There have been rare reports of sensitivity occurrence with ordinary henna tattoos; however, henna containing paraphenylene diamine, a popular chemical for use in black henna to darken the tattoo and reduce fixation time, increases skin sensitivities [13,14].

Short-term exposure to high levels of PPD (acute effects) may cause severe dermatitis, eye irritation and tearing, asthma, gastritis, renal failure, vertigo, tremors, convulsions, and coma in humans. Recently para-phenylenediamine has been mixed with natural henna to give an ebony color (black henna) instead of the orange/reddish color given by natural henna. The other reason for adding PPD to the natural henna is to speed up (shorten the time) of the tattooing process, while natural henna staining takes 4 to 12 hours, addition of PPD can reduce this time to an hour or two and also there will be a longer lasting effect as well. Thus, a new pattern of exposure to PPD has been recognized through henna art which increases the risk of developing adverse health effects related to PPD [15].

Acute allergic contact dermatitis, eczema, chemical burn, acute renal failure, acute and severe angioneurotic edema, abdominal pain and vomiting as adverse health effects associated with the use of henna containing PPD (black henna) are well documented in the literature [16]. In addition, people developeing sensitization from use of black henna are susceptible to cross reaction to oxidative hair dyes and to clothing dyes.

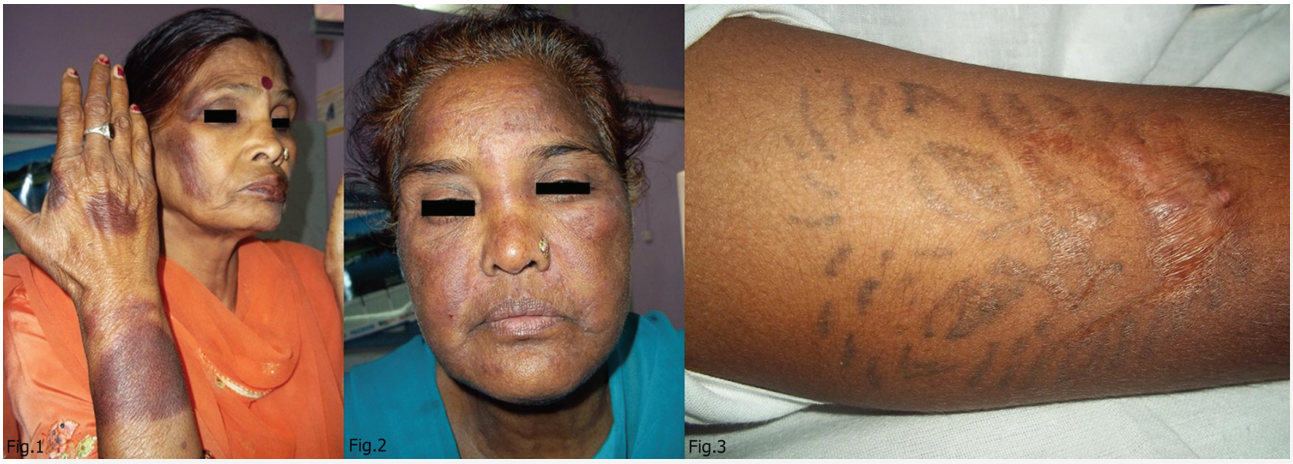

Figure 1. Severe allergic reaction to black henna in a 48 year old female.
Figure 2. Severe keloidal reaction to a black henna tattoo in a 20 year old male.
Figure 3. Keloidal reaction to black dye.

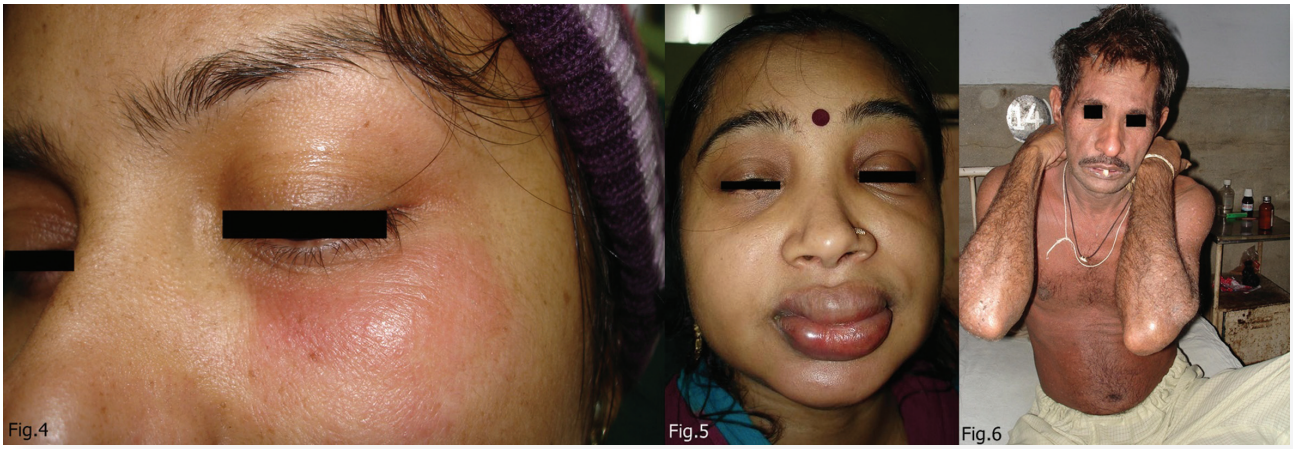

Figure 4. Erythematous scaly plaques in a 37 years old female.
Figure 5. Angioneurotic oedema in a 30 years old female after application of khadi black henna.
Figure 6. Erythrodermic reaction in a 53 years old man after applying hair dye.

Conclusion

The rate of adverse allergic skin reactions to hair dyes was higher than expected from patch test studies. Only by studying the clinical types of adverse reactions to hair dyes will it be possible to gather a complete epidemiological picture of the nature and extent of the problems related to hair dye ingredients.

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UNGUAL DYSCHROMIA

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Nil
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None

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Nails can has different color it may be called ungual dyschromia or chromonychia that means abnormalities in color of the substance.

The transparency of the nail it's important for dyschromia, the pigment may accumulate due to overproduction such as melanin, storage as copper, haemosiderin, drugs, or by surface deposition [1].

Ungual dyschromia may be endogenous and exogenous if the pigment is due to endogenous source the discoloration corresponds to the shape of the lunula (Fig. 1) and if it exogenous corresponds to the contour of the proximal nail fold (Fig. 2).

Dyschromia can affect one, several or twenty nails depends of the cause that may be congenital, dermatological, drug side effect, trauma, systemic diseases, miscellaneous, benign and malignant tumors, infectious diseases, others.

Nail dyschromia may be white, black, green brown, yellow, red, and blue, gray, purple and others, but the most common are white and black.

The white color is called leukonychia and the black discoloration is called melanonychia.

There are three types of leuconychia: true leukonychia, pseudoleuconychia and apparent leuconychia. True leukonychia, the nail plate involvement source is in the matrix, may be partial such as transverse (Fig. 3), punctate (Fig. 4), lineal (Fig. 5) or total, in pseudoleukonychia the matrix is not affected example white superficial onychomycosis (Fig. 6, 7) and apparent leukonychia is called also apparent leukopathia with involvement of the subungual tissue, subungual kyperkeratosis, (Fig. 8), onycholysis (Fig. 9, 10), apparent leukopathia such as Terry´s nail (Fig. 11) associated to cirrhosis, half & half nails with chronic renal failure (Fig. 12, 13), Muehrcke´s bands due to hypoproteinemia and cytostatics drugs (Fig. 14) and anemia. Melanonychia may be longitudinal, transverse, total can affect fingernails and feet within its causes have to melanonychia racial (Fig. 15), idiopathic Addison's disease (Fig. 16), drugs such as cytostatics (Fig. 17, 18), retinoids such melanonychia together with the onychomadesis, onycholysis and periungual pyogenic granulomas are the most common drug nail disease [2], puvaterapia, lichen planus, infections by bacteria, fungi, trauma frictional melanonychia (Fig. 19), carpal tunnel syndrome tumors such as basal cell carcinoma, squamous and melanoma can manifest as a longitudinal melanonychia which may be the first manifestation of the same [3] is very important to consider the A, B, C, D, E, F of injury.

The green nail can be caused by *Pseudomona* (Fig. 20) and Candida infections, the yellow color can be seen in the yellow nail syndrome (Fig. 21), onychomycosis (Fig. 22), dye shoes (Fig. 23), jaundice, cyanosis blue (Fig. 24) be related to hypoxia, argiria, the orange nail polish, the hair dyes (Fig. 25), coffee, smoking (Fig. 26), potassium permanganate, gentian violet (Fig. 27), nevi, racial, Laugier syndrome-Hunzinker-Baran, malnutrition, pregnancy, red for subungual nail hematoma (Fig. 28), splinter hemorrhages (Fig. 29), paint, red lunula (Fig. 30) is associated cardiopulmonary disorders, collagen diseases, malignancies hematologic, alopecia areata, psoriasis, trauma, idiopathic longitudinal view erytronychia Bowen's disease and other, red purpuric may be associated with drugs such as clofazimine, heparin, warfarin, capecitabine, puvaterapia, polycythemia and some glomus tumor vascular tumors, trauma (Fig. 31) [4,5]. Nails can have one, two or three color in the same nail and for different causes.

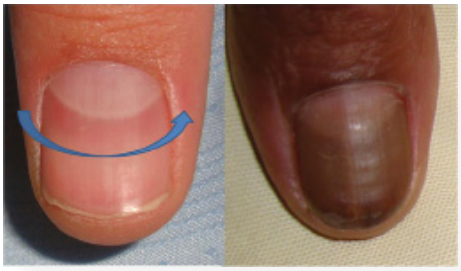

Figure 1. Endogenous cause of dyschromia, discoloration tends to follow the countor of the lunula.

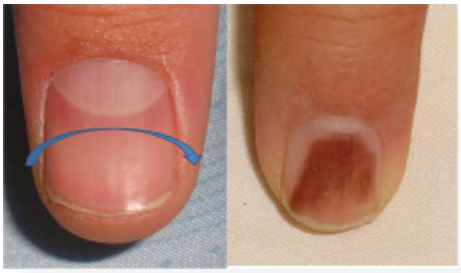

Figure 2. Exogenous cause of dyschromia, discoloration tends to follow the contour of the proximal nail fold.

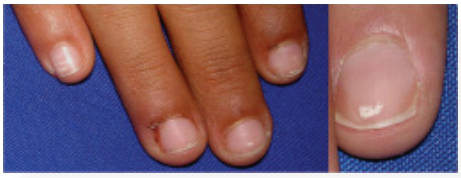

Figure 3. Leukonychia Transverse.

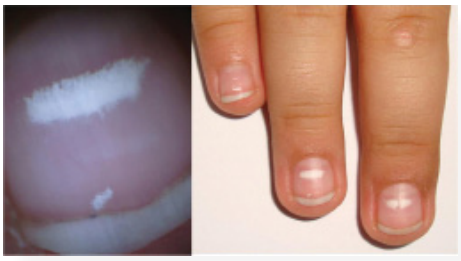

Figure 4. Leukonychia puntata.

Figure 5. Leukonychia lineal.

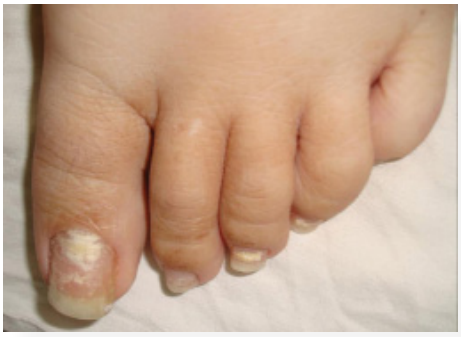

Figure 6. White superficial onychomycosis.

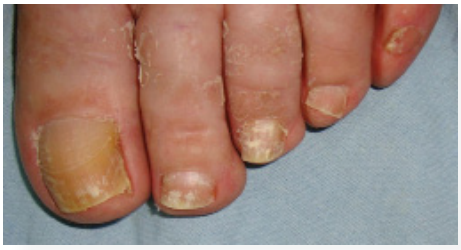

Figure 7. White superficial onychomycosis.

Figure 8. Subungual hyperkeratosis.

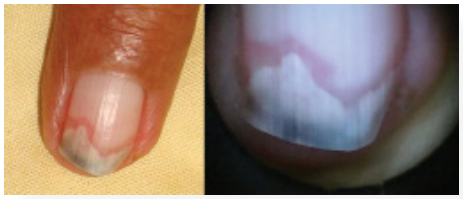

Figure 9. Traumatic onycholysis.

