Volume 5, Number 1, January 2014
p. 1 - 102
Issue online since Saturday, January 11, 2014

ISSN: 2081-9390
DOI: 10.7241/ourd
Universal Impact Factor {UIF} (= 0.7319)

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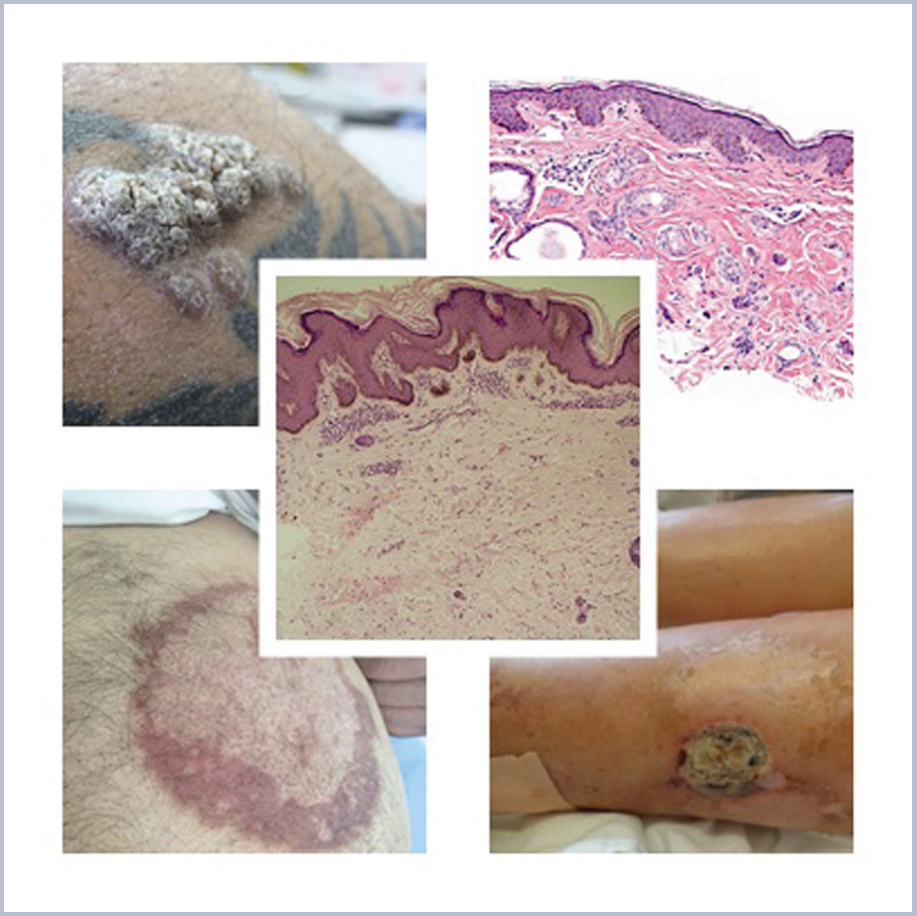

1 / 2014

Editorial Pages

NASZA DERMATOLOGIA Online
OUR DERMATOLOGY Online

e-ISSN: 2081-9390

DOI: 10.7241/ourd

Quarterly

published since 01/06/2010 years

Our Dermatol Online

www.odermatol.com

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Indexed in:

Universal Impact Factor for year 2012 is = 0.7319
system of opinion of scientific periodicals INDEX COPERNICUS (6,70)
(Academic Search) EBSCO
(Academic Search Premier) EBSCO
MNiSW (kbn)-Ministerstwo Nauki i Szkolnictwa Wyższego (4.00)
DOAJ (Directory of Open Acces Journals)

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Previous website:	issue 1.2010	**www.ndermatol.like.pl**
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DOI: 10.7241/ourd.20141.01

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TOPICAL CORTICOSTEROID ABUSE ON THE FACE: A PROSPECTIVE, STUDY ON OUTPATIENTS OF DERMATOLOGY

Hariharasubramony Ambika, C. Sujatha Vinod, Harikishan Yadalla, Raghunath Nithya, Anagha Ramesh Babu

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 5-8 Date of submission: 09.09.2013 / acceptance: 23.09.2013

Abstract

Introduction: Topical corticosteroids (TCS) are widely misused. Uncontrolled use of steroids can cause undesirable adverse effects especially on face.

Aim: The aim of this study was to assess the skin manifestations of TCS misuse over the face in the patients attending dermatology outpatient and to analyze various factors contributing to such misuse.

Methods and Methods: A total of 200 patients with facial dermatoses using topical steroids over face for minimum period of 1 month, reported between June 2010 and May 2011 were enrolled in the study. Details about the usage of topical corticosteroids and their side effects were recorded. The patients were educated about the misuse.

Results: Majority of the patients were females (71%). The most common reason for misuse was acne (61%) followed by use as a fairness cream (23%). The average duration of usage was 6 months to 1 year, longest being 8 years. The drug most commonly misused was Betamethaone Valerate (71%). The commonest side effect noted was acne form eruptions (52%) followed by steroid dependent face (SDF) (36%). There were no cases of allergic contact dermatitis or perioral dermatitis. The exacerbation of the lesions on stoppage of steroid cream (90%) fairness effect (10%) were the reasons for continued use. (100%) were unaware of side effects of topical steroids.

Conclusions: Steroids have been misused by patients on their own or by doctors for various reasons. Hence the awareness about their correct usage is essential.

Key words: steroid abuse; face; steroid rosacea; acneform erruptions

Cite this article:
Hariharasubramony Ambika, C. Sujatha Vinod, Harikishan Yadalla, Raghunath Nithya, Anagha Ramesh Babu: Topical corticosteroid abuse on the face: a prospective, study on outpatients of dermatology. Our Dermatol Online. 2014; 5(1): 5-8.

Introduction

In spite of the widely prevalent steroid phobia, misuse of topical corticosteroids (TCS) on face continues occur as the benefits of steroids outweigh the risks. The instant subjective and objective relief that steroid give for various dermatosis of face, and the fairness effect are the important reasons for continued use of it even among the literate population. Aim of this study is to make awareness about misuse of steroids on face.

Material and Methods

A total of 200 outpatients with facial dermatosis using TCS on face for minimum period of one month were taken up for study, after obtaining institutional ethical clearance and informed consent from patients. Details about age, sex,reason for steroid application, source of steroid, duration, reason for continued use, and awareness of side effects, were recorded in proforma. Detailed examination for side effects of steroid like acne, erythema scaling, telengectasia dyspigmentation, hypertrichosis or any others noted were recorded (Fig. 1 - 4). Various data were analysed.

Results

Most of patients were between age group of 15 to 30 (55%) (Tabl. I). Females (71%) outnumbered males (29%). Most common reason for use of steroid was acne (41%) as fairness cream (23%) pigmentation including melasma (18%) various other dermatoses of face (18%) (Fig. 5). Duration of application was <6 months in majority, longest being 8 years (Fig. 6). Source of steroid prescription was self medication as advised by friends in 64% and prescribed by dermatologist or general physician in 36% (p value 0.0001 significant). All the 200 (100%) patients were unaware about the side effects of topical steroid.

Steroids of varying potency were used by patients commonest being betamethasone valerate (Tabl. II). Exacerbation on stopping steroid and same was reason for continued use in (90%) of patients. 10% of patients did not experience any exacerbation of lesion but continued using steroid for its fairness effect. Commonest presenting symptom was acne form eruption followed by (SDF) steroid dependent face (eryhema burning and scaling) (Fig. 7). On examination of patient there were overlap of side of side effect. We did not observe any allergic contact dermatitis to steroid or perioral dermatitis. All the patients were educated about side effects of steroid and TCS was tapered off or replaced with mild steroid and stopped completely. Orally doxycycline or azithromycin was given. Topical tacrolimus was used in some cases. All patients showed good response.

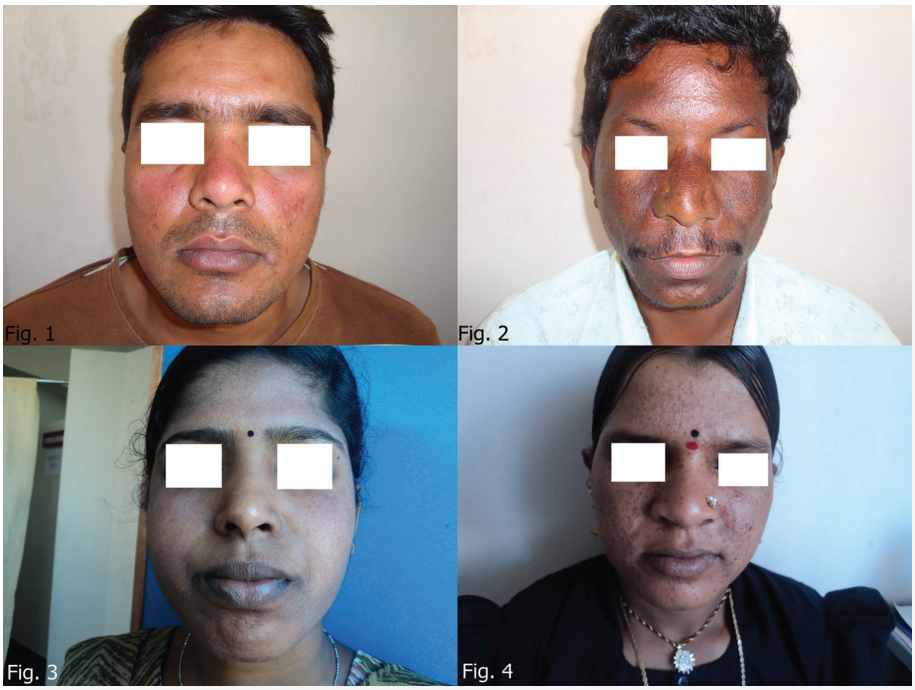

Figure 1. Erythema of central face - steroid rosacea.
Figure 2. Acneform eruption following steroid application for pigmentation of face.
Figure 3. Steroid dependent face (SDF) showing diffuse erythema and scaling.
Figure 4. Steroid induced pigmented monomorphic acne.