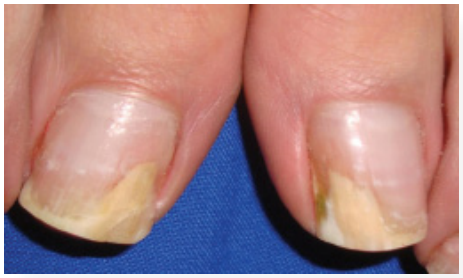

Figure 10. Traumatic onycholysis.

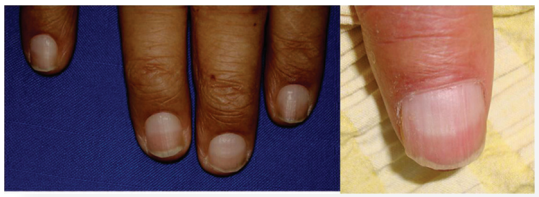

Figure 11. Nails half and half associated to chronic renal failure.

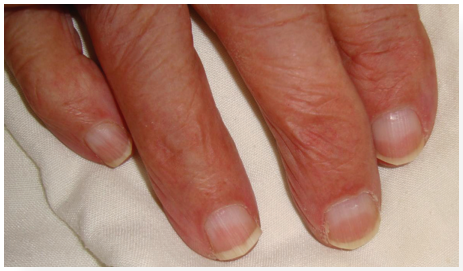

Figure 12. Nails half and half associated to chronic renal failure.

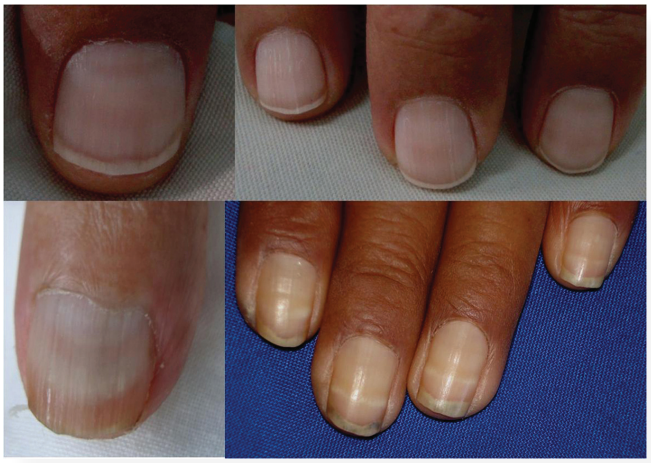

Figure 13. Muehrcke's bands due to hypoproteinemia and cytostatic drugs.

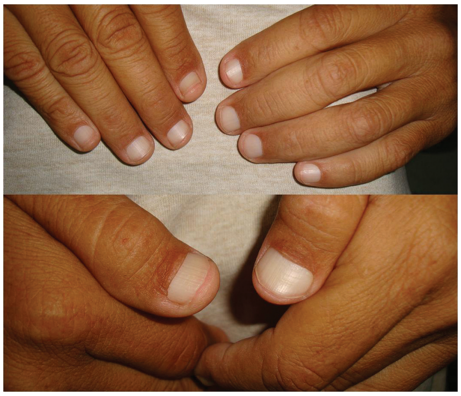

Figure 14. Apparent leukopatia due to anemia.

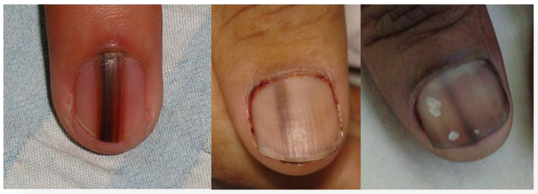

Figure 15. Racial melanonychia.

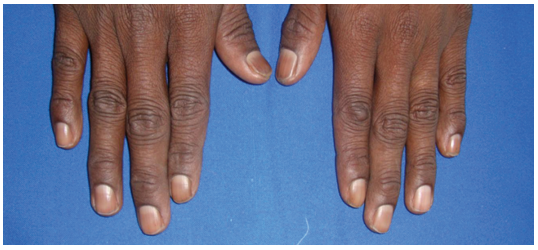

Figure 16. Melanonychia due to Addison´s disease.

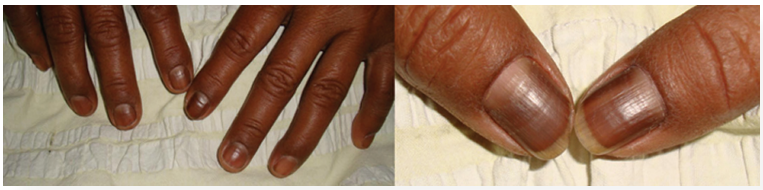

Figure 17. Melanonychia due to cytostatics drugs.

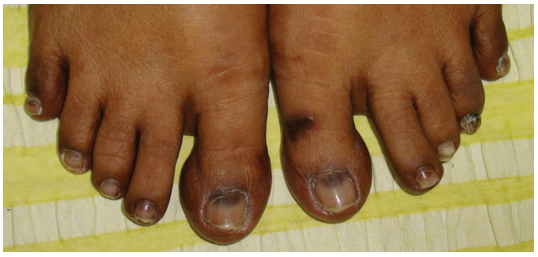

Figure 18. Melanonychia due to cytostatics drugs.

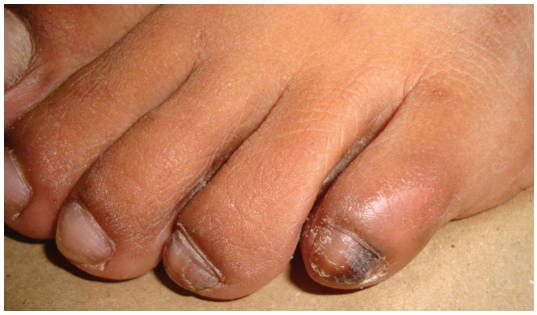

Figure 19. Melanonychia frictional.

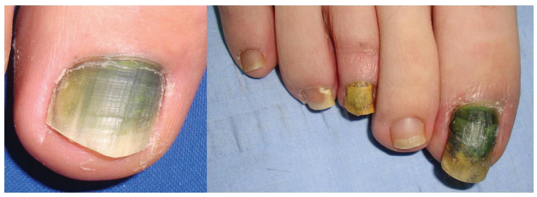

Figure 20. Green color due to *pseudomona* infection.

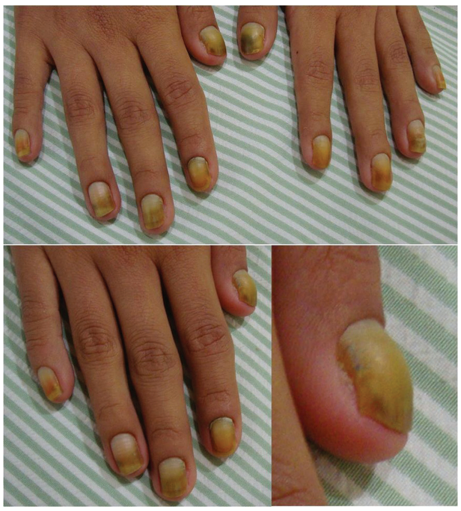

Figure 21. Yellow nail syndrome.

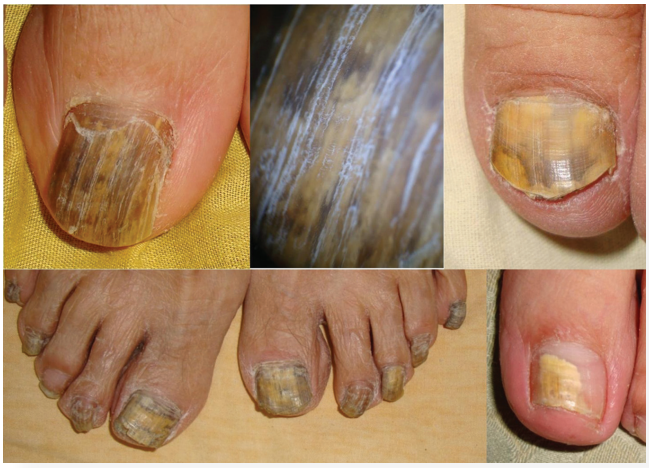

Figure 22. Onychomycosis.

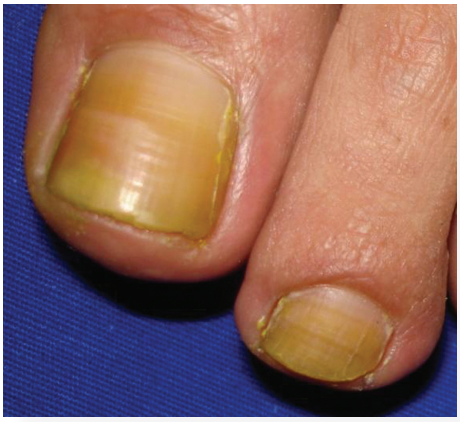

Figure 23. Yellow nails due to shoe dye.

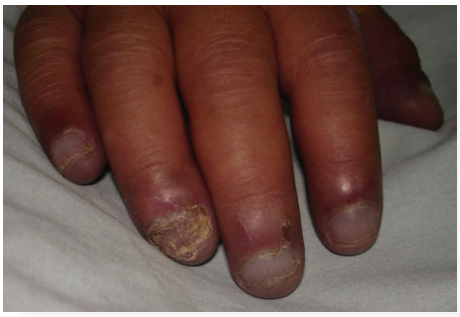

Figure 24. Acrocianosis due to sepsis.

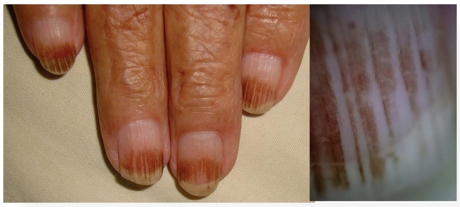

Figure 25. Dye hair.

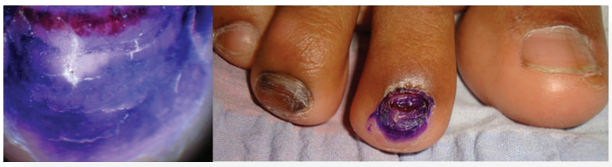

Figure 26. Dyschormia gentiant violet dye.

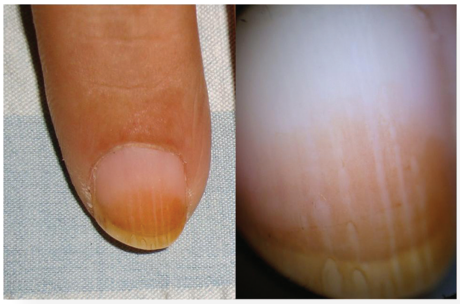

Figure 27. Dyschromia due to tabaco.

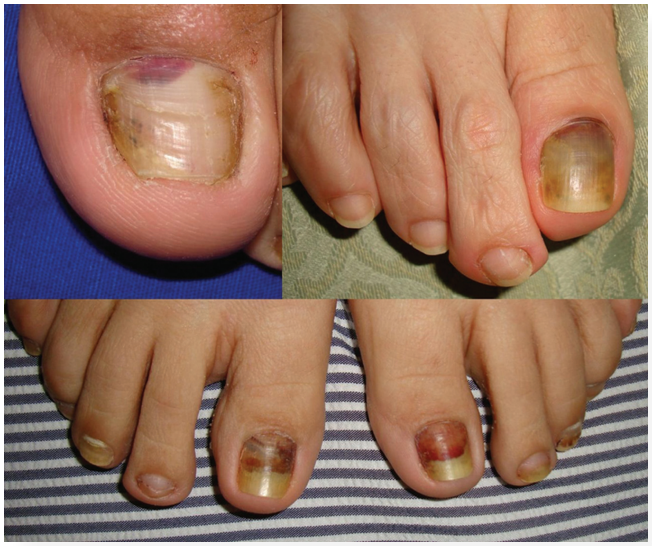

Figure 28. Red color due to hematoma.

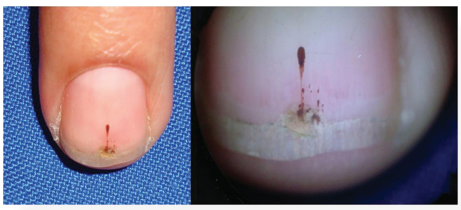

Figure 29. Trauma.

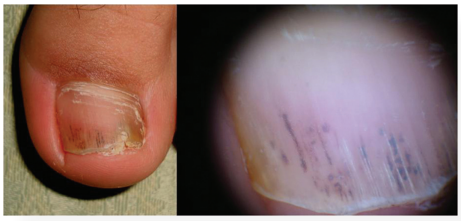

Figure 30. Splinter hemorraghe.

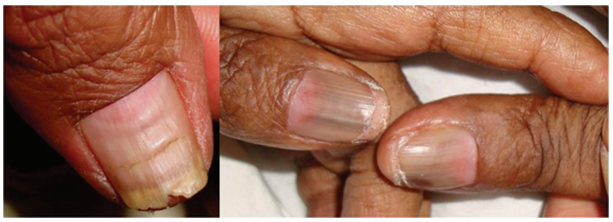

Figure 31. Red lunula.

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PEDICULOSIS CAPITIS

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Pediculosis capitis is an infection of the hair and skin caused by the Pediculus humanus capitis [1].
Head-lice infestation is widely endemic, especially in children, are generally spread through direct head-to-head contact with an infected person [2].
Females get head lice twice more often than males and infestation in persons of Afro-Caribbean or other black descent is rare because of hair consistency [3].
The head lice infestation is Pediculus capitis scalp. 7-10 female eggs produced per day, the maximum number of eggs produced by female throughout its cycle is 110-140; this adheres their host eggs to hair by a water insoluble substance and glue-like. The live eggs (with embryo) are gray gelatinous and are located close to the scalp at 3-4 mm [4].
Scalp pruritus is the most common and characteristic manifestation of the head louse infection localized in retroauricular region, occiput and nape. Secondary bacterial infection (impetigo) may occur as a result of scratching with painful regional lymphadenitis [5].
The empty egg cases or nits can be identified, adult lice and nymphs may be seen in heavy infection [6].
The diagnosed is done by the presence of lice or eggs in the hair, trough using a magnifying glass or running a comb through the child's hair, dermatoscope and microscope [7].
There are different types of topical treatments available: chemical insecticides such as malathion or pyrethrins, physical acting products such as silicones (dimethicone) and so-called natural oils and essences type [8]. Ivermectin It should be administered at 200 mg / kg, single dose. Some studies recommend repeat the dose at 7, 10 or 15 days [9].

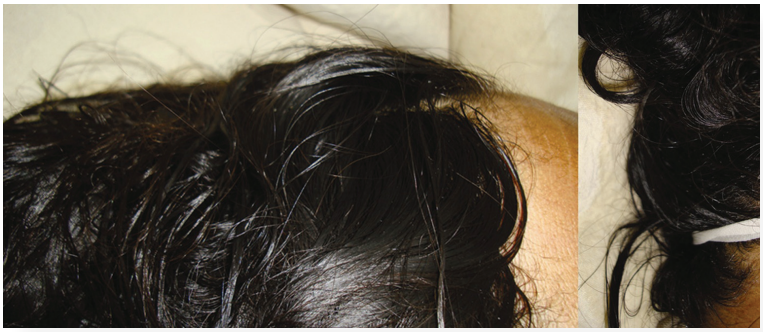
Case 1

Female patient 40 years old hospitalized due to cholecystectomy, during her clinical examination head louse was seen, dermatological examination showed the presence of lice and nits (Fig. 1a, b). Rest of the physical exam was normal.

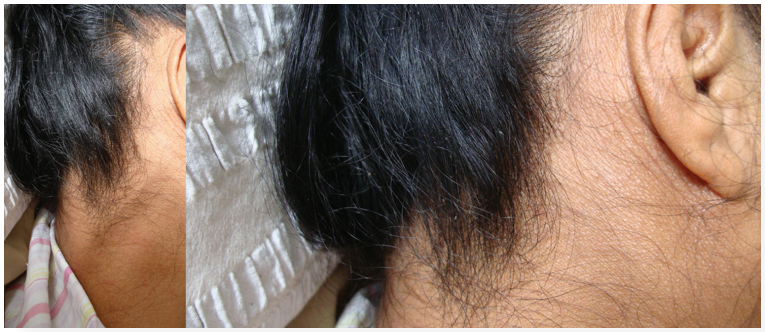
Case 2

Female patient 50 years old hospitalized due to appendectomy, during her clinical examination head louse was seen, dermatological examination showed the presen ce of nits (Fig. 2a, b) and lice (Fig. 3 a, b), histopathology showed the morphology of an adult louse, head comprising an antenna and eye traces (Fig. 4) is also observed part of the chest showing fragments of the legs and abdomen of seven segments where you can see remains of the spiracles where respiration occurs (Fig. 5), at the bottom remains anus and genitalia (Fig. 6). Rest of the physical exam was normal.

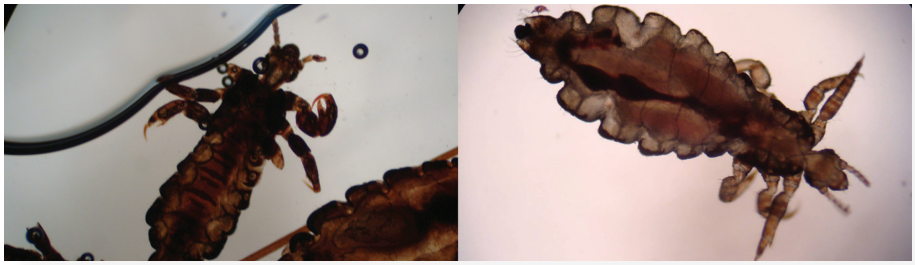
Both patient received ivermectin 200 mg/kg one single dose and cured of their pediculosis capitis.



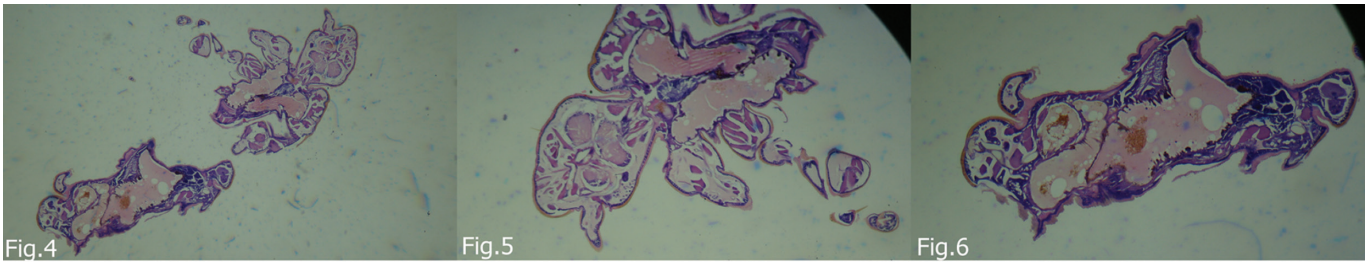
Figures 1a, b. Nits on hair in female patients (case 1).



Figures 2a, b. Nits on hair in female patients (case 2).



Figures 3a. Microscopic views of the lice. b. close up of the louse.



Figures 4. Histopathology showed the morphology of an adult louse, head comprising an antenna and eye traces.
Figures 5. It is also observed part of the chest showing fragments of the legs and abdomen of seven segments where you can see remains of the spiracles where respiration occurs.
Figures 6. At the bottom was observed remains anus and genitalia.

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RED LUNULA

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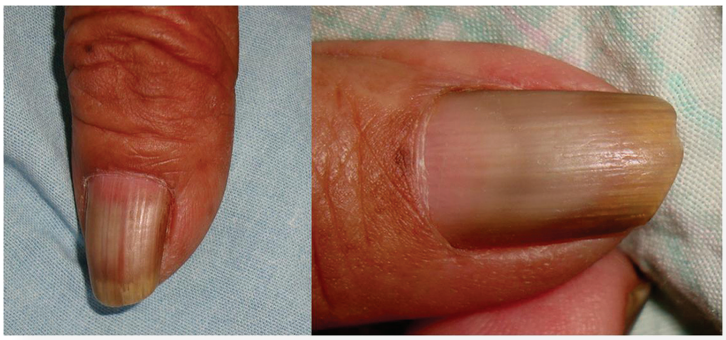
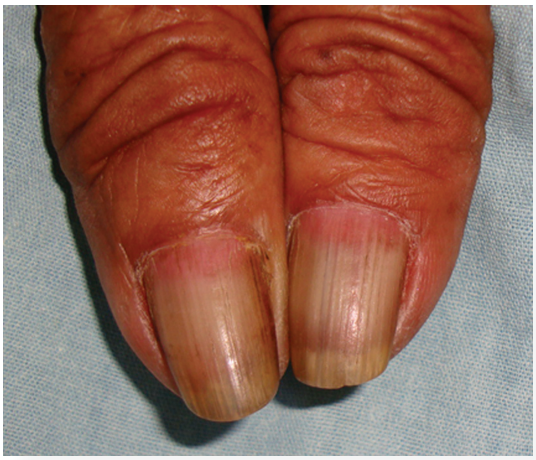
Case 1
Male patient, 80 years old hospitalized due to tumor on his left neck to diagnosis, his nails were seen by chance when he was waiting for his lung X ray examination. He had not noticed anything on his fingernails, we observed red lunula on both thumb nails (Fig. 1, 2). Personal history: controlled diabetes mellitus and high blood pressure

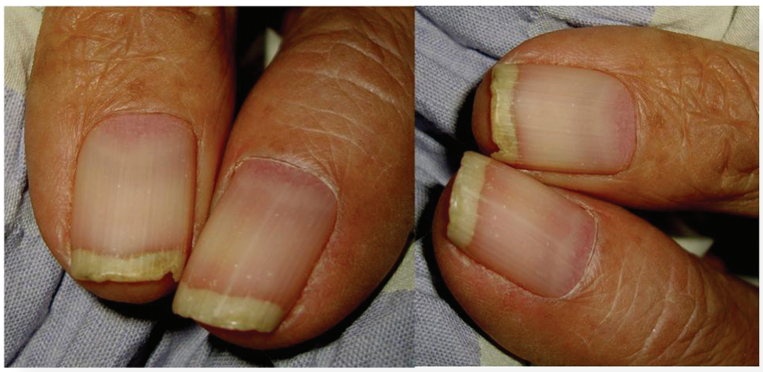
Case 2
Male patient, 65 years old hospitalized due to urinary tract infection , his nails also was seen by chance when he was waiting for his clinical evaluation by infectologist. He had not noticed the change in color of his fingernails. Clinical examination showed red color at the lunulas of both thumbnails (Fig.3). Personal history non contributory. The red lunula is an uncommon nail dyschromia; all the cases we have seen until now have been by chance.



Figures 1. Panoramic view of red lunula at both thumbs.



Figures 2. Close Up of the onychophaty lesions



Figures 3. Red lunula on thumbnails .

The lunula is the white half-moon–shaped area located at the base of fingernails and toenails; it is the only visible part of the nail matrix, which is responsible of producing keratin to form the nail plate. Anomalies of shape, form or color in lunula may be an indication of injury or serious disease, as a deficiency or infection [1,2].

Color anomalies, known as lunula dyschromias, can be confluent or spotted, or can be characterized by longitudinal colored bands. Colors with a red or blue tinge can be indicative of heart or lung disease, rheumatoid arthritis or hypertension. Dark hues can indicate conditions such as infection or heavy metal intoxication. More subtle tones may be a sign of conditions like respiratory illness, vitamin deficiency or anemia [2].

Red lunula is associated with rheumatoid arthritis, systemic lupus erythematosus (20% of the patients with SLE have been reported to have this abnormality) [3], cardiac failure, hepatic cirrhosis, lymphogranuloma venereum, pulmonary disease, carbon monoxide poisoning, among others [4]. It may be idiopathic, and it also has been reported in patients with dermatological diseases, such as chronic urticaria, psoriasis vulgaris, lichen sclerosis and atrophic or alopecia areata [1,4]. It can affect all the nails or only part of them [5].

Red lunula can be classified into three kinds: a complete form- in which the all lunula is erythematous - an incomplete form- where the proximal zone is red and in the distal zone appears a white arrow band, proximal to the pink nail bed- and the third one, a mottled form that can be observed in rheumatoid arthritis [5]. It mainly involves the thumbs where the lunula is usually clearly visible [5,6].

The pathogenesis of red lunula remains undetermined [4,6]. However it has been described as a possible result of the increment of arteriolar blood flow, a vasodilatory capacitance phenomenon, or changes in the optical properties of the overlying nail, so that normal blood vessels become more apparent [4].

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SPLINTER *HEMORRHAGE* AS A SIDE EFFECT OF CIPROFLOXACIN

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Sir

A 40-year-old man presented painless red lesions under his fingernails that appeared after ciprofloxacin treatment . He was complaining about fever, abdominal pain and urgency with urination. Urine sample obtained and bacteriologic examination performed. According to urinalysis and culture results, patient evaluated as urinary tract infection and oral ciprofloxacin was initiated. He had a history of kidney stone. One week later on physical examination, at an outpatient clinic control linear reddish-brown streaks were noted on both fingernails (Fig.1). The patient had no history of trauma to his nails and had no underlying systemic disease in his past medical history. He was not taking any medication except ciprofloxacin. His personal and family histories were unremarkable. Two weeks after the initial presentation, both fingernails showed signs of resolution without treatment.