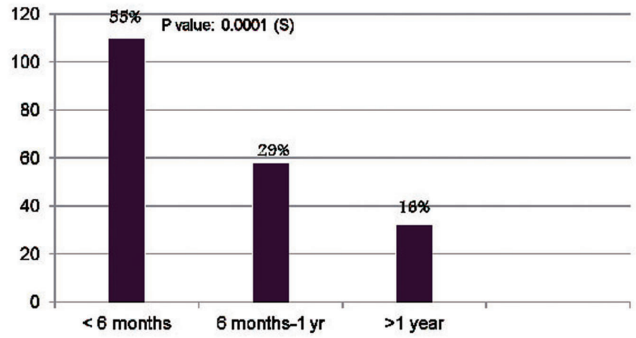

Figure 5. Duration of steroid application.

Age	No of patients
1-15	24
16-30	110
31-45	50
45-60	16

Table I. Age distribution of patients.

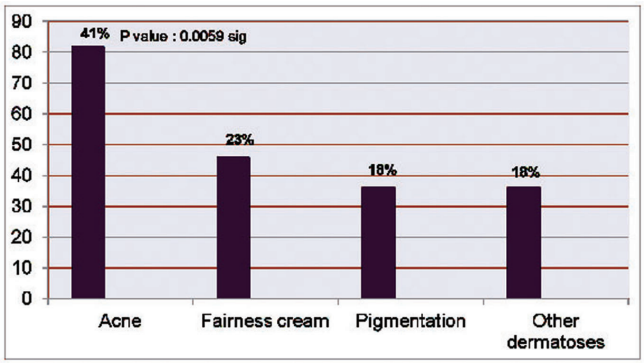

Figure 6. Reason for steroid application.

Potency of steroid	No of patients
Very potent and potent	46
Moderately potent	126
Mild	28

Table II. Potency of steroid applied and number of patients.

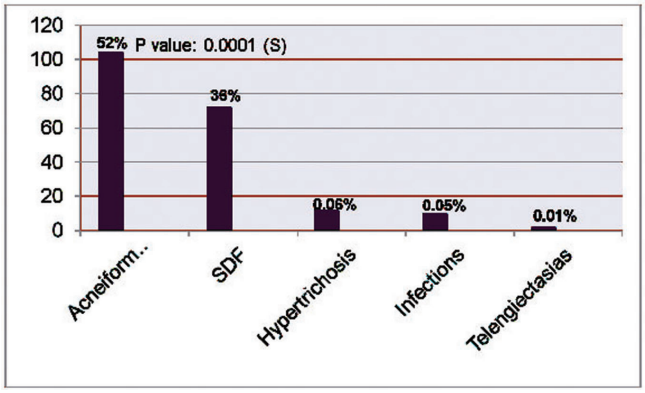

Figure 7. Type of skin lesion.

Discussion

Ever since the invention, topical steroids are misused both by prescribing doctor and patient themselves, as it gives instant relief to signs and symptoms [1].

Face is the commonest site of such misuse as its effect is cosmetically appreciable and it is most often used as fairness cream also [2]. 23% of our patient were using it for fairness effect and 10% continued to use it for the same reason. Different names are given to steroid abuse lesions on face, most often called as steroid rosacea [3]. Red face syndrome [4] and SDF [1] also refers to same effect. Sequence events that lead to steroid abuse is as follows-doctor will prescribe moderately potent steroid to get benefit and avoid side effects of potent steroid, (like in our study and by Rathy SK et al [4] where it was betamethasone valerate) for some dermatosis of face, impressed by response, patient continues to use it and often refer to friends also. Saraswat et all observed use of potent and super potent steroids in majority [1]. Effect of steroid reduces due to tachyphylaxis [5] and patient is forced to use potent steroid and cycle continues. On stopping the medication there is rebound erythema and scaling which occur due to release of cytokines, accumulation of nitric oxide causing vasodilatation and doubtful role of demodex mites [6].

Acne form eruptions are also commonly observed following TCS application. Our study showed acne form lesions as commonest side effect. Bhat YJ et al [3] observed more rosasea than acne. It is interesting to observe that majority of our patients used steroid for treatment of various forms of inflammatory acne. Initially they had relief and on continued use developed monomorphic pigmented papules which was the commonest lesion observed in our study.

Other common side effects like telengectasia, hypertrichosis, infections were less commonly observed in our study as in other studies [7]. Systemic side effects like adrenal axis suppression, diabetes, hypertension etc following topical application are reported only if applied to larger areas as in other diseases [8], are rare with use on face. Allergic dermatitis to TCS are reported [9]. None of our patients had allergic reaction to TCS. Most of time allergic response is to base used and SDF which manifests as erythema and scaling is mistaken as allergy [10]. Perioral dermatitis an entity initially described following use of fluorinated steroid on face [11], and reported in studies [12], was not seen in our study.

Management of patient with SDF include initial careful education about dependency and counselling as to recurrence of lesions on stoppage of steroids. Slow tapering by decreasing frequency or switching to lower potent steroid is to be done. Oral tetracyclines are proved to be effective [13]. Other drugs like low dose doxycycline and azithromycin also have shown to be effective [3]. Recently topical tacrolimus is reported to be effective [14]. Studies show effectives of pimicrolimus also similar to tacrolimus [15,16]. There is always a doubt as to which steroid is safe for face [17], in fact no steroid is safe for face, and to be prescribed only if specifically indicated for shorter duration. And it is very essential to educate patient about side effects and dependency in order to prevent the consequences of abuse. This kind of awareness among doctors and patient is highly essential as magnitude of problem is high.

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DOI: 10.7241/ourd.20141.02

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FORMULATION OF HYPOPIGMENTATION CREAM AND EVALUATION OF ITS EFFECT ON SKIN PIGMENT. PART I: FORMULATION OF THE PRODUCT

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Source of Support:
None
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 9-13 Date of submission: 11.11.2013 / acceptance: 23.12.2013

Abstract

Introduction: Melasma is a commonly acquired hypermelanosis of facial skin due to various etiological factors including hormonal imbalance. Although it affects any one is particularly common in women, especially pregnant women and those who taking oral or patch contraceptives or hormone replacement therapy.

Aim: This research aimed to formulate stable water in oil (w/o) cream containing plant extract of Glycyrrhiza glabra as active material obtained by concentrating the alcoholic extract of the plant roots, was entrapped in the inner aqueous phase of w/o cream.

Material and Methods: Base containing no active material and a formulation containing ethanolic extract of the plant which was prepared in Samarra Drugs Industry laboratories. Samples of base and formulation were stored at different accelerated conditions (8°C, 25°C, 30°C, 40°C, 40°C +75% RH) for four weeks to predict the stability of the creams.

Results: It was concluded that the formulation was stable chemically and physically over the studied storage conditions and without induction of allergic or contact dermatitis.

Key words: Melasma; plant extract; topical treatment

Cite this article:
Amina Hamed Alobaidi, Eqbal Salih Hamad, Kudair Abas Kudair, Abdulghani Mohamed Alsamarai. Formulation of Hypopigmentation Cream and Evaluation of its Effect on Skin Pigment. Part I: Formulation of the Product. Our Dermatol Online. 2014; 5(1): 9-13.

Introduction

The term melasma is derived from the Greek word 'melas' meaning black [1]. It is a disorder of pigmentary system characterized by irregular brown or greyish-brown, acquired hypermelanosis of sun-exposed areas especially the face [2]. Melanin largely decides our skin color and is an essential defense mechanism against the sun for us. Melanin also overproduces with acne and this is what causes the dark skin spots to remain long after the red acne spots have gone [1]. Topical polyherbal formulations are the latest additions to the dermatologists repertoire of treatment. Scientists have known for decades that some plants are amazingly good at reducing and diverting the production of Melanin [3]. Particularly advantageous cosmetic emulsion preparations are obtained when antioxidants are used as active ingredients [4]. Many antioxidatively acting compounds are isolated from natural herbs and spices (extracts) and used as potential antioxidants in cosmetics [5]. An extract of *Glycyrrhiza glabra* is rich of natural antioxidants [6].The best natural antioxidants in extract of *Glycyrrhiza glabra* are glycyrrhizin (glycyrrhizic acid) and flavonoids [7]. The role of plant extract on skin is mainly attributed to its antioxidant activity particularly to its potent antioxidants triterpene, saponins and flavonoids [8]. Skin whitening [9], skin depigmenting [10], skin lightening [11], antiaging [12], anti-erythemic [13], emollient [14], anti-acne [15] and photoprotection effects [16,17].