Splinter hemorrhages are nonblanchable, 1- to 3 mm, red to reddish-brown, longitudinal hemorrhages appearing under the nail plate [1]. They occur in the dermis after rupture of the capillaries that follow the linear configuration of the epidermal-dermal ridges [2]. The blood attaches to the nail plate and moves distally as the nail grows. Splinter hemorrhages can be caused by environmental factors, skin disorders, systemic diseases, and medication use. However, nail trauma (e.g., from sports, housework,) is the most common cause, accounting for 20 percent of cases [1-4]. Splinter hemorrhages could be associated with nail psoriasis, but can also occur with eczema, vasculitis, or onychomycosis [1]. Systemic disease may be the cause if the splinter hemorrhages appear in several nails, are located in the proximal portion of the nail plate, or are painful [1,6]. Petechiae and splinter hemorrhages are classic lesions of subacute endocarditis, especially when accompanied by fever, Roth spots, Osler nodes, Janeway lesions, or a murmur. Splinter hemorrhages can occur with systemic lupus erythematosus, along with other nail changes such as periungual telangiectasias, hyperkeratotic ragged cuticles, onycholysis, and red lunula [8].

Splinter hemorrhages can be an adverse effect of medications that impair blood vessels in the nail bed, although this is uncommon. These lesions are usually dose-related, involve several or all nails, and resolve after the medication is discontinued [8]. In the present case all lesions resolved day by day after the cession of ciprofloxacin treatment. Medications that may lead to splinter hemorrhages include antithrombotics and anticoagulants, such as aspirin and warfarin; cancer chemotherapeutic agents, such as taxanes; tetracycline; and ganciclovir [9-11]. idiopathic atraumatic splinter hemorrhages can occur in healthy individuals [1].

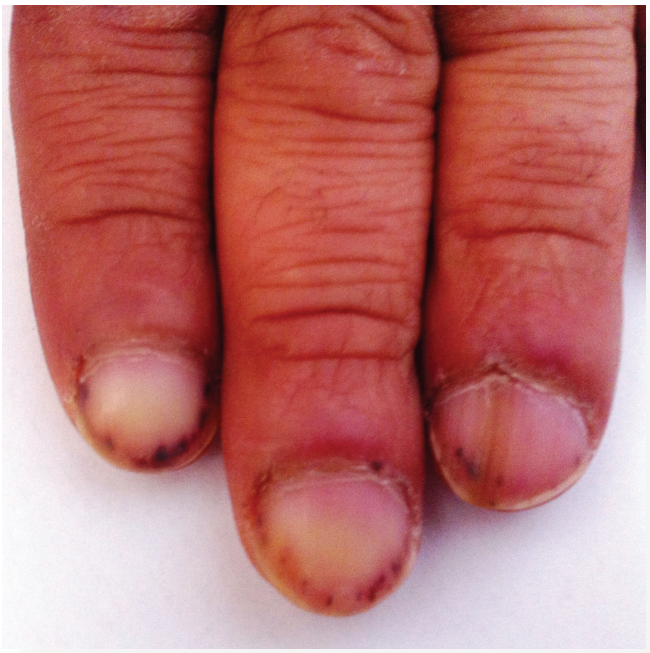

Figure 1. Splinter hemorrhages can be seen under each three fingernails.

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EPONYMS LINKED TO VACCINES AND ITS REACTIONS

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In this manuscript, We shall look to some eponyms in the medical literature from the vaccination window.

The impact of vaccination on the health of the world's peoples is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth [1].

Vaccination has controlled the following 14 major diseases, at least in parts of the world: smallpox, diphtheria, tetanus, yellow fever, pertussis, Haemophilus influenzae type b disease, poliomyelitis, measles, mumps, rubella, typhoid, rabies, rotavirus, and hepatitis B [1].

The most famous vaccine is BCG, which is a live, attenuated organism used to provide protective immunity against tuberculosis. It is a widely accepted immunotherapeutic modality of superficial and in situ transitional cell carcinoma of urinary bladder. BCG immunotherapy has also been described for the treatment of malignant melanoma [2]. It has been used also to treat viral warts.

A large number of local and generalized reactions have been reported after BCG vaccination. Examples are erythema multiforme, extensive ulceration and lupus vulgaris [2].

In Table I [3-26], We listed selected eponyms linked to vaccines and the reported reactions associated with its use. Neverthless, We want to stress that this table is only to highlight on some eponyms encountered in the literature of vaccinations and not inclusive for the all reported reactions associated with vaccinations.

Eponyms linked to vaccines and its reactions	Remarks
BCG [3-5]	Bacillus Calmette–Guérin (Historically Vaccin Bilié de Calmette et Guérin commonly referred as Bacille de Calmette et Guérin or BCG) is a vaccine against tuberculosis that is prepared from a strain of the attenuated live bovine tuberculosis bacillus, Mycobacterium bovis. It is named for, Léon Charles Albert Calmette (1863-1933), (Fig. 1), who was a French physician, bacteriologist and immunologist and Jean-Marie Camille Guérin (1872–1961), (Fig. 2), who was a French veterinarian, bacteriologist and immunologist.

Figure 1. Léon Charles Albert Calmette (1863-1933).

Figure 2. Jean-Marie Camille Guérin (1872-1961).

Table I. Eponyms linked to vaccines and its reactions

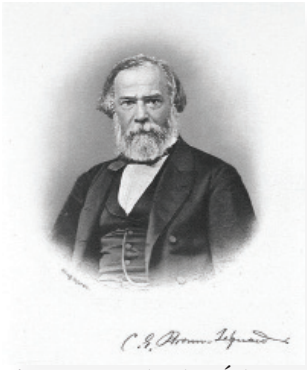


Figure 3. Charles-Édouard Brown-Séquard (1817-1896).

Figure 4. Charlotte Dravet.

Figure 5. Jean Baptiste Octave Landry de Thézillat (1826-1865).

Eponyms linked to vaccines and its reactions	Remarks
Brown-Séquard syndrome [6,7]	Also known as Brown-Séquard's hemiplegia and Brown-Séquard's paralysis, is a loss of sensation and motor function that is caused by the lateral hemisection of the spinal cord. It was first described in 1850 by the famed British / Mauritian neurologist Charles-Édouard Brown--Séquard (1817–1896), (Fig. 3), who studied the anatomy and physiology of the spinal cord. He described this injury after observing spinal cord trauma happen to farmers while cutting sugar cane in Mauritius. Transverse myelitis with Brown-Séquard syndrome following a prophylactic influenza vaccination has been reported.
Dravet syndrome [8]	Also known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a rare and catastrophic form of intractable epilepsy that begins in infancy. Vaccination might trigger earlier onset of Dravet syndrome in children who, because of an SCN1A mutation, are destined to develop the disease. Dravet syndrome has been found recently as an important underlying condition in cases of alleged vaccine encephalopathy after pertussis vaccination, where vaccination seemed to have precipitated the occurrence of the disease without modifying the long-term course. Dravet syndrome was first described by French physician, Dr. Charlotte Dravet, (Fig. 4), in 1978.
Evans syndrome [9]	Evans syndrome is an autoimmune disease in which an individual's antibodies attack their own red blood cells and platelets. The syndrome was first described in 1951 by R. S. Evans and colleagues. It has been reported to be occur after vaccination.
Gianotti-Crosti syndrome [10]	Also known as papular acrodermatitis of childhood. Documented to follow several vaccines. It is named for Ferdinando Gianotti (1920-1984),who was an Italian physician and Agostino Crosti Agostino Crosti (1896-1988), who was an Italian dermatologist.
Guillain-Barré syndrome [11]	Guillain–Barré syndrome (GBS) sometimes Landry's paralysis or Guillain–Barré–Strohl syndrome, is an acute polyneuropathy, a disorder affecting the peripheral nervous system. The disease is usually triggered by an infection but reported to follow vaccination. The French physician Jean Landry (1826-1865), (Fig. 5), first described the disorder in 1859. In 1916, Georges Guillain (1876-1961), (Fig. 6), who was a French neurologist and Jean Alexandre Barré (1880-1967), (Fig. 7), who was a French neurologist, and André Strohl André Strohl (1887-1977), (Fig. 8), who was a French physiologist diagnosed two soldiers with the illness and described the key diagnostic abnormality of increased spinal-fluid protein production, but normal cell count. Canadian-born neurologist, C. Miller Fisher , described the variant that bears his name in 1956. Charles Miller Fisher, usually known as C. Miller Fisher (1913- 2012), (Fig. 9), was a pioneering neurologist.
Henoch-Schönlein purpura [12,13]	Also known as, Schönlein–Henoch purpura. It is named for,Eduard Heinrich Henoch (1820–1910), (Fig.10), a German pediatrician, and his teacher Johann Lukas Schönlein (1793–1864), (Fig. 11), who described it in the 1860s. This type of vasculitis has been reported to follow vaccination.

Table I. Eponyms linked to vaccines and its reactions (continued)

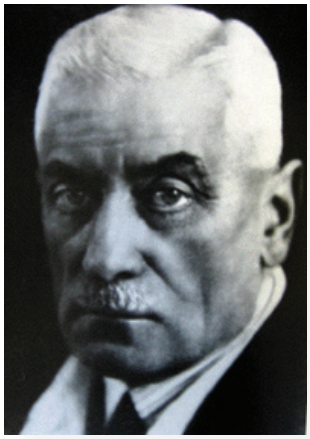


Figure 6. Georges Charles Guillain (1876-1961).

Figure 7. Jean Alexandre Barré (1880-1967).

Figure 8. André Strohl (1887-1977).

Figure 9. C. Miller Fisher (1913-2012).

Figure 10. Eduard Heinrich Henoch (1820-1910).

Figure 11. Johann Lukas Schönlein (1793-1864).

Eponyms linked to vaccines and its reactions	Remarks
Hughes syndrome [14]	It is another name for antiphospholipid syndrome, a pro-thrombotic condition was described in 1983 which was characterised by the presence of circulating antiphospholipid antibodies, as well as peripheral thrombosis, a tendency to internal organ involvement, repeated miscarriage, and, occasionally, thrombocytopenia. Named after, Graham Robert Vivian Hughes, (Fig. 12), an English rheumatologist. It is reported to follow vaccination.
Jenner's cowpox vaccine [15,16]	Edward Jenner (1749-1823), (Fig. 13), an English doctor, was the first to study and report on the effects of the use of cowpox vaccination to prevent smallpox.
Lambert-Eaton myasthenic syndrome (LEMS) [17,18]	Also known as, Lambert-Eaton-Rooke syndrome. It is a rare autoimmune disorder that is characterised by muscle weakness of the limbs. Around 60% of those with LEMS have an underlying malignancy. Lambert, Eaton and Rooke at the Mayo Clinic were the first physicians to substantially describe the clinical and electrophysiological findings of the disease in 1956. Lealdes (Lee) McKendree Eaton (1905-1958), an american neurologist, Edward Howard Lambert (1915-2003), (Fig. 14), an american neurophysiologist, and Edward Douglas Rooke (1912-2001), a canadian physician.
Marjolin's ulcer [19]	The term „Marjolin's ulcer" has been generally accepted to refer to a long-term malignant complication of the scars resulting from burns. However, vaccination, snake bites, osteomyelitis, pilonidal abscesses, pressure sores, and venous stasis may also induce this tumor. It is named after Jean-Nicolas Marjolin (1780 –1850), (Fig. 15), who was a French surgeon and pathologist. It was pointed out that Marjolin did not describe the condition he is eponymously credited with, but that the false ascription to him arose over time.

Table I. Eponyms linked to vaccines and its reactions (continued)

Figure 12. Graham Robert Vivian Hughes.

Figure 13. Edward Jenner (1749-1823). A courtesy of National library of Medicine.

Figure 14. Edward Howard Lambert (1915-2003).

Figure 15. Jean-Nicolas Marjolin (1780-1850).

Figure 16. Yehuda Shoenfeld, M.D, FRCP(Hon).