Materials and Methods

Materials

The materials used in this study were supplied by the State Company for Drugs Industries (SDI) which include the following:

· Paraffin oil and coconut oil. (Wacker Chemicals Ltd./Germany)
· Cetomacrogol 1000. (Merck KGa/Germany)
· Cetostearyl alcohol. (Merck KGa/Germany)

· Beeswax. (Merck KGa/Germany)
· Glycerin. (Merck KGa/Germany)
· Lemon oil. (Merck KGa/Germany)
· Distilled Water.
· Extract of Glycyrrhiza glabra (ethanolic) is to be prepared by in the State Company for Drug Industries.

Preparation of Base and Formulation
Water in oil (W/O) cream was prepared by the addition of aqueous phase to the oily phase with continuous agitation. To prepare base(placebo); oily phase that consisted of paraffin oil, beeswax, coconut oil and surfactants (cetomacrogol 1000 and cetosteatyl alcohol), is heated up to 75°C±1°C. Aqueous phase consisting of glycerin and water is heated to the same temperature. The formulation was also prepared by same method; the only difference is the addition of *Glycyrrhiza glabra* extract (active drug) that is added in aqueous phase consisting of glycerin and water. Each formulation consists of preserved water (propyl paraben 0.02% w/w and methyl paraben 0.1% w/w) to 100g. The formulations were neutralized by Triethanolamine to pH=5.5 at 25°C (Tabl. I).

Patch Test
On the first day of skin testing, patch tests are to be performed on the forearms of each volunteer. 5cm x 4cm regions were marked on both the forearms. Basic values for erythema and melanin are to be measured with the help of Mexameter. 1.0g of base and formulation each are applied to the 5cm X 4cm marked regions separately on each forearm. The regions are covered with the surgical dressing after application. After 24 hours, dressings are removed and the measurements of erythema and melanin are repeated on both forearms.

Panel Test
Every individual is provided with a form prepared previously to test the sensory values of cream. This form consisted of parameters to be evaluated and every parameter is assigned 11 values from –5 to +5 indicating very bad to very good, respectively. This form is asked to be completed independently by each individual on day 28.

Dermatological tests
Erythema of the skin are determined on the first day before application of any cream and then on days 7, 14, 21 and 28.

Parameters for Evaluation of Formulation Characteristics These parameters include

Centrifugation Tests for Creams:
Centrifugation test is to be performed for both the base and formulation kept at different storage conditions up to a period of 28 days at different time intervals. Phase separation on centrifugation is to be recorded in any of the samples kept at different storage conditions i.e. 8^0C, 25^0C, 40^0C and 40^0C+ 75% relative humidity up to 28th day of observation. This parameter indicate both creams stability at all the storage conditions for 28 days. It is evident that proper homogenization speed during emulsion formulation prevented the base and formulation breakage during stress conditions.

Stability Tests
Physical analysis, types of cream, pH determination, was analyzed to assure the formulation of desired properties. Stability tests were performed at different conditions for cream to note the effect of these conditions on the storage of creams. These tests on samples were kept at 8°C ± 0.1°C (in refrigerator), 25°C ± 0.1°C (R.T), 30°C(in oven), 40°C ± 0.1°C (in oven) and 40°C ± 0.1°C (in oven) with 75% relative humidity (RH). Samples are observed with respect to change in color, liquefaction and phase separation.

Color
The freshly prepared base is creamy white while formulation is pale yellow in color (due to the presence of *Glycyrrhiza glabra* extract). It is presumed that there is no change in color of any sample of base and formulation at different storage condition i.e. 8^0C, 25^0C, 40^0C and at 40^0C+ 75% relative humidity up to the observation period of 28 days.

Liquefaction
Liquefaction is to be observed in any of the sample of base and formulation kept at 8^0C and 25^0C during whole observation period of 28 days.

Phase Separation
Phase separation was observed in any of samples of base and formulation kept at 8^0C, 25^0C, 40^0C and at 40^0C + 75% relative humidity up to observation period of 28 days.

Formula	Composition % (W/W)						
	Licorice	Glycerin	Paraffin oil	Coconut oil	Beeswax	Cetoma-crogol 1000	Cetosteatyl Alcohol
F 1	1.0	18	20	3.0	5.0	1.0	5.0
F2	1.0	18	20	3.0	5.0	1.5	5.0
F3	1.5	18	20	2.0	5.0	1.8	6.0
F4	1.5	18	20	1.0	5.0	1.8	6.0
F5	2.0	18	20	1.0	5.0	2.0	6.0
F6	2.5	18	20	1.0	5.0	2.0	6.0
placebo	0.0	18	20	1.0	5.0	2.0	6.0

Table I. Formulations composition.

pH
Base and formulation pH was measured during the storage period and at different storage temperatures.

Erythema
The side effect of base and formulation as presented by contact or allergic dermatitis was tested. The indicator used to determine such side effect was the recording of erythema following application of base and formulation to the skin of the volunteers.

Ethical Approval
The research protocol was approved by the ethical committee of Tikrit University College of Medicine and informed consent was taken from any individual shared in the study.

Results

Physical analysis

Color
The freshly prepared base is creamy white while formulation is pale yellow in color (due to the presence of *Glycyrrhiza glabra* extract). There is no change in color of any sample of base and formulation at different storage condition i.e. 8°C, 25°C, 30°C, 40 °C and at 40°C+ 75% relative humidity up to the observation period of 28 days.

Liquefaction
No liquefaction was observed in any of the sample of base and formulation kept at 8°C and 25°C and 30°C during whole observation period of 28 days but slight liquefaction was observed in samples kept at 40°C and 40°C + 75% RH from 21st day of observation but there was no increase in liquefaction till the end of study period.

pH Measurements
The pH is a significant parameter in so far as the effectiveness of the cream is concerned and it can be used as an indicator of the formulation stability. All the samples have a pH close to the skin pH with range 5.5 for the formulation and decreased in case of base to 4.9 during the observation of study period as shown in Table II and III.

Phase Separation
Phase separation was not observed in any of samples of base and formulation kept at 8°C, 25°C and 30°C, but there was a little bit of separation in samples kept at 40°C and 40°C + 75% RH from the 21 day of observation.

Erythema
For confirming the safety of dermatological preparations, the important point is that must not cause any contact dermatitis when applied to the skin. In this study it was found that erythema contents were decreased from 1st to 4th week after the application of base and formulation.

Patch Test
On the first day of skin testing, patch tests was performed on the forearms of each volunteer. 5cm x 4cm regions were marked on both the forearms. Basic values for erythema are to be measured with a ruler. 1.0g of base and formulation each were applied to the 5cm x 4cm marked regions separately on each forearm. The regions were covered with the surgical dressing after application. After 24 hours, dressings were removed and the measurements of erythema were repeated on both forearms.

Time	8°C	25°C	30°C	40°C	40°C+ RH	Mean
	For formulation					
0.00	5.44	5.38	5.41	5.6	5.82	5.53
1st week	5.53	5.61	5.45	5.37	5.46	5.48
2nd week	5.4	5.58	5.7	5.58	5.72	5.67
3rd week	5.41	5.6	5.63	5.49	5.52	5.53
4th week	5.32	5.35	5.44	5.63	5.52	5.5
Mean	5.5	5.49	5.52	5.53	5.6	5.54
For base						
0.00	5.76	5.63	5.66	5.51	5.53	5.65
1st week	5.43	5.37	5.25	5.2	5.17	5.2
2nd week	5.2	5.12	5.07	5.1	5.0	5
3rd week	4.9	4.76	4.73	4.59	4.51	4.6
4th week	4.53	4.41	4.37	4.25	4.08	4.3
Mean	5.1	5	4.97	4.91	4.82	4.9

Table II. Measurements pH values of formulation and base during 28 days at different study conditions.

Time	8°C	25°C	30°C	40°C	40°C+ RH	Mean	*p*
	For formulation						
0.00	5.44	5.38	5.41	5.6	5.82	5.53	NS
1st week	5.53	5.61	5.45	5.37	5.46	5.48	NS
2nd week	5.4	5.58	5.7	5.58	5.72	5.67	NS
3rd week	5.41	5.6	5.63	5.49	5.52	5.53	NS
4th week	5.32	5.35	5.44	5.63	5.52	5.5	NS
Mean	5.5	5.49	5.52	5.53	5.6	5.54	
P	NS	NS	NS	NS	NS		
For base							
0.00	5.76	5.63	5.66	5.51	5.53	5.65	NS
1st week	5.43	5.37	5.25	5.2	5.17	5.2	NS
2nd week	5.2	5.12	5.07	5.1	5.0	5	NS
3rd week	4.9	4.76	4.73	4.59	4.51	4.6	NS
4th week	4.53	4.41	4.37	4.25	4.08	4.3	NS
Mean	5.1	5	4.97	4.91	4.82	4.9	
P	NS	NS	NS	NS	NS		

Table III. Measurements pH values and p values of formulation and base during 28 days at different study conditions.