Eponyms linked to vaccines and its reactions	Remarks
Nicolau syndrome [20]	Nicolau syndrome-also known as Embolia Cutis Medicamentosa-is a rare complication of intramuscular and subcutaneous drug injections manifesting as necrosis of skin and the underlying tissue s. It may follow vaccination. It was first described by Freudenthal in 1924 and Nicolau in 1925 in patients treated for syphilis withbismuth salts.
Shoenfeld syndrome [21,22]	In the 1990s the term „functional somatic syndromes" was applied to several syndromes, including Sick building syndrome (SBS) (a term coined for a set of clinically recognizable symptoms and ailments without a clear cause reported by occupants of a building), multiple chemical sensitivity, repetition stress injury, the side effects of silicone breast implants, the Gulf War syndrome (GWS), chronic fatigue syndrome, the irritable bowel syndrome, and fibromyalgia. Recently, Shoenfeld and Agmon-Levin suggested that four conditions-siliconosis, macrophagic myofascitis, the GWS, and post-vaccination phenomena-which share clinical and pathogenic resemblances, may be included under a common syndrome entitled the „autoimmune (auto-inflammatory) syndrome induced by adjuvants"(ASIA), also known as Shoenfeld's syndrome. ASIA may also be precipitated by silicon in silicone-filled breast implants (Silicone implant incompatibility syndrome; SIIS). Shoenfeld's syndrome is named for Yehuda Shoenfeld, M.D., FRCP (Hon). (Fig. 16), the head of Zbludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center at Tel-Hashomer, who and his team elaborated on the above medical conditions.
Stevens-Johnson syndrome [23]	It is a hypersensitivity reaction that affects the skin and the mucous membranes. The main known cause is certain medications, followed by infections and, rarely, cancers. It may also occur after vaccination. It is named for Albert Mason Stevens (1884-1945) and Frank Chambliss Johnson (1894-1934), american pediatricians who jointly published a description of the disorder in the American Journal of Diseases of Children in 1922.

Table I. Eponyms linked to vaccines and its reactions (continued)

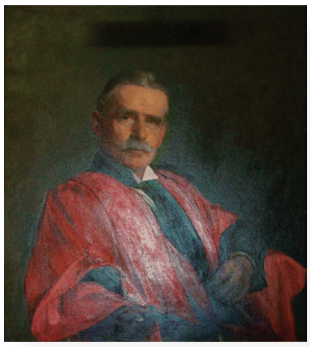
Eponyms linked to vaccines and its reactions	Remarks
Still's disease [24-27]	Adult-onset Still's disease may be precipitated or relapsed after vaccination for hepatitis. In one study no long-term adverse events were reported after influenza vaccination in juvenile idiopathic arthritis (JIA) and control group. Thirty-five percent of children with JIA experienced flare of the disease after vaccination. Protective antibodies against at least 2 vaccine viruses 6 months after vaccination were detected in all patients. Adult-onset Still's disease is a systemic inflammatory disease. The classic presentation is the triad of persistent high spiking fever, joint pain and a distinctive salmon-colored rash. Still's disease is named after English physician Sir George Frederic Still (1861-1941), (Fig. 17).  **Figure 17. The original legend read as „Portrait of George Frederick Still (from the painting by Gerald Kelly, RA), reproduced with permission from Corporate and Legal Services, Kings College Hospital NHS Trust'', from reference number 27.**

Table I. Eponyms linked to vaccines and its reactions (continued)

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EPONYMS IN THE DERMATOLOGY LITERATURE LINKED TO „BODIES", SEEN IN SKIN BIOPSIES

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In dermatology practice, it is very common to hear about „Bodies'', which refer to a pthological structure with a particular features.

Most of them are large and can be seen by light microscopy, but there are few very tiny bodies which can only be seen by electron microscopy.

Examples for the latter are comma-shaped body, and the worm-shaped body, seen in histiocytoses like benign cephalic histiocytosis (however; they are not specific), and zebra body, seen in mucopolysaccharidoses.

Some of the bodies were seen in one disease and they are characteristic for one disease whereas others can be seen in multiple conditions.

As an example for the former group, is caterpillar body, which is pale amorphous pink linear structures in the epidermis of porphyria cutanea tarda. Another example is the papillary mesenchymal body which is structure thought to be an abortive attempt of fibroblasts to form mesenchyme necessary for hair induction, reminiscent of early hair germ. They are seen in trichoblastoma and trichoepithelioma.

Examples for the bodies which can be seen in multiple conditions include ,asteroid body for example might be seen in several conditions like sarcoidosis and berylliosis.

Also, psammoma body is a concentric laminated, calcified bodies seen in papillary thyroid carcinoma, benign nevi, meningiomas, and other conditions.

Most of the „bodies'' are known by a single term. As an exception medlar bodies which are seen in chromoblastomycosis are also called sclerotic bodies and copper penny bodies.

Eponyms are very common in the nomenclature of „bodies''. In Table I [1-21], we are highlighting on Eponyms in the dermatology literature linked to „Bodies'', seen in skin biopsies.

Eponyms in the dermatology literature linked to „Bodies", seen in skin biopsies	Remarks
Birbeck Granules [1]	These are Tennis-racquet-shaped cytoplasmic bodies seen by electron microscopy in Langerhans cells. They were discovered by Michael Stanley Clive Birbeck (1925-2005), a British scientist and electron microscopist. Langerhans cells are dendritic cells (antigen-presenting immune cells) of the skin and mucosa. It is named for Paul Langerhans (1847-1888), who was a German pathologist.
Civatte Bodies [2]	These might be referred as colloid Bodies. However, some references refer to colloid Bodies as apoptotic cell remnants in papillary dermis, whereas Civatte bodies as apoptotic cell remnants in epidermis. They appeared as an eosinophilic hyaline ovoid structures. They are usually seen in lichen planus and lupus erythematosus. They can also be found in several dermatoses such as erythema multiforme, bullous pemphigoid and diseases with suprabasal clefts. Achille Civatte (1877-1956), (Fig. 1), was a French physician. He was the director of the Musée d'Histologie de Saint-Louis.

Table I. Selected Eponyms in the dermatology literature linked to „Bodies'', seen in skin biopsies.

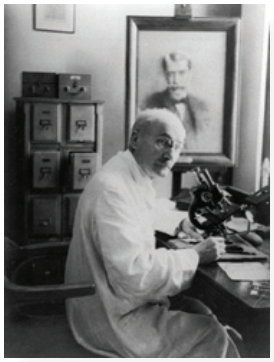

Figure 1. Achille Civatte (1877-1956).

Figure 2. Edmund Vincent Cowdry (1888-1975).

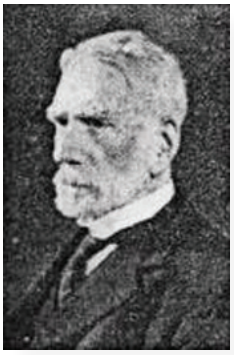

Figure 3. William Russell (1852-1940).

Eponyms in the dermatology literature linked to „Bodies", seen in skin biopsies	Remarks
Cowdry A and B Bodies [3]	Cowdry A Body (Lipschutz Body), is intranuclear eosinophilic globules seen in herpes infection. Cowdry B Body is intranuclear inclusions seen in adenovirus and poliovirus infection. They are named for, Edmund Vincent Cowdry (1888-1975), (Fig. 2), who was Canadian-American biologist. An interesting page about him in the internet, can be accessed at; http://beckerexhibits.wustl.edu/mig/bios/cowdry.html
Donovan Bodies [4]	Donovan bodies are rod-shaped, oval organisms that can be seen in the cytoplasm of mononuclear phagocytes or histiocytes in tissue samples from patients with granuloma inguinale. They were discovered by Charles Donovan (1863-1951). In 1905 he identified the microorganism responsible for the disease granuloma inguinale. This also bears his name Donovania granulomatosis. Donovan was born in Calcutta. At the age of thirteen he was sent to Cork City to live with his grandfather to advance his secondary and university education.
Dutcher Bodies [5]	Dutcher bodies are PAS-positive, diastase-resistant nuclear pseudoinclusions of eosinophilic cytoplasm found in plasma cells described by Dutcher and Fahey in Waldenstrom macroglobulinemia. Dutcher bodies are a feature of clinically indolent, mucosa-associated lymphoid tissue (MALT) lymphomas. There are no essential differences between Dutcher bodies, single or multiple Russell bodies, and the inclusions of Mott cells. They are all aspects of the same phenomenon, representing spherical cytoplasmic inclusions that are either clearly within the cytoplasm or are overlying the nucleus or invaginated into it. Russell bodies, is named after William Russell (1852-1940), (Fig. 3), Scottish pathologist and physician.Mott cell is named after Mott, who described it in 1905. Dutcher bodies may rarely occur in a benign reactive condition, such as synovitis. While Dutcher bodies may be a clue to the presence of low-grade lymphoma, they are not a definitive feature, particularly in unusual contexts.
Guarnieri Bodies [6]	These are eosinophilic cytoplasmic inclusions seen in smallpox. They are named after the Italian physician Giuseppe Guarnieri (1856-1918).
Henderson-Paterson Bodies [7]	These are large intracytoplasmic inclusion bodies seen in molluscum contagiosum. They were reported by Henderson and Paterson, in 1841.Also, called molluscum bodies.
Kamino Bodies [8]	Kamino bodies named after contemporary American dermatopathologist, Hideko Kamino, (Fig. 4). They are dull pink areas of trapped basement membrane material within the epidermis seen in Spitz nevi.
Lafora bodies [9]	These are inclusion bodies within neurons and the cells of the heart, liver, muscle, and skin, seen in Lafora disease. Lafora disease also called Lafora progressive myoclonic epilepsy is a fatal autosomal recessive disorder. The disease is named after Gonzalo Rodriguez Lafora (1886–1971), (Fig. 5), a Spanish neuropathologist who first recognized small inclusion bodies in Lafora patients in 1911.

Table I. Selected Eponyms in the dermatology literature linked to „Bodies", seen in skin biopsies (continued).

Figure 4. Hideko Kamino.

Figure 5. Gonzalo Rodriguez Lafora (1886-1971).

Figure 6. William Boog Leishman (1865-1926).
A courtesay of National Library of Medicine.

Eponyms in the dermatology literature linked to „Bodies", seen in skin biopsies	Remarks
Leishman-Donovan Bodies [4]	Intracytoplasmic, nonflagellated parasites seen in leishmaniasis. Leishmaniasis is a zoonotic infection caused by protozoa that belong to the genus Leishmania. The disease is named after Leishman, who first described it in London in May 1903. Lieutenant-General Sir William Boog Leishman (1865-1926), (Fig. 6), was a Scottish pathologist and British Army medical officer. In 1901, while examining pathologic specimens of a spleen from a patient who had died of kala azar he observed oval bodies and published his account of them in 1903. Captain Charles Donovan confirmed the finding of what became known as Leishman-Donovan bodies in smears taken from patients in Madras in southern India.
Lipschutz Bodies (Cowdry A Body) [10]	Eosinophilic nuclear inclusions in epithelial or neuronal cells. Most often seen in herpes simplex or zoster infections. It is named after Benjamin Lipschütz (1878-1931), who was an Austrian dermatologist and microbiologist.
Michaelis-Gutman Bodies [11]	Concentric, laminated, calcified bodies within and external to the cells seen in Malakoplakia, an inflammatory condition that affects the genitourinary tract. Leonor Michaelis (1875-1949), (Fig. 7), was a German-American biochemist. Carl Gutmann, was a German physician, born 1872.
Negri Bodies [12]	Cytoplasmic Inclusion bodies found in the purkinje cells of the brain in cases of rabies. It can be seen in the skin.It is named for, Adelchi Negri (1876-1912), (Fig. 8), who was an Italian pathologist, and microbiologist. His teacher was, the Nobel Prize winning Camillo Golgi (1843-1926).

Table I. Selected Eponyms in the dermatology literature linked to „Bodies'', seen in skin biopsies (continued).

Figure 7. Leonor Michaelis (1875-1949).

Figure 8. Adelchi Negri (1876-1912).

Figure 9. George Odland (1922-1997).

Figure 10. Jörgen Nilsen Schaumann (1879-1953).
A courtesy of the Hagströmer Medico - Historical Library, Karolinska Institutet, Stockholm, Sweden.

Figure 11. Jose Juan Verocay (1876-1927).

Eponyms in the dermatology literature linked to „Bodies", seen in skin biopsies	Remarks
Odland bodies [13]	This is another name for lamellar granules (otherwise known as membrane-coating granules (MCGs), lamellar bodies, or keratinosomes). They are secretory organelles found in type II pneumocytes and keratinocytes. They are oblong structures, appearing about 300-400 nm in width and 100-150 nm in length in transmission electron microscopy images. Lamellar granules fuse with the cell membrane and release their contents into the extracellular space. Named after, George Odland (1922-1997), (Fig. 9), who was a world expert in skin research and longtime head of the dermatology division at the University of Washington School of Medicine.
Pustulo-ovoid bodies of Milian [14-16]	This name is used recently to refer to the aggregations of granules in granular cell tumor, which is also known as Abrikossoff tumor, after Aleksei Ivanovich Abrikossoff (1875-1955), who was a Russian/Soviet pathologist.
Russell bodies [5]	Inclusions secondary to collections of immunoglobulin in the cytoplasm of plasma cells. Seen in rhinoscleroma, granuloma inguinale, syphilis, (See above, in Dutcher bodies).
Schaumann Bodies [17]	Calcium-containing inclusion bodies found in the cytoplasm of giant cells in sarcoidosis, berylliosis and uncommonly, in Crohn's disease and tuberculosis. These bodies were first described by the German physician Oscar von Schüppel (1837-1881) in 1871, and by Max Askanazy (1865-1940) in 1921 as Kalkdrusen. But it is named for Jörgen Nilsen Schaumann (1879-1953),(Fig. 10), a Swedish dermatologist. It is to be mentioned that, a number of cytoplasmic structures/inclusions can be identified within the granulomas of sarcoidosis, including asteroid bodies, Schaumann's bodies, calcium oxalate crystals, and Hamazaki-Wesenberg bodies; the last two of these can cause difficulties in differential diagnosis. Hamazaki-Wesenberg bodies (alternatively termed yellow-brown bodies, yellow bodies, Hamazaki corpuscles) are structures of unknown significance, which have been periodically documented in the sinuses of lymph nodes in numerous anatomic locations and myriad medical conditions, including appendicitis, cirrhosis, lymphoid tumours, colon carcinoma and numerous others, most famously sarcoidosis. Initially described by Hamazaki in 1938 in mesenteric lymph nodes, 6 and later noted by Menne in 1952 in 70% of mesenteric lymph nodes removed during appendectomies.
Verocay Body [18]	A peculiar microscopic pattern seen in schwannomas, consisting of palisading cell around a cellular area. It is named after, Jose Juan Verocay (1876-1927), (Fig. 11). He was a Uruguayan physician who trained and worked for most of his adult life in Europe in the late nineteenth and early twentieth century.

Table I. Selected Eponyms in the dermatology literature linked to „Bodies", seen in skin biopsies (continued).

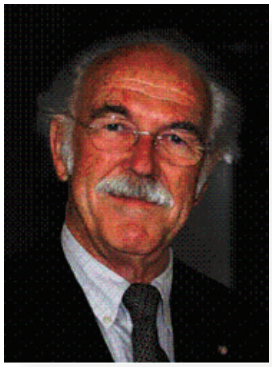

Figure 12. Ewald Rudolf Weibel.

Figure 13. George Emil Palade (1912-2008).

Eponyms in the dermatology literature linked to „Bodies", seen in skin biopsies	Remarks
Weibel-Palade Bodies (WPBs) [19-21]	WPBs are elongated secretory organelles specific to endothelial cells that contain von Willebrand factor (VWF) and a variety of other proteins that contribute to inflammation, angiogenesis, and tissue repair. Weibel–Palade bodies were initially described, by the Swiss anatomist and biologist, Ewald Rudolf Weibel, born 1929, (Fig. 12), and the Romanian physiologist George Emil Palade (1912-2008), (Fig. 13). Palade was described as „the most influential cell biologist ever". In 1974 he was awarded the Nobel Prize in Physiology and Medicine, for his work on the function of organelles in cells together with Albert Claude and Christian de Duve.

Table I. Selected Eponyms in the dermatology literature linked to „Bodies", seen in skin biopsies (continued).

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EPONYMS IN THE DERMATOLOGY LITERATURE LINKED TO STAINS USED IN SKIN BIOPSIES

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Staining is an auxiliary technique used in microscopy to enhance contrast in the microscopic image. Stains and dyes are frequently used in biology and medicine to highlight structures in biological tissues for viewing, often with the aid of different microscopes [1].

Hematoxylin and eosin stain (H&E stain or HE stain), is the routine staining for skin biopsies. However, in some circumstances, dermatopathologists use other stains.

For example, the Fontana-Masson Stain is used for melanin as it can be difficult to decide whether a brown pigment is lipofuscin, hemosiderin, or melanin. At pH4, melanin granules reduce silver nitrate to metallic silver, a histochemical reaction that reveals accumulations of black material wherever melanin is located. The Fontana-Masson Stain can be used, also, to detect melanin of dematiaceous fungi [2].

Each stain may give a particular colour to a specific structure in the tissue. For example, Alizarin red binds directly to calcium ions, resulting in an orange-red color [3].

In Foote's or Snook's stain, the reticulin fibers will be black. Leder stain (Naphthol ASD chloroacetate esterase), will stain Mast cell cytoplasm red (not dependent on presence of granules). Also stains myloid cells (example, leukemia cutis).

Lipid will be stained by Oil red O (requires fresh frozen tissue, as lipid is removed during processing). In addition to Sudan black and Osmium tetroxide (both require fresh tissue).

Iron will be stained by Prussian blue, also known as Perls stain, after its inventor, German pathologist Max Perls (1843-1881). In this stain ferric ions react to form a deep blue. It is useful to distinguish melanin from hemosiderin (example:hemosiderin in pigmented purpuric dermatosis). It does not demonstrate iron in intact red blood cells.

There are also several other stains which are not used commonly in dermatopathology. For example:

Movat's stain which is a pentachrome stain originally developed by Henry Zoltan Movat in 1955 and later modified by H. K. Russell, Jr. in 1972. It is used to highlight the various constituents of connective tissue. In this stain, the nuclei , elastic fibres will be black; collagen fibres, reticular fibres will be yellow; ground substance, mucin will be blue; Fibrin will be bright red Muscle will be red.

Also, Weigert's elastic stain which will show elastic fibers, blue coloured while cell nuclei gets red or blue. It is named for, Karl Weigert, or Carl Weigert (1845-1904), (Fig. 1), who was a German pathologist.

There are several eponyms linked to the stains used in dermatopathology practice. In Table I [4-19], we listed some examples.

Eponyms in the dermatology literature linked to stains used in skin biopsies	Remarks
Bodian stain [4]	Nerve fibers will appear black with this stain. Nerve fiber can also be stained by PGP 9.5 and neurofilament. Named after David Bodian (1910-1992), (Fig. 2). Bodian received his Ph.D. in anatomy in 1934 and his M.D. in 1937 from the University of Chicago. He made major contributions to the knowledge of the basic structure of nerve cells.
Feulgen stain [5]	It stains, DNA magenta. Named for, Robert Feulgen (1884–1955), (Fig. 3), who was a German physician and chemist. He developed a method for staining DNA, in 1914.

Table I. Selected Eponyms in the dermatology literature linked to stains used in skin biopsies.

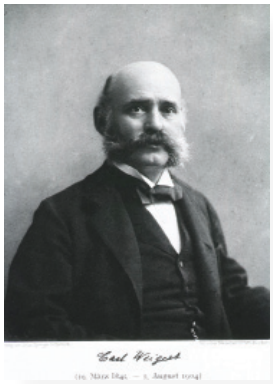

Figure 1. Carl Weigert (1845 -1904).

Figure 2. David Bodian (1910-1992).

Figure 3. Robert Feulgen (1884-1955).

Eponyms in the dermatology literature linked to stains used in skin biopsies	Remarks
Fite stain [6]	Also known as, Fite-Faraco stain. Fite is preferred for „partially acid-fast'' organisms such as lepra bacilli, atypical mycobacteria, and Nocardia.Fite preseves color due to use of peanut oil before staining and gentle decolorization. George Liddle Fite (1933-1993), (Fig. 4), who was arguably the most important American figure in the fight against leprosy.The crowning achievement of a life devoted to the treatment of leprsosy was a chief pathologist of the laboratory at the States Leprosarium in Carville, Louisiana.
Giemsa stain [7]	It stains myeloid and mast cell granules purple (it is the heparin in the mast cells that is staining). Also good for many types of organisms, including bacteria, Leishmania, and Histoplasma. Gustav Giemsa (1867-1948), (Fig. 5), was a German chemist and bacteriologist who was a native of Medar-Blechhammer. Giemsa improved the Romanowsky stain (Eosin Yand Methylene Blue) by stabilizing this dye solution with glycerol. This allowed for reproducible staining of cells for microscopy purposes. Romanowsky staining was named after the Russian Physician, Dmitri Leonidovich Romanowsky (1861-1921), who invented it in 1891.
Gomori's aldehyde-fuchsin stain [8,9]	Stain elastic tissue purple.Elastic tissue can be also stained by Verhoeff von Gieson (blue-black), and by Orcein-Giemsa (black). It is named for György Gömöri also George Gömöri or George Gomori or George Gömöri (1904-1957), who was a Hungarian-American physician who became famous as histochemist.
Gomori methenamine silver (GMS) [9]	Also called, Grocott-Gomori's (or Gömöri) methenamine silver stain.It is abbreviated as GMS. It stains fungi which can also be stained by PAS (Periodic acid-Schiff).
Gram staining [10]	Gram staining (or Gram's method) is a method of differentiating bacterial species into two large groups (Gram-positive and Gram-negative). Named for Hans Christian Gram (1853-1938), (Fig. 6), who was a Danish bacteriologist who developed the technique while working with Carl Friedländer in the morgue of the city hospital in Berlin in 1884. Brown-Hopps tissue Gram stain is a modification of Brown-Brenn technique. Gram-positive organisms stain blue and Gram-negative organisms stain red.
Masson's trichrome stain [11]	In this stain, Collagen will appear blue\green and muscle,nerve, and keratin will be red. It is a three-colour staining protocol used in histology. The recipes evolved from Claude L. Pierre Masson's, original formulation to different specific applications, but all are suited for distinguishing cells from surrounding connective tissue. Most recipes produce dark brown to black cell nuclei. Claude L. Pierre Masson (1880-1959), (Fig. 7), was a French-born Canadian pathologist. He was the chair of anatomic pathology at the hospital and medical school at Strasbourg, France. In 1927, while he was 46 years old, Masson resigned his position at Strasbourg and a ccepted the position of chief of anatomic pathology at the University of Montreal Medical School. Pierre Masson died at the age of 79 years. He is buried, as he wished, at the cemetery of Notre-Dame-des-Neiges, atop Mont Royal, where today one has a grand view of the University of Montreal.

Table I. Selected Eponyms in the dermatology literature linked to stains used in skin biopsies (continued).

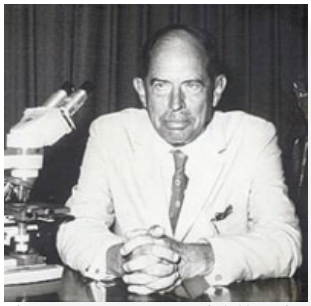

Figure 4. George Liddle Fite (1933-1993).

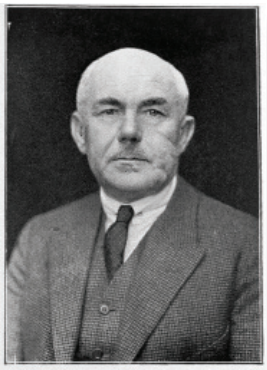

Figure 5. Gustav Giemsa (1867-1948).

Figure 6. Hans Christian Gram (1853-1938).

Eponyms in the dermatology literature linked to stains used in skin biopsies	Remarks
McCallum - Goodpasture stain [12,13]	It is a stain for bacteria using aniline fuchsin.. Named after William George Maccallum (1874-1944), (Fig. 8), who was a Canadian pathologist and Ernest William Goodpasture (1886-1960), (Fig. 9), who was an American pathologist.
Verhoeff-Van Gieson stain [14,15]	Also known as Verhoeff's Stain or Verhoeff's Elastic Stain (VEG) .In this stain, elastic fibers will appear black.As an examples of its uses in dermatology,elastic fibers will be absent or reduced in scar, middermal elastolysis, anetoderma, and cutis laxa.As another example,the elastic fibers,will be distorted in pseudoxanthoma elasticum.The stain was developed by Verhoeff in 1908.Frederick Herman Verhoeff (1874-1968), (Fig. 10), was an american ophthalmic surgeon and pathologist .Ira Thompson Van Gieson (1866-1913), (Fig. 11), was an american neuropsychiatrist and pathologist.
Von Kossa Stain [16]	A silver stain that stains calcium salts black originally developed by Von Kossa in 1901. Examples of its uses in dermatology include, pseudoxanthoma elasticum, calcinosis cutis, and calciphylaxis.
Warthin-Starry (WS) stain [17]	Technically more difficult than the other stains, so sometimes referred as the ,'worthless Starry". It is one of the Silver stains, which include, Dieterle stain and Steiner stain (a modified Dieterle stain). It stains spirochetes black. Examples of its uses include, lyme disease, and syphilis. Aso stain Legionella, Bartonella, and Donovan bodies of granuloma inguinale. WS was first introduced in 1920 by American pathologists, Aldred Scott Warthin (1866-1931), (Fig. 12), and Allen Chronister Starry (1890-1973). Currently immunohistochemistry is the best method to diagnose syphilis in skin biopsies.
Ziehl-Neelsen stain [18,19]	Also known as the acid-fast stain, which is used to identify acid-fast bacteria. In this stain, Mycobacteria will appear bright red. Dr. Franz Ziehl (1857-1926), (Fig. 13), was a German bacteriologist. He was a professor in Lübeck. Franz Ziehl introduced the carbolfuchsin stain for the tubercle bacillus in 1882. With a Friedrich Carl Adolf Neelsen (1854-1898), (Fig. 14), who was a German pathologist, he developed the Ziehl-Neelsen stain.