Discussion

Every case of melasma starts off in the epidermis, where melanocytes are actively producing pigment [18]. A normal case of melasma can turn into dermal melasma if skin becomes over- irritated and inflamed. When this happens, it causes a temporary split between the dermis and epidermis. During this time, hyperpigmented cells can drop from the epidermis into dermis [19]. Once in the dermis, these cells become very resistant to topical treatment. Dermal melasma is particularly difficult to treat since active tyrosinase activity is only found in epidermal melanocytes. In dermal melanin, tyrosinase activity is not present; therefore dermal melasma is resistant to topical treatment [20].

The current work aimed to formulate a stable water in containing *Glycyrrhiza glabra* (*G. glabra*) extract and studying its effect on skin pigment (Melanin). Base containing no active material and formulation containing alcoholic extract of *G. glabra* at different concentrations. Six formulations were prepared and formulation number (6) was selected depending on a pilot study which included 50 volunteers who were intended to the daily dermatology clinics.

No phase separation was seen in any of samples of base and formulation kept at 8°C, 25°C and 30°C, but there was a little bit of separation in samples kept at 40°C and 40°C +75% RH from the 21 day of observation. This indicated both creams were stable at 8°C, 25°C and 30°C. Proper homogenization speed during cream formulation prevented the base and formulation breakage during stress conditions [21].

In the present both base and formulation did not show any change in color of samples at different storage conditions up to the observation period of 28 days. *G. glabra* extract containing poly phenols that have antimicrobial activities [22] and thus prevent color change of the formulation. In addition, no liquefication was observed in any of the sample of the base and formulation kept at 8°C, 25°C and 30°C. However, slight liquefication was observed in samples kept at 40°C and 40°C+RH after 3 weeks of observation, but there was no increase in liquefication till the end of study period. Thus, the above findings (color, liquefication and phase separation) indicated that both base and formulation were stable at 8°C, 25°C and 30°C storage conditions for 28 days.

pH is a significant parameter of effectiveness of cream stability [23] and it was a key indicator factor of aqueous phase [24]. Skin pH range between 5 and 6, and 5.5 is considered to the average pH of the skin [25]. In the present study, the pH of the freshly prepared base and formulation was 5.65 and 5.53, this is very close to the skin pH. The pH of the base kept at different storage conditions was found to be decreased gradually over storage period. However, the change in pH was not statistically significant over time. Different storage temperatures show no significant changes in pH. The formulation samples pH was with a non- constant pattern (i.e. increased or decreased), however, there was a non significant pH changes over time and also insignificant at different storage temperature. The change in pH of formulation may be due to presence of *G. glabra* extract [24].

In the present study indicated that erythema induced by application of base and formulation was decreased after 24 hr. of their application. Thus it is concluded that both base and formulation produced non skin irritation after performing patch test of 24 hrs. It may be attributed to the presence of a good emollient glycerin in the base and formulation, and/or *G. glabra* [26] in the formulation, which has the ability to reduce skin erythema [27].

An important criterion for any cosmetic is that it must not cause any contact dermatitis following application to the skin. Contact dermatitis was not always due to ingredients of the cosmetic.

Environmental factors, skin types, cosmetic misuses and physical conditions may all causes contact dermatitis [28]. Skin irritation is caused by a direct toxicity of chemicals on cells or blood vessels in the skin and is different from contact allergy which is caused by immune response [29].

The present study was indicated that erythema induced by application of base and formulation decreased over time. The decrease in erythema over time may be due to in the presence of coconut oil in base which is a good emollient [30] and decrease inflammation [31]. In addition, presence of *G. glabra* extract in the formulation may act as soothe and calm agent to the skin [32].

In conclusion, the hypopigmentation formulation presented in this study was stable physically and chemically and not induced contact or allergic dermatitis and may be suitable as treatment for melasma.

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DOI: 10.7241/ourd.20141.03

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PSORIASIS UNCOVERED - COMORBID CONDITIONS WITH SPECIAL REFERENCE TO METABOLIC SYNDROME

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Source of Support:
Nil
Competing Interests:
None

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Our Dermatol Online. 2014; 5(1): 14-17 Date of submission: 12.09.2013 / acceptance: 23.09.2013

Abstract

Introduction: Psoriasis is a chronic immune-inflammatory-mediated disease affecting approximately 1-3% of the population worldwide. All around the world, there is growing evidence of the association between psoriasis and comorbidities, especially metabolic syndrome which increases the risk of cardiovascular disease. Co-morbidities are likely linked to underlying chronic inflammatory nature of psoriasis.

Aim: The objectives of our study were to determine the prevalence of diabetes, lipid abnormalities, and cardiovascular risk factors in patients with plaque psoriasis, and also to investigate metabolic syndrome associated with plaque psoriasis.

Material and Methods: One hundred and twenty patients with psoriasis vulgaris diagnosed clinically and histopathologically were recruited. A detailed history and examination was recorded for all study subjects, including the age and gender of the patients, extent of psoriasis, duration, and age at onset. Metabolic syndrome was diagnosed in the presence of three or more criteria of abdominal obesity, blood pressure >130/85 mmHg, fasting blood glucose ≥100 mg/dl, hypertriglyceridemia >150 mg/dl, and low HDL cholesterol (<40 mg/dl for males, <50mg/dl for females).

Results: Prevalence of various comorbidities was: central obesity (58.3%), hypertension (46.79%), dyslipidaemia (43.3%), diabetes mellitus (26.7%), metabolic syndrome (25%), ischaemic heart disease (5%) and stroke (2.4%). Prevalence of metabolic syndrome was more in patients who had longer mean disease duration of psoriasis.

Conclusions: The perception of psoriasis being merely 'skin deep' has to change among clinicians. Active screening for these cardiovascular comorbidities in all psoriasis patients is highly recommended.

Key words: psoriasis vulgaris; comorbidities; metabolic syndrome

Cite this article:
Belliappa Pemmanda Raju, Umashankar Nagaraju. Psoriasis Uncovered - Comorbid Conditions with Special Reference to Metabolic Syndrome. Our Dermatol Online. 2014; 5(1): 14-17.

Introduction

Psoriasis is a chronic immune-inflammatory-mediated disease affecting approximately 1-3% of the general population [1,2]. Psoriasis is not just a disease of skin and joints, but is a systemic disease that is connected with a range of comorbidities-especially metabolic syndrome and cardiovascular disease. Co-morbid conditions linked with psoriasis are associated with increasing rates of morbidity and mortality [3]. Metabolic syndrome is a cluster of risk factors including central obesity, atherogenic dyslipidaemia, hypertension and glucose intolerance. It is a strong predictor of cardiovascular diseases, diabetes and stroke [4]. Similarities exist among psoriasis, metabolic syndrome and atherosclerosis, with all three conditions characterized by an inflammatory process driven by Th1 cytokines [5,6]. Increasing population-based studies have suggested a relationship between psoriasis and metabolic syndrome [7]. Purpose of our study was to determine the prevalence of comorbidities in patients with psoriasis vulgaris, with special emphasis on metabolic syndrome, as it remains largely unelucidated in the Indian population.

Material and Methods

Prospective, observational hospital based study. One hundred and twenty patients with psoriasis vulgaris diagnosed clinically and histopathologically were included in this study which was carried out of our Department of Dermatology from March 2011 to August 2012 for a period of 18 months. Patients with plaque-type psoriasis aged above 18 years were included in the study. Patients receiving systemic treatment for their psoriasis in the last one month were excluded. Informed consent was taken from patients who were enrolled. Information sheets for the patients included age, gender, weight, height, body mass index (BMI), waist circumference, smoking habits, blood pressure, age of onset, and duration of the disease.

Severity of psoriasis was assessed by percent body surface area (%BSA) and psoriasis area severity index (PASI). BSA is calculated using the "rule of nines". BSA is the arithmetic mean of the affected skin surface based on the assumption that the head (H) presents 10%, the upper extremities (U) 20%, the trunk (T) 30%, and the lower extremities (L) 40% of the total body surface [8]. PASI is a composite score from 0 to 72. PASI assesses the degree of erythema (E), infiltration (I), and desquamation (D) in the above-mentioned sites (H, U, T, L) [9]. These features are appraised in these sites using a four-point scale: 0: no symptoms; 1: slight symptoms; 2: moderate symptoms; 3: marked symptoms; 4: very marked symptoms. The scores used to describe the coverage of skin disease in the distinct areas are: 0: 0%; 1: < 10%; 2: 10–29%; 3: 30–49%; 4: 50–69%; 5: 70–89%; 6: 90–100%. Therefore, PASI takes both coverage (A) and severity (E, I and D) into consideration. It is calculated by:

PASI = 0.1 * (EH + IH + DH) AH + 0.2 * (EU + IU + DU) AU+ 0.3 * (ET + IT + DT) AT + 0.4 * (EL + IL + DL) AL

It was classified as moderate to severe in patients with PASI > 10, and mild in patients with PASI ≤ 10. BMI was calculated as weight/height (kg/m^2). Metabolic syndrome was diagnosed using the South Asian Modified National Cholesterol Education Program Adult Treatment Panel III criteria (SAM-NCEP criteria) [10]. If three or more of the following were present, the patient was diagnosed as having metabolic syndrome: abdominal obesity (definition of abdominal obesity was modified using Asia Pacific WHO guidelines as waist circumference ≥90cm for males and ≥80cm for females), blood pressure >130/85 mmHg, fasting blood glucose ≥100 mg/dl, hypertriglyceridemia >150 mg/dl, or low HDL cholesterol (<40 mg/dl for males and <50 mg/dl for females). ECG was done in all patients and angiogram wherever required. Statistical comparisons were performed using the Student's t- test. The data were considered statistically significant if p values were less than 0.05 ($p<0.05$).

Results

The study group included 120 patients, with 86 (71.7%) males and 34 (28.3%) females with a male to female ratio of 2.53:1. Age of the patients ranged from 18 years to 62 years with a mean age of 37.34 years. Duration of the disease ranged from 2 months to 30 years, with a mean duration of 6.67 years. Mean age at onset was 31.41 years, with minimum age 12 years and maximum age 60 years at onset. Severity of psoriasis was moderate to severe in 68 (56.7%) of the patients and mild in 52 (43.3%) of the patients with a Median PASI of 13.05. PASI score ranged from 5 to 70. BSA involved ranged from 6% to 80%, with a Median BSA of 20%.

Central obesity was the most prevalent comorbidity, affecting 70 (58.3%) patients with psoriasis, followed by hypertension, dyslipidaemia, diabetes mellitus, metabolic syndrome, ischaemic heart disease and stroke (Tabl. I). Waist circumference ≥90cm in men and ≥ 80cm in women was observed in 42 (35%) and 28 (23.3%) patients respectively. Obesity measured by BMI was present in 64 (53.3%) patients. Metabolic syndrome was seen in 30 (25%) patients of psoriasis. Distribution of risk factors and different components of Metabolic Syndrome are given in Table II.

On analyzing psoriatic patients with and without metabolic syndrome, we found that patients with metabolic syndrome had longer mean disease duration than psoriatic patients without metabolic syndrome, which was significant. There was no significant difference regarding psoriasis severity, gender or prevalance of smoking between psoriatic patients with and without metabolic syndrome (Tabl III). Metabolic syndrome in psoriasis was seen more commonly in the patients aged above sixty years, however we also observed early onset of metabolic syndrome in psoriasis (Tabl. IV).

Discussion

Recent studies on western population show that psoriasis is associated with metabolic disorders such as hypertension, type II diabetes mellitus, dyslipidemia, abdominal obesity, insulin resistance, and cardiac disorders and the risk of metabolic syndrome is increased in patients with psoriasis [11-19]. Meta-analysis of studies has shown that psoriatics had increased odds (two-fold) of developing metabolic syndrome compared with the general population.

Metabolic syndrome has a high prevalence among psoriasis. Possible biologic mechanisms for this may be due to: chronically elevated free fatty acid (FFA) levels which lead to adipocyte dysfunction which in turn inhibit insulin secretion and up-regulation of proinflammatory adipokines like adiponectin, leptin, resistin and visfatin [7].

Comorbidities	Number (%)
Central obesity	70 (58.3%)
Hypertension	56 (46.7%)
Dyslipidemia	52 (43.3%)
Diabetes Mellitus	32 (26.7%)
Metabolic Syndrome	30 (25%)
Ischaemic Heart Disease (IHD)	6 (5%)
Stroke	3 (2.4%)

Table I. Prevalence of different comorbidities in psoriasis.

Risk factors/Components of Metabolic Syndrome	Number (%)
Smokers	18 (15%)
Alcoholic	46 (38.3%)
Waist circumference: Male Female	 42 (35%) 28 (23.3%)
Hypertension	56 (46.7%)
Hypertriglyceridemia	52 (43.3%)
Low Level HDL	40 (33.3%)
Diabetes Mellitus (FBS>100mg/dl)	32 (26.7%)

Table II. Distribution of risk factors and components of Metabolic Syndrome.

Characteristic	With MS (n=30)	Without MS (n=90)	t-test
Sex (M / F)	21 / 9	65 / 25	NS
Disease duration	13.67 ± 11.87	6.46 ± 5.80	(P<0.0005)
Smoker	6	12	NS
PASI >10	21	47	NS
BSA >10%	23	55	NS
Mean PASI	14.30 ± 12.37	16.77 ± 14.53	NS
Mean BSA	25.80 ± 21.17	27.55 ± 25.7	NS

Table III. Descriptive features of psoriatic patients with and without Metabolic Syndrome (MS).

NS=Not significant

Comorbidities (%)	Nisa et al	Khunger et al	Madanagobalane et al	Present study
Smoking	42%	-	16.1%	15%
Hypertriglyeridemia	48.6%	16%	33.9%	43.3%
Hypertension	49.3%	26%	30.5%	46.7%
Low HDL levels	56.6%	-	36.4%	33.3%
Obesity	14.6%	38%	34.7%	58.3%
Diabetes Mellitus	18%	16%	61%	26.7%

Table IV. Comparision of prevalence of metabolic syndrome components in different Indian studies.

Studies on the Indian population with relation to psoriasis and its comorbidities and metabolic syndrome are limited. The prevalence of metabolic syndrome in psoriasis was 25% in our study, which is consistent with other Indian studies, which have shown a prevalence ranging from 18.2% - 44.1% [4,20-23]. This wide variation in the prevalence of metabolic syndrome could be due to ethnic, dietary and lifestyle changes in different parts of the country. Prevalence of different metabolic syndrome components in our study is compared with other Indian studies in Table V. Association with smoking was seen in 15% of our patients which is consistent with a study by Madanagobalane et al [20]. Association with smoking may be partly explained by the action of nicotine in promoting Th1 mediated inflammation [6]. Smoking induces an overproduction of IL-1β, TNF-α and TGF-β, which have been associated with psoriasis severity [24]. In our study 38.3% of patients were alcoholic, other Indian studies have reported an association of 9.1% to 17.7% [20,23]. Alcoholism has been related with psoriasis, and studies have reported 1.3–1.6 fold increased risk in development of psoriasis in alcoholics [25]. Hypertriglyceridemia and low HDL levels were seen in 43.3% and 33.3% of our patients which is consistent with a study by Madanagobalane et al [20].

Pro-inflammatory cytokines TNF-α and IL-6 over expressed in psoriasis contributes to dyslipidaemia [26]. Obesity was observed in 58.3% of our patients which is much higher than other Indian studies which have reported an association of 14.6% to 38% [21,22].

Leptin produced by adipose tissue and increased TNF-α acts as a potential link between obesity and psoriasis [27,28]. Diabetes mellitus was seen in 26.7% of our patients, while other Indian studies have reported a prevalence ranging from 16% to 61% [20,22]. Chronically elevated FFA levels inhibit insulin secretion, and TNF-α and IL-6 contributes to insulin resistance [7,26]. Fifty six (46.7%) patients were hypertensive in our study which is consistent with another Indian study by Nisa et al.[21]. Henselar et al in 40,000 dermatological patients found 1.9 fold greater likelihood of hypertension in psoriatics compared to other dermatological conditions [11].

Our study showed a significant relationship between duration of psoriasis and metabolic syndrome, which is consistent with a study by Nisa et al.[21].

There was no significant relationship between psoriasis severity and metabolic syndrome in our study, which is consistent with other Indian studies [20,21].

Age Group	%
18-30 Yrs	12.9%
31-40 Yrs	29.7%
41-50 Yrs	44.4%
51-60 Yrs	37.5%
>60 Yrs	50%

Table V. Prevalance of Metabolic Syndrome among different age groups.

However, Langan et al found a robust dose-response relationship between psoriasis severity and prevalence of metabolic syndrome [29]. This observation was supported by the translational data that T- helper inflammatory cytokines are increased in skin and sera of psoriatic patients and these exert systemic effects on insulin regulation and lipid metabolism [30]. Onset of metabolic syndrome in psoriasis was seen at a younger age in our study which is consistent with a study reported by Nisa et al.[21]. Relative risk of cardiovascular mortality is highest in younger patients less than forty years, with severe psoriasis [15]. So early therapeutic intervention would diminish the risk of cardiovascular disease and mortality in psoriasis.

Our results showed that psoriasis predisposes to the development of a distinct cluster of concomitant diseases, including hypertension, dyslipidemia, obesity and metabolic syndrome. Hence all patients with psoriasis should be monitored for associated co-morbid conditions. For effective management of psoriasis and related co-morbidities, an integrated approach targeting both cutaneous and systemic manifestations may be beneficial.

Limitation of this study was that the sample size was not large enough to represent the general population. Further large prospective, randomized, controlled, population-based studies should be undertaken to confirm the association and causality between psoriasis and metabolic syndrome.

Conclusion

Approach psoriasis as a potentially multisystem disorder and alert patients to the potentially negative effects of psoriasis as it relates to other aspects of their health.

Can we now consider psoriasis as a cutaneous marker for metabolic syndrome?

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PSORIASIS UNCOVERED - COMORBID CONDITIONS WITH SPECIAL REFERENCE TO METABOLIC SYNDROME

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 18 Date of submission: 26.12.2014 / acceptance: 06.01.2014

Cite this article:
Rania Mounir Abdel Hay. Comment: Eruptive syringomas of the neck. Our Dermatol Online. 2014; 5(1): 18.

Very interesting article, we should take care that the management of psoriasis should be shifted towards comprehensive disease management.
- Obesity may increase risk of liver and renal toxicity to Methotrexate and cyclosporine,
- Obesity may decrease the short-term clinical response to all systemic treatment,
- Decreasing body weight improves the response of obese patients to low dose cyclosporine therapy,
- Drugs indicated in co morbidities may exacerbate psoriasis; e.g ACEI, anticoagulants, diuretics, B blockers, and psycholeptics.

Drugs used to treat psoriasis can aggravate metabolic syndrome and co morbidities; e.g Cyclosporine may lead to hypertension, or impairment of kidneys, also Acitretine may change glucose tolerance, induce hyperlipidaemia or hepatopathy, also methotrexate may have hepatopathic effects.

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 18 Date of submission: 31.12.2014 / acceptance: 06.01.2014

Cite this article:
Manuel Valdebran. Comment: Eruptive syringomas of the neck. Our Dermatol Online. 2014; 5(1): 18.

The association of psoriasis with cardiovascular disease, in particular, has been subject of research for many years, however, inconclusive results were always obtained as cardiovascular disease risk factors could act as confounders. Recently the topic have caught more attention as better designed studies have been performed thus confirming its association. Among these studies, it is very interesting to cite the meta-analysis performed by Miller et al [1] where they revised 75 relevant articles including more than 500,000 cases and found that psoriasis was associated with cardiovascular disease, ischemic heart disease, peripheral vascular disease, atherosclerosis, diabetes, hypertension, dyslipidemia, obesity by body mass index and by abdominal fat and metabolic syndrome but not associated with cerebrovascular disease and cardiovascular mortality. It is important to note that these associations were stronger in hospital based studies whereas population based studies did not show significant associations with the exception of dyslipidemia.

The present article which shows the results of a hospital based study shows results similar of what has been published in the international literature. It is very important to have regional statistical data and I personally hope that this study may become a reference for larger hospital and population based studies in India.

It is important to call attention to dermatologists and medical practitioners in general about the association of psoriasis and cardiovascular disease, and metabolic syndrome. I agree with the authors with the fact that we should get a more detailed and systematic evaluation of psoriatic patients addressing possible risk factors for metabolic syndrome and cardiovascular disease.

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DOI: 10.7241/ourd.20141.04

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ASSOCIATION BETWEEN *HERPES SIMPLEX VIRUS* TYPE 2 (HSV 2) AND BAD OBSTETRIC OUTCOMES

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Source of Support:
Kirkuk Health Authority
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 19-28 Date of submission: 04.10.2013 / acceptance: 05.12.2013

Abstract
Introduction: HSV is a common human pathogen that lead to lifelong latent infection. Maternal infections may be associate with transmission to the fetus. The risk factors associated with HSV 2 seropositivity in pregnant women in Iraq are not well studied.
Aim: The present study conducted to verify the prevalence of HSV 2 infections in women with bad obstetric history (BOH) in Kirkuk Governorate.
Material and Methods: HSV 2 seropositivity among women aged 14 to 48 years was investigated by determination of HSV 2 IgG and IgM in a prospective, case control descriptive study.
Results: The overall HSV 2 seroprevalence was 29.9%, with a non significant difference between women with BOH and women with normal pregnancy. HSV 2 IgM, as an indicator of current infection was demonstrated in 2% of the studied population, and was significantly (P=0.002) higher in women with BOH compared to women with normal pregnancy. Both HSV 2 IgG and IgM were significantly varied with age groups, with trends of increasing with older ages. HSV 2 IgG was statistically significantly higher in working women (P=0.03) as compared to housewife.
Conclusions: Significant association was found between HSV 2 seroprevalence and education levels, residence, smoking and animal exposure. Presence of pregnancy in women with HSV-2 latent infection was a risk factor for development of BOH.

Key words: TORCH; HSV; BOH, IgM; IgG; Kirkuk; Iraq

Cite this article:
Hala Mohamed Majeed Hassan, Abdulghani Mohamed Alsamarai, Zainab Khalil Mohamed Aljumaili, Firah Ghali Alsalihi. Association between Herpes Simplex virus type 2 (HSV 2) and bad obstetric outcomes. Our Dermatol Online. 2014; 5(1): 19-28.

Introduction

Viral infections accounts for major part of maternal infections which was responsible of the unfavorable outcome of pregnancy, mainly rubella, cytomegalovirus (CMV) and Herpes Simplex Virus (HSV) infections [1]. Genital herpes simplex viral infection is one of the most common sexually transmitted diseases [2].

Herpes simplex virus (HSV) infections are caused by two strains, HSV-1 and HSV-2. Orolabial infection is mainly caused by HSV-1, however, this strain is responsible for up to 53% of primary genital herpetic infection [3]. 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 [4-6]. In addition to agent factor, genetic may play a role in susceptibility to HSV infection [7].

Primary genital HSV-1 or HSV-2 infection in pregnant women can result in abortion, premature labor and congenital and neonatal herpes [8-10]. HSV-2 infections in the newborn are particularly severe and can involve the CNS [11].

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 [12,13]. Little is known about the risk factors associated with HSV seropositivity in pregnant Iraqi women [14-17]. 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, still it represent a problem in developing countries [18]. 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. Using healthcare database, seroprevalence of TORCH complex was determined among women with bad obstetric history (BOH) [18,19].

Only four studies reported concerning seroprevalence of HSV 2 in Iraqi women with bad obstetric history [14-17]. These four studies reported a wide range of HSV 2 seropositivity (with range from 5.8% to 73.9 for IgM), while other study for Iraq, reported seroprevalence of 28.9% HSV 2 IgM in pregnant women [20]. In addition, the study population of the 3 studies ranged from 100 to 162 subjects, which is lower than sample size required for HSV 2 seroprevalence study. Recently, Zainab et al [15] in a large study population, reported a HSV-2 IgM seroprevalence of 5.8% in women with BOH in Kirkuk, Iraq. In addition, only two studies reported Seroprevalen of HSV-2 in Iraqi women with BOH, their rate was 60.6% [14] and 34.5% [15]. Furthermore, the studies performed in Arab countries reported a range of 0.5% [21] to 7.6% [22] for HSV2 IgM and 6.5% [21] to 27.1% [23] for HSV2 IgG in pregnant women.

The literature review [19] 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 [15]. The prevalence of maternal infection reported by the studies identified in literature regarding HSV 2 may be an underestimate of actual rates of infection as not all pregnant women in Iraq may have access to or choose to access formalized antenatal care. This could be due to financial constraints, difficulties in accessing these facilities, personal or cultural beliefs and interest of health professional education and research institutions. 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, including Iraq [19].

This literature review highlights the high microbial maternal infection rates in the developing world, including Iraq. 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 Iraq, data from seroepidemiological research will be beneficial in guiding public health policy, research interests and donor funding towards achieving improvement in health care delivery [19].

The aim of this study was to identify seroprevalence of HSV 2 IgG and IgM in women with bad obstetric history compared to those with normal pregnancy and the association of these markers with socio-demographic variables of Iraqi population in Kirkuk Governorate.

Patients and Methods

Study Design and Settings

The study design is a Descriptive Case Control Study and was performed in Kirkuk General Hospital. The study proposal was approved by Tikrit University College of Science ethical committee and Kirkuk Health Authority Research Committee. Informed consent taken from each women included in the study.

Study Population

The study population is women with childbearing age. Study population was recruited from Kirkuk General Hospital. A 838 women with age range from 14 to 48 were included in the study. Of the total, 547 women were with bad obstetric history (BOH) and 291 women with normal previous pregnancy as control group. The demographic information of these groups are shown in Table I. For serological analysis, 5-10 mL of venous blood was collected in a sterile container with strict aseptic precautions from each study subject. The serum was separated and stored in numbered aliquots at -20 oC till assayed. All the serum samples collected from the study and control groups were tested for HSV 2 IgM and IgG antibodies by commercially- available (ELISA) kits. The results read by a Microwell reader and compared in a parallel manner with controls; optical density read at 450nm on an ELISA reader.

Collection of data

All recruited women were subject for clinical examination and laboratory investigations were carried out for the study subjects to exclude other causes of foetal wastage, such as hypertension, diabetes mellitus, syphilis, Rh (rhesus) incompatibility, physical causes of abortion, and consanguinity. Subjects with known causes of foetal wastage were excluded from the study. All of them were interviewed to ascertain age, medical and obstetric information.

Group		Number	Mean age ± SD in years
Women with bad obstetric history	Pregnant	292	28.35 ± 7.25
	Non pregnant	255	28.24 ± 6.81
	Total	547	
Women with normal pregnancy	Pregnant	140	27.40 ± 6.24
	Non pregnant	151	28.06 ± 10.51
	Total	291	
Grand total		838	28.42 ± 7.72
P value	ANOVA	NS	

Table I. Study population.

Determination of HSV-2 IgM and IgG

ELISA was used for determination of IgM and IgG for HSV-2 and the test was performed according to manufacturer instructions. The kit purchased from BioCheck, Inc, 323 Vintage Park Dr, Foster City, CA 94404.

Statistical Analysis

The proportion and the mean value were computed in appropriate situations. To find out any association between categorical data, Chi square test was employed using the SPSS (Version 16). If the sample size in BOH group not reach the targeted number Power Analysis were performed to determine the accuracy of findings. The study finding data were presented as frequency ± SD and 95% Confidence Interval. The determinants for HSV 2 infection is determined by calculation of Odd Ratio. Chi square used to determine the significance of differences between the groups.

Results

A total of 838 women were recruited to study, of them 547 were with BOH and 291 were with normal previous pregnancy. The demographic of the study population included in the statistical analysis was as shown in Table I. There was no significant differences in mean of age between the study groups.

The overall HSV 2 seroprevalence in our study population was 29.9%, with a non significant (X^2=0.59, P=>0.05) difference between women with BOH (29.1%) and women with normal pregnancy (31.6%). However, there was significant difference between pregnant and non pregnant women in BOH (X^2 =10.45, P=0.001) group, while women with normal pregnancy outcome demonstrate the same pattern but not reach the significant level (Tabl. II).

HSV 2 IgM, as an indicator of current infection was demonstrated in 2% of the studied population, and was significantly (X^2=9.23, P=0.002) higher in women with BOH (3.1%) compared to women with normal pregnancy (0%). There was significant (X^2=11.63, P=0.001) difference in HSV 2 IgG seroprevalence between pregnant and non pregnant women (Tabl. III).

Both HSV 2 IgG and IgM were significantly varied with age groups, with trends of increasing with older ages (X^2=30.2, P=0.000 for IgG; X^2=7.93, P=0.048 for IgM). HSV 2 IgG seroprevalence was higher in women with age of above 40 (47.9%), while lower rate was in the age of 20-29 years (24.6%). HSV 2 IgM was not detected in women with age of less than 20 years, however, the higher seroprevalence rate (5.5%) was in women with age of 20 – 29 years (Tabl. IV).

Group [Number]		Number positive [Percent]	
		IgM	IgG
Bad obstetric history	Pregnant [292]	8 [2.7]	102 [34.9]
	Non- pregnant [255]	9 [3.5]	57 [22.4]
	X^2	0.28	10.45
	P value	NS	0.001
	Total [547]	17 [3.1]	159 [29.1]
Normal pregnancy	Pregnant [140]	0 [0]	42 [30]
	Non- pregnant [151]	0 [0]	50 [33.1]
	X^2	-	2.09
	P value	-	NS
	Total [291]	0[0]	92 [31.6]
Grand total [838]		17 [2]	251 [29.9]
X^2 BOH versus Normal Pregnancy		9.23	0.59
P value BOH versus Normal Pregnancy		0.002	NS

Table II. Herpes Simplex virus seroprevalence in women with bad obstetric history.

Group [Number]	Number positive [Percent]	
	IgM	IgG
Pregnant [432]	8 [1.9]	152 [35.2]
Non - pregnant [406]	9 [2.2]	99 [24.4]
X^2	0.14	11.63
P value	NS	0.001

Table III. Herpes Simplex virus seroprevalence in pregnant compared to non-pregnant women.

Age group in years	IgM Number positive\total [%]				IgGNumber positive\total [%]			
	Control	Patient	X2	Pvalue	Control	Patient	X2	PValue
14 – 19	0\47 [0]	0\45 [0]	ND	-	7\47 [14.9]	14\45 [31.1]	3.43	0.053
20 – 29	0\126 [0]	13\240 [5.5]	7.1	0.008	60\126 [47.6]	59\240 [24.6]	20.0	0.000
30 – 39	0\86 [0]	3\214 [1.4]	1.2	NS	21\86 [24.4]	63\214 [29.4]	0.76	NS
40 – 48	0\32 [0]	1\48[2.1]	0.67	NS	4\32 [12.5]	23\48 [47.9]	10.8	0.001
X^2	ND	7.93			28.5	30.2		
P value	-	0.048			0.000	0.000		

Table IV. Comparison of Frequency of HSV-2 in BOH compared to control agents in regard to age.

ND = Non determinable.

HSV-2 IgG seroprevalence was significantly different between women with BOH and control in age groups of 20-29 years (X^2=20, P=0.000) and 40-48 years (X^2=10.8, P=0.001). However, IgM seroprevalence was significantly (X^2=7.1, P=0.008) higher in women of 20-29 years of age with BOH (5.5%) than in control group (0%). As shown in Table V, HSV-2 IgM was significantly higher in women with BOH of age less than 30 years (X^2=4.17, P=0.044) and significantly higher in this age group as compared to control (X^2=8.12, P=0.004). HSV-2 IgG seroprevalence was significantly higher in control (X^2=8.72, P=0.003) as compared to women with BOH of age <30 yrs. However, it was significantly higher in women with BOH (X^2=5.33, P=0.021) as compared to control in women of >30 yrs age. Furthermore, Odd ratio indicated a significant association between recent/present infection (positive IgM) and younger age (<30 yrs) (OR=3.083, P=0.041) (Tabl. V, VI).

The frequency of IgM was higher in urban (8.6%) than in rural (1.1%) areas with a marginal p value (0.055). Acute HSV-2 infection as demonstrated by IgM detection was higher in housewife (3.2%), uneducated (3.3%), smoker (3.4%), and large size family (3.6%) as compared to working, educated, non smoker women and small size family, respectively. However, the frequency of acute HSV-2 infection was significantly higher in women with less frequent (6.9%, X^2=5.51, p=0.01) infection (1-2) (Tabl. VII). OR confirmed a positive association (OR=3.473, p=0.01) between abortion and recent HSV-2 infection (Tabl VII). Hemoglobin level, animal exposure and presence of congenital anomalies did not show a significant differences and this finding was confirmed by OR calculation (Tabl. VII, VIII).

The pattern of HSV-2 IgG seroprevalence (remote or latent infections) was different from that of acute infection. HSV-2 IgG seroprevalence was significantly higher (X^2=15.667, p=0.000) in urban (34.3%) than in rural (17.8%) areas. OR confirmed the significant association (OR=2.41, p=0.0001) between residence and HSV-2 IgG seroprevalence (Tabl. VII, VIII).

HSV 2 IgG was statistically significantly (X^2=4.115, P=0.03) higher in working women (42.2%) as compared to housewife (27.9%), however, OR not confirmed an association with mother occupation (OR=1.183, p=NS) (Tabl. VII, VIII).

HSV-2 IgG seroprevalence was significantly lower (X^2=5.05, p=0.025) in uneducated (27.1%) as compared to educated (38.7%) women. This differences also confirmed by OR calculation (OR=1.7, p=0.02) (Tabl. VII, VIII).

Smoking significantly influence HSV 2 IgG (X^2=19.42, P=0.000) seroprevalence and OR (OR=2.465, p=0.000) confirmed this association (Tabl. VI, VII). HSV 2 IgG seroprevalence was higher (30.4%) in small size (CR $\leq$ 3) than that in large size family (26.1%), but the difference was not statistically significant (X^2=0.84, p=NS) and such association was confirmed by OR (OR=1.237, p=NS) (Tabl. VII, VIII).

HSV-2 IgG was significantly (X^2=13.41, p=0.000) higher (38.7%) in women exposed to animals as compared to non exposed (23.8%). This association confirmed by OR (OR=2.018, p=0.0002) calculation. However, hemoglobin level, number of abortion, and congenital anomalies did not show any association with HSV-2 IgG prevalence. Pregnancy presence with HSV latent infection was a risk factor for development of BOH (OR=1.683,p=0.0007) in women with latent HSV-2 infections, while not a risk factor in acute infection (OR=1.202, p= >0.05) (Tabl. VIII).

Ageinyears	Total No.		IgM Number positive [%]				IgG Number positive[%]			
	Control	Patient	Control	Patient	X^2	P	Control	Patient	X^2	P
1-29	173	285	0 [0]	13 [4.6]	8.12	0.004	67 [38.7]	73 [25.6]	8.72	0.003
30-48	118	262	0 [0]	4 [1.5]	1.82	NS	25 [21.2]	86 [30.5]	5.33	0.021
X^2			ND	4.17			9.98	3.44		
P			-	0.044			0.002	0.06		

Table V. Frequency of HSV -2 according to age of <30 and above.

Variable	Odd ratio [95% Confidence interval]	P value
HSV 2 IgM	3.083 [0.992 – 9.577]	0.041
HSV 2 IgG	1.419 [0.979 – 2.055]	NS

Table VI. Odd ratio of TORCH agents in regards to age of women lower than 30 years.

Variable	[Number]	Number positive [Percent]	
		IgM	IgG
Residence	Rural [174]	2 [1.1]	31 [17.8]
	Urban [373]	15 [8.6]	128 [34.3]
	X^2	3.25	15.667
	P value	0.055	0.000
Occupation	House wife [502]	16 [3.2]	140 [27.9]
	Working [45]	1 [2.2]	19 [42.2]
	X^2	0.128	4.115
	P value	NS	0.03
Education	Uneducated [454]	15 [3.3]	123 [27.1]
	Educated [93]	2 [2.2]	36 [38.7]
	X^2	0.341	5.05
	P value	NS	0.025
Smoking	Present [327]	11 [3.4]	118 [36.1]
	No smoking [220]	6 [2.7]	41 [18.6]
	X^2	0.17	19.42
	P value	NS	0.000
Crowding Index	≤ 3 [478]	11 [2.9]	116 [30.4]
	3.1– 8 [60]	6 [3.6]	43 [26.1]
	X^2	0.04	0.84
	PS value	NS	NS
Haemoglobin	< 11 [151]	3 [2]	36 [23.8]
	11-19 [396]	14 [3.5]	123 [31.1]
	X^2	0.43	2.42
	P value	NS	NS
Animal exposure	Present [194]	5 [2.6]	75 [38.7]
	Absent [353]	12 [3.4]	84 [23.8]
	X^2	0.28	13.41
	P value	NS	0.000
Abortion	1–2 [116]	8 [6.9]	31 [26.7]
	3–8 [431]	9 [2.1]	128 [29.7]
	X^2	5.51	0.26
	P value	0.01	NS
Congenital anomalies	Absent [498]	16 [3.2]	146 [29.3]
	Present [49]	1 [2.1]	13 [26.53]
	X^2	0.204	0.168
	P value	NS	NS

Table VII. Frequency of HSV 2 IgG and IgM in regard to sociodemographic characteristics.

Organism	Variable	Odd ratio [95% Confidence interval]	P value
Residence	IgM	0.277 [0.063 – 1.287]	NS
	IgG	2.410 [1.547 – 3.754]	0.0001
Occupation	IgM	1.448 [0.187 – 11.182]	NS
	IgG	1.183 [0.628 - 2.228]	NS
Education	IgM	0.643 [0.115 – 2.862]	NS
	IgG	1.700 [1.100 – 2.700]	0.02
Crowding index	IgM	0.786 [0.286 – 1.865]	NS
	IgG	1.237 [0.821 – 1.865]	NS
Smoking	IgM	0.805 [0.293 – 2.211]	NS
	IgG	2.465 [1.640 – 3.705]	0.000
Haemoglobin	IgM	0.553 [0.157 – 1.953]	NS
	IgG	0.695 [0.452 – 1.069]	NS
Animal exposure	IgM	0.752 [0.261 – 2.166]	NS
	IgG	2.018 [1.382 – 2.948]	0.0002
Abortion	IgM	3.473 [1.309 – 9.123]	0.01
	IgG	0.863 [0.545 – 1.368]	NS
Congenital anomalies	IgM	1.593 [0.207 – 12.278]	NS
	IgG	1.149 [0.592 – 2.229]	NS
Pregnancy	IgM	1.202 [0.459 – 3.145]	NS
	IgG	1.683 [1.246 – 2.274]	0.0007

Table VIII. Association of HSV 2 seropositivity with sociodemographic characteristics using Bivariate analysis.

Discussion

Infection with herpes simplex is one of the most common sexually transmitted infections. Because the infection is common in women of reproductive age it can be contracted and transmitted to the fetus during pregnancy and the newborn [15,19]. Herpes simplex virus is an important cause of neonatal infection, which can lead to death or long-term disabilities. Rarely in the uterus, it occurs frequently during the transmission delivery [24]. The greatest risk of transmission to the fetus and the newborn occurs in case of an initial maternal infection contracted in the second half of pregnancy. However, the transmission risk of maternal-fetal-neonatal herpes simplex can be decreased by performing a treatment with antiviral drugs or delivery by caesarean section [24]. Different geographical areas and studied populations reported in literature indicated a different trends and patterns [25].

In the present study, an overall HSV IgG seroprevalence of 29.9% was found among women, and there was no significant difference between women with BOH (29.1%) as compared to women with normal pregnancy (31.6%). However, there was a significant difference (X^2=11.63, p=0.001) in seroprevalence between pregnant (35.2%) and non pregnant (24.4%) women. The present study seroprevalence was significantly (X^2=5.2, p=0.022) higher (29.9%) to that reported in a recent study in women (24.2%) from Kirkuk population [15]. This variation could be due that sample size in the present study was larger than the previously reported one.

This study HSV 2 seroprevalence (35.2%) in pregnant women was higher to that reported for Italy (7.6-8.4%) [24], China (10.8%) [26], Indonesia (9.9%) [27], Bangladesh (9.91%) [28], and UK (10.4%) [29], Tanzania (20.7%) [30], Australia (30%) [31], USA (22%) [32], Switzerland (21.2%) [33], Canada (17.3%) [34], Senegal (22%) [35], Belgium (18.2%) [36], China (23.5%) [37], and Korea (17%) [38], Turkey (4.4%-5%) [39,40], Kashmir (7.5%) [41], India (8.7%) [42], Croatia (6.8%) [43].

In contrast to our study, a much higher HSV 2 seroprevalence has been reported from Zimbabwe (51.1%) [44], Germany (82%) [45], Turkey (63.1%) [46], and Iran (43.75%) [47].

In women with BOH, our HSV2 IgG seroprevalence (29.1%) was lower to that reported for India (33.58%) [48] and Nepal (33.3%) [49]. However, it was higher to that reported for India (16.8-18.6%) [50,51]. Furthermore, the seroprevalence was much lower to that reported for Waset (60.6%), Iraq [14] in women with spontaneous abortion. In pregnant women, this study HSV IgG seroprevalence was higher to that reported for Saudi Arabia (6.5%-27.1%) [21,23,52], Qatar (26.3%) [22], Babylon, Iraq (22.2%) [20]. However, it was lower to that reported for Syria (52%) [53]. The HSV 2 seroepidemiology in women with BOH as this study indicated was lower (29.1%) to a recently reported study (34.5%) from the same geographical area [15]. However, the difference was not statistically significant (X^2=2.36,p >0.05). In addition, in BOH women, HSV-2 seroprevalence was significantly higher (X^2=10.45,p=0.001) in BOH pregnant (34.9%) than that in BOH non pregnant (22.4%) women. This pattern of seroprevalence was inverse to that reported recently for Kirkuk in which the seroprevalence rate was higher in non pregnant BOH women [15]. This variation was due to influence of sample size which is more in this study. The pregnancy was a risk factor (OR=1.683, p=0.0007) for development on BOH in women.

This could be due to that pregnancy may activate the latent HSV-2 infection and subsequently lead to foetal infection. The activation could be influence by hormonal changes during pregnancy which may affect systemic and mainly local immunity or increased body mass index due to fluid retention.

The HSV 2 IgG seroepidemiology varies between different countries, and between groups of individuals included in the studies reported. For example, studies performed in Iraq (11.1-60.6%), Saudi Arabia (6.5-27.1%), and Turkey (4.4%-63.1%), demonstrated a wide range of seroprevalence [15,19]. These variations may be attributed to various sexual behavior, number of previous pregnancies, duration of sexual activity, residence, education, occupation and socioeconomic status, sample size, sampling method, race, and sexual behavior of the studied population [41,42,52,54-56]. Comparison of the HSV-2 seroprevalence in the present study with the mean of that reported for Iraq and global (Tabl. IX) indicated no significant differences (X^2=2.01, p>0.05). In addition, bivariate analysis indicated no significant difference in seroprevalence between the present study and that reported recently for Kirkuk (X^2=2.36, p>0.05); present study and mean rate of seroprevalence with the mean of previously reported Iraqi studies (X^2=1.45, p>0.05); and present versus global studies (X^2=0.025, p>0.05).

HSV-2 IgG Seropositivity in the present study was found to be not significantly associated with history of previous abortion (X^2=0.59, P=NS), a finding not agreed with that reported by others [15,55,57].

However, HSV-2 IgG seroprevalence was more (in women with repeated abortion of ≥ 3, indication that seroprevalence rate increased with increased number of abortion, a phenomenon could be related to the virulence of the latent virus that may be affected by treatment used for abortion. In contrast, HSV-2 IgM seroprevalence was significantly more in women with BOH (X^2=9.23, p=0.002) as compared to control, in addition, IgM seroprevalence rate significantly (X^2=5.51, p=0.01) associated with number of repeated abortion. Furthermore, odd ratio confirmed the association (OR=3.473, p=0.01) between recent infection and development of BOH in women.

In our study, the HSV 2 IgG seroprevalence was more in the older age (40-48 yrs) group (47.9%), and lower (24.6%) in women with age of 20-29 years. In addition, the seroprevalence was higher in women with BOH of ≥30 years , while the pattern reversed in control group. There was a significant variation (X^2=30.2, P=0.000) in HSV 2 IgG seroprevalence between age groups. These findings are comparable to studies reported for other geographical areas [31,36,41,46,52,54-56]. The HSV-2 IgM seroprevalence was significantly higher (X^2=4.17, p=0.044) in women with BOH of 14-19 years of age, OR confirmed such association.

Residence seems to influence HSV 2 seroprevalence as this study demonstrated a significant differences between rural