Table I. Selected Eponyms in the dermatology literature linked to stains used in skin biopsies (continued).

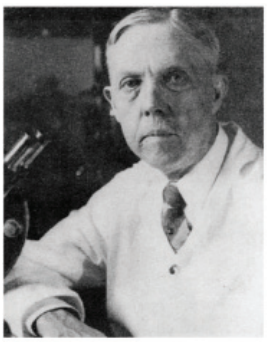

Figure 7. Claude L. Pierre Masson (1880-1959).

Figure 8. William George Maccallum (1874-1944).

Figure 9. Ernest William Goodpasture (1886-1960).

Figure 10. Frederick Herman Verhoeff (1874-1968).

Figure 11. Ira Thompson Van Gieson (1866-1913).

Figure 12. Aldred Scott Warthin (1866-1931).

Figure 13. Franz Ziehl (1857-1926).

Figure 14. Friedrich Carl Adolf Neelsen (1854-1898).

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EPONYMS IN THE DERMATOLOGY LITERATURE LINKED TO *PALMO-PLANTAR KERATODERMA*

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Palmoplantar keratodermas (PPKs) represent a diverse group of hereditary and acquired disorders characterized by hyperkeratosis of the skin on the palms and soles [1]. The three major patterns of involvement are diffuse, focal and punctate. There are clinical distinguishing features for each disease in this group, for example, transmigration to areas beyond the palmoplantar skin. Also the extent of associated systemic symptoms if present help in characterization of each type. Although a number of classifications of keratodermashave been published, none unite satisfactorily clinical presentation, pathology and molecular pathogenesis.

We based our concise review of selected eponyms linked to PPK (Tabl. I) [2-36], on the classifications published in the current editions of two major textbooks in dermatology; Rook's Textbook of Dermatology and Dermatology by Jean L Bolognia.

Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK)	Remarks
Bart–Pumphrey Syndrome [2]	This syndrome is characterized by knuckle pads,leukonychia, palmoplanter keratoderma (PPK) andsensorineural deafness. This syndrome is first described by Dr Schwann, from Poland and appeared later in English literature by RobertS. Bart (Dermatologist) and Robert E. Pumphrey-(Otolaryngologist); both from. Dr Robert S Bart (Fig. 1) reported this syndrome, in1967, while he was working as an assistant professor ofclinical dermatology, New York University School of Medicine and Post-Graduate Medical School.
Brünauer–Fuhs–Siemens PPK [3,4]	It is a type of focal Palmoplantar Keratoderma (Isolated). Also known as, PPK striata/areata, striate PPK, focal non-epidermolytic PPK, Wachters PPK (Focal/areate/nummularkeratoderma). Focal, areate or nummular, and linear or striate keratodermas have been distinguished. The occurrence of both areate and striate forms within a family led Wachters to suggest a single entity, keratoderma varians.Stefan Robert Brünauer, born in 1887, is an Austrian physician. Herbert Fuhs (1891-1960), is an Austrian dermatologist. Hermann Werner Siemens (1891-1969), is a German dermatologist.
Buschke–Fischer–Brauer type [5]	Also known as, Brauer–Buschke–Fischer keratoderma. It is a synonym for Punctate Palmoplantar Keratoderma. August Brauer (1883-1945) (Fig. 2), a German physician. Abraham Buschke (1868-1943) (Fig. 3), a German dermatologist. Heinrich Fischer (1884-1943), a German dermatologist.
Camisa's syndrome or Camisa variant of Vohwinkel syndrome [6]	Also known Loricrin keratoderma, Mutilating keratoderma with ichthyosis, and Variant Vohwinkel's syndrome. It is atype of Transgredient keratodermas. Named for Dr. Camisa (Fig. 4), who is is currently the Director of the Phototherapy Department at Riverchase Dermatology and an Affiliate Associate Professor of Dermatology at the University of South Florida in Tampa.

Table I. Selected Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK).

Figure 1. Robert Bart, Image courtesy of The Archives of the Frederick L. Ehrman Medical Library, available online at http://archives.med.nyu.edu /resources/imagedb/detail.php?recordID=35090002763282

Figure 2. August Brauer (1883-1945).

Figure 3. Abraham Buschke (1868-1943).

Figure 4. Charles Camisa, M.D., FAAD.

Figure 5. José María Cantú Garza (1938-2007).

Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK)	Remarks
Cantu syndrome [7,8]	Hyperkeratosis–hyperpigmentation syndrome first reported in 1978. The same name is a pplied to a syndrome characterized by congenital hypertrichosis, distinctive facial features, osteochondrodysplasia and cardiac defects, first reported in 1982. Both are named for José María Cantú Garza (1938-2007), (Fig. 5), who was a Mexican genetic researcher.
Carvajal syndrome [9]	Striate EPPK with woolly hair and dilated left ventricular cardiomyopathy. Carvajal-Huerta (1998) described 18 patients with a confirmation of epidermolytic palmoplantar keratoderma, woolly hair, and dilated cardiomyopathy, examined clinically and histologically in Ecuador between 1970 and 1997. CS might be a variant of Naxos disease (ND), which was first described by Protonotarios et al., in families originating from the Greek island of Naxos. ND is a rare autosomal recessive inherited association of right ventricular dysplasia/dilated cardiomyopathy with woolly hair and palmoplantar keratoderma. Any patient with a PPK and woolly hair (or alopecia) should be sent for a cardiac evaluation.
Cole disease [11]	Guttate hypopigmentation with punctate PPK. First described by Cole in 1976.
Costa/Dowd kertoderm [12]	This an eponym for, marginal popular keratoderma. In which there are will be crateriform punctate keratoses at the margin of the sole (Wallace's line). Costa reported 13 cases with cornified and umbilicated papules distributed along the borders of the hands and feet. He introduced the term acrokeratoelastoidosis. However, Dowd et al., reported 15 cases, several familial, with similar oval or polygonal crateriform papules along the borders of the hands and feet in whom there was no solar damage or elastorrhexis. To distinguish this entity, it was termed focal acral hyperkeratosis. Many patients with these disorders are of Afro-Caribbean origin.

Table I. Selected Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK) (continued).

Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK)	Remarks
Gamborg–Nielsen (Norrbotten) type [15]	A type of Diffuse ppk with no association. It is an autosomal recessive transgredient mutilating keratoderma. with knuckle pads identified by Gamborg-Nielsen in 1985. Patients with the transgredient PPK were also reported in Japan by Nakajima.
Greither syndrome [16]	A type of diffuse Palmoplantar Keratoderma (transgrediens and progrediens PPK), originally described in 1952. It is characterized by a diffuse transgredient PPK with onset in early infancy. Named for, Aloys Greither (1914-1986), a German dermatologist.
Ichthyosis hystrix Curth–Macklin [17]	This is a rare type of Ichthyoses with associated keratoderma. There are horny or velvety spikes rather thanthickened scales. Named for Helene Ollendorff Curth (1899-1982), (Fig. 6) and Madge Thurlow Macklin (1893–1962), an American medical geneticist.The described the condition in 1954.
Jadassohn–Lewandowsky type of Pachyonychia congenital (PC) [18]	Type 1 PC. Type 2 is known as Jackson–Lawler type. Josef Jadassohn (1863-1936), (Fig. 7) and his assistant, Felix Lewandowsky (1879-1921), (Fig. 8), were eminent German dermatologists.
Naegeli–Franceschetti–Jadassohn syndrome (NFJS) [19]	It is a rare symptom complex out of the spectrum of ectodermal dysplasia. The main clinical findings are absence of dermatoglyphs, reticular or mottled hyperpigmentation, hypohidrosis and nail dystrophy. NFJS is named after Oskar Naegeli, Adolphe Franceschetti and Josef Jadassohn. Oskar Naegeli (1885-1959), (Fig. 9), was a Swiss dermatologist. Adolphe Franceschetti (1896-1968), (Fig. 10), was a Swiss ophthalmologist. Josef Jadassohn (1863-1936), (Fig. 7), was a German dermatologist.
Haim–Munk syndrome [20].	It is a PPK with periodontitis, arachnodactyly and acro-osteolysis. In 1965, Dr. Salim Haim (1919-1983), (Fig. 11), dermatologist and Dr. Munk, a radiologist, from Haifa reported this rsyndrome, which is characterized by palmoplantar keratosis, pes planus, onychogryphosis periodontitis, arachnodactyly, and acroosteolysis.
Haxthausen's disease [21]	This is another name for Keratoderma climactericum. The specificity of this syndrome described in women over the age of 45 is uncertain, as many patients are obese. Pressure areas of the heel and the forefoot are involved first. Erythema and heavy hyperkeratosis with fissuring make walking painful. It was described in 1934.
Howel–Evans Syndrome [22]	Focal non-epidermolytic PPK with carcinoma of the esophagus. It was described in 1958.
Huriez Syndrome [23]	Palmoplantar keratoderma with scleroatrophy. Named for French dermatologist, Claude Huriez (1907-1984), (Fig. 12). In 1960s, Huriez and his colleagues reported 2 families from northern France with, this syndrome, which is characterized by scleroatrophy of the hands and feet, nail hypoplasia, mild palmoplantar keratoderma and hypohidrosis.

Table I. Selected Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK) (continued).

Figure 6. Helene Ollendorff Curth (1899-1982).

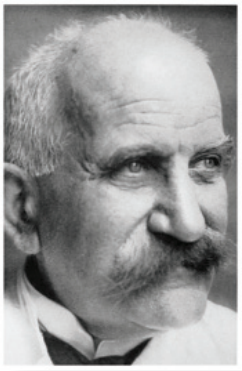

Figure 7. Josef Jadassohn (1863-1936).

Figure 8. Felix Lewandowsky (1879–1927). Reproduced with the kind permission of the Alumni Association of the Medical Faculty of the University of Basel, Switzerland.

Figure 9. Oskar Naegeli (1885-1959). A courtesy of Archives of the Institute for the History of Medicine, University of Zurich, Switzerland.

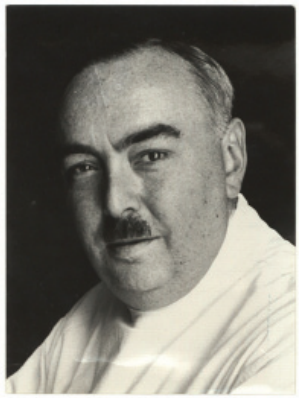

Figure 10. Adolphe Franceschetti (1896-1968). A courtesy of Library, university of Basel, Switzerland.

Figure 11. Salim Haim (1919-1983).

Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK)	Remarks
Netherton syndrome (NS) [9]	NS is characterized by the triad of trichorrhexis invaginata, ichthyosis linearis circumflexa, and an atopic diathesis. It is named after E.W. Netherton, Who described a 4-year old girl with scaly red and different hair, which he called bamboo hair, because of how it looked in the microscope. Nine years earlier, the Italian dermatologist Come described a condition in a young woman with a ring shape change in her skin, which he called itcthyosis Linearis circumflex. These two descriptions were considered to be related.
Olmsted Syndrome [24]	Mutilating PPK with periorificial plaques. First described in 1927.
Papillon–Lefèvre Syndrome [1]	An autosomal recessive disorder, first described it in 1924.It is characterized by diffuse, transgredient PPK in association with destructive periodontitis (beginning in childhood) and premature loss of teeth. It is named for Papillon and Paul Lefèvre. Both are French dermatologists.
Papuloverrucous palmoplantar keratoderma of Jakac-Wolf [25]	Papuloverrucous PPK is a rare type first reported in 1975.
Refsum syndrome [26]	It is an example of occurance of PPK in the disorders of Ichthyoses. Refsum disease is an autosomal recessive inborn error of lipid metabolism classically characterized by a tetrad of clinical abnormalities: retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and elevated protein levels in the cerebrospinal fluid (CSF) without an increase in the number of cells. Sigvald Bernhard Refsum (1907-1991), (Fig. 13), was an outstanding Norwegian neurologist.
Richner–Hanhart Syndrome [27]	It is a type of focal Palmoplantar Keratoderma with Associated Features. It is a rare autosomal recessive disease characterized by ocular changes, painful palmoplantar hyperkeratosis, and mental retardation. Many of the reported families are of Italian origin.This syndrome is reported first by, Dr. Hermann Richner, Swiss dermatologist, born September 6, 1908, in Zürich. Ernst Hanhart (1891-1973), (Fig. 14), was Swiss internist and human geneticist.
Schöpf–Schulz–Passarge syndrome [28]	A type of ectodermal dysplasias with associated keratoderma. PPK with hidrocystomas, hypodontia and hypotrichosis. It was characterized in 1971.
Sjögren–Larsson syndrome [29]	It is an example of occurance of PPK in the disorders of Ichthyoses. It is a rare autosomal recessive condition comprising congenital ichthyotic hyperkeratosis, spastic diplegia, mild to moderate mental retardation, and retinopathy.It is named for Karl Gustaf Torsten Sjögren (1896-1974) and Tage Konrad Leopold Larsson (1905-1998). Sjögren (Fig. 15), a Swedish psychiatrist and geneticist, was a pioneer of modern Swedish psychiatry. Tage K.L. Larsson, was a lecturer of statistics at the University of Lund.

Table I. Selected Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK) (continued).

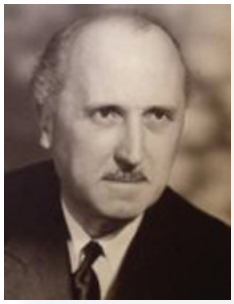

Figure 12. Claude Huriez (1907-1984); with kind permission from; Museum Association Regional Hospital of Lille - France.

Figure 13. Sigvald Bernhard Refsum (1907-1991). This figure is reproduced with permission from the great Norwegian encyclopedia (Store norske leksikon), Available Online at; http://snl.no/Sigvald_Bernhard_Refsum

Figure 14. Ernst Hanhart (1891-1973). A courtesy of Archives of the Institute for the History of Medicine, University of Zurich, Switzerland.

Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK)	Remarks
Sybert type PPK [30-32]  **Figure 16. Virginia Sybert.**	It is a type of diffuse ppk with no other association. It is a severe transgredient keratoderma reported by Sybert et al. (Virginia Sybert, (Fig. 16), is a contemporary American dermatologist and medical geneticist) resembled mal de Meleda but had dominant inheritance. Onset was earlier than in Greither's syndrome. Glove and stocking hyperkeratosis, including autoamputation of toes, extended also to the elbow knees, posterior aspects of the forearms, shins, groins and natal cleft. Mal de Meleda is a rare autosomal recessive transgredient keratoderma named after the Croatian island of Meleda (Mljet) where it was first identified. Nagashima-type" keratosis is a nonprogressive, autosomal-recessive palmoplantar keratoderma that resembles a mild form of mal de Meleda. Lind et al, described an autosomal dominant form of diffuse nonepidermolytic PPK, designated PPK type Bothnia, which has a high prevalence of 0.3 to 0.55% in the 2 northernmost provinces of Sweden, situated to the west and the northwest of the Gulf of Bothnia.
Unna–Thost PPK [33,34]	Also known as, Thost–Unna keratoderma. It is a type of diffuse Palmoplantar Keratoderma. In 1880, Thost described a family with diffuse non-transgrediens PPK. This was followed by Unna's description of a clinically identical, autosomal dominant PPK in two families. Paul Gerson Unna (1850- 1929), (Fig. 17), was a German dermatologist. Herrmann Arthur Thost (1854-1937), (Fig. 18), was a German physician.
Vohwinkel syndrome [35]	Vohwinkel first described this autosomal dominant disorder in 1929. Honeycombed, diffuse hyperkeratosis of the palms and soles appears in infancy and then becomes transgredient. This is followed by the development of constricting bands of the digits during early childhood, which may lead to digital autoamputation, i.e. pseudoainhum. Peculiar starfish-shaped keratoses appear over the knuckles of the fingers and toes and are said to be characteristic of the disorder. Hearing loss of at least a moderate degree is seen in many patients. Additional reported findings are alopecia and ichthyosis
Vörner keratoderma [36]	First described by Vorner in 1901. Similar to Unna-Thost keratoderma but there epidermolysis in histology. Both are autosomal dominant and manifested as diffuse PPK without transgrediens or associated ectodermal features

Table I. Selected Eponyms in the dermatology literature linked to Palmo-Plantar Keratoderma (PPK) (continued).

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Figure 15. Karl Gustaf Torsten Sjögren (1896-1974). Image is provided by the Center for History of Science, the Royal Swedish Academy of Sciences. Permission For republication is granted by Norstedts, Sweden.

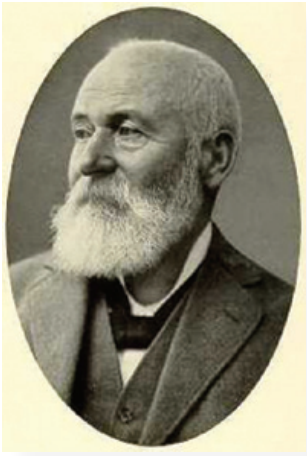

Figure 17. Paul Gerson Unna (1850- 1929).

Figure 18. Herrmann Arthur Thost (1854-1937).

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EPONYMS LINKED TO „SIGNS" IN THE DERMATOLOGY LITERATURE

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The word "sign" refers to important physical finding or observation made by the physician when examining the patient. Dermatologic diagnosis relies on the careful observation and documentation of signs, which can be highly pathognomonic for a certain conditions. Most of the signs appear either de novo or have to be elicited by the physician [1].

There are important publications which gathered the signs seen in dermatology practice. In addition, Dr Piotr Brzeziński, the Editor – in-Chief of this journal along with other authors had published alphabetical series entitled ,'DERMATOLOGY EPONYMS – SIGN – LEXICON'', where they elaborated on the signs seen in dermatology.

In this communication, we aimed to highlight on selected eponyms linked to ,'signs'' in the dermatology literature, shown in Table I [1-11].

Eponyms linked to „signs" in the dermatology literature	Remarks
Albright's dimple sign [1-5]	This is seen in Albright's hereditary osteodystrophy in which there is presence of a dimple over the knuckle of the typically affected fourth metacarpal and can be enhanced by clenching of the fist.It is named for Fuller Albright (1900-1969), (Fig. 1), who was an American endocrinologist who made numerous contributions to his field, especially to the area of calcium metabolism.
Asboe-Hansen sign (Blister spread sign) [6]	The Asboe-Hansen sign (also known as „indirect Nikolsky sign" refers to the extension of a blister to adjacent unblistered skin when pressure is put on the top of the bulla. This sign is named for Gustav Asboe-Hansen (1917–1989), (Fig. 2), who was a Professor and Head of the Department of Dermatology and Venereology at the University Hospital in Copenhagen, Denmark. His article was published in 1960. Asboe-Hansen noticed the differences between the blister-spread patterns in pemphigus and those in bullous pemphigoid. Whereas in pemphigus vulgaris, the blister extension had a sharp angle, in bullous pemphigoid, the advanced border was rounded as in a pressure bulla.
Auspitz sign [1-3]	It is seen in psoriasis, where there is pinpoint bleeding on removal of scales from the lesions of psoriasis. The test by which Auspitz sign is elicited is called as Grattage test. Other dermatoses where Auspitz sign can be positive is Darier's disease and actinic keratosis. Auspitz sign is named for, Heinrich Auspitz (1835-1886), (Fig. 3), who was an Austrian dermatologist.
Cullen sign [1-3]	Periumbilical ecchymosis in cases of acute hemorrhagic pancreatitis and ruptured ectopic pregnancy is termed Cullen's sign. Similar changes in the flank is called as Grey-Turner sign. Thomas Stephen Cullen (1868-1953), (Fig. 4), was a Canadian gynecologist associated with Johns Hopkins Hospital.

Table I. Selected Eponyms linked to „signs'' in the dermatology literature

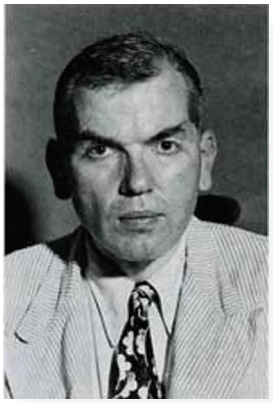

Figure 1. Fuller Albright (1900-1969).

Figure 2. Gustav Asboe-Hansen (1917–1989).

Figure 3. Heinrich Auspitz (1835-1886).

Eponyms linked to „signs" in the dermatology literature	Remarks
Darier sign [1-3]	Rubbing a lesion of mastocytoma causes urtication, flare, swelling and sometimes blister formation due to release of histamine. In contrast, pseudo-Darer's sign is seen in smooth muscle hamartoma where there is increase in induration and piloerection after firm stroking. Other conditions where one could find positive Darier's sign are leukemia cutis, juvenile xanthogranuloma, and Langerhans cell histiocytosis. Darier sign is named after the French dermatologist Ferdinand-Jean Darier (1856-1938), (Fig. 5), who first described it.
Forscheimer sign [1-3]	Also known as Forchheimer spots. It is seen in 20% of rubella patients, where there is an enanthem of dull-red macules or petechiae confined to the soft palate during the prodromal period or on the first day of the rash. Can also be seen in infectious mononucleosis. It is named for Frederick Forchheimer (1853–1913), (Fig. 6), who was an American pediatrician .
Gorlin sign [1-3]	It is the ability of patients of Ehlers-Danlos syndrome to touch the tip of the nose with the tip of their tongue Named for Robert James Gorlin (1923-2006), (Fig. 7), who was a professor and researcher at the University of Minnesota known for pioneering research into craniofacial disorders, genetic defects, syndromes, and oral and maxillofacial pathology.
Higoumenaki sign [1-3]	It refers enlargement of the sternal end of the (right) clavicle, frequently observed in patients with late congenital syphilis .It is named for, George Higoumenakis (1895-1983), (Fig. 8), who was a Greek dermatologist.
Nikolsky sign [7-9]	The sign is encountered in blistering disorders, and it is present when slight rubbing of the skin results in exfoliation of the outermost layer of the skin. Named for, Russian dermatologist Pyotr Vasiliyevich Nikolskiy (1858-1940), (Fig. 9).

Table I. Selected Eponyms linked to „signs" in the dermatology literature (continued)

Figure 4. Thomas Stephen Cullen (1868-1953).

Figure 5. Ferdinand-Jean Darier (1856–1938).

Figure 6. Frederick Forchheimer (1853–1913).

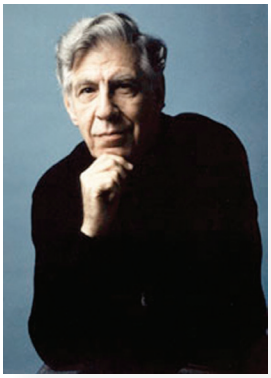

Figure 7. Robert James Gorlin (1923-2006).

Figure 8. George Higoumenakis (1895–1983).

Figure 9. Piotr Vasiliyevich Nikolskiy (1858-1940).

Eponyms linked to „signs" in the dermatology literature	Remarks
Winterbottom sign [1,10,11]	It is seen in early stages of African trypanosomiasis caused by Trypanosoma brucei rhodensiense and Trypanosoma brucei gambiense known Sleeping sickness. Winterbottom's sign is enlargement of lymph nodes in the posterior cervical chain. It is named for Thomas Masterman Winterbottom (1766-1859), (Fig. 10), who was an English physician. Winterbottom noted that slave traders used the sign of neck swelling as an indicator of sleepiness, and would avoid those slaves. He had no children, so his considerable estate was left to a number of charities which he had supported during his life. The bulk of this bequest was to found the South Shields Marine College, which he had established in 1837.

Table I. Selected Eponyms linked to „signs" in the dermatology literature (continued)

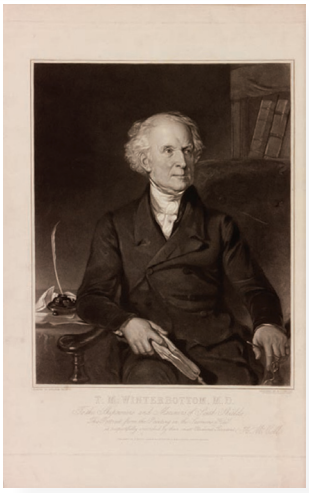

Figure 10. Thomas Masterman Winterbottom (1766-1859). A courtesy of The Bridgeman Art Library Ltd.

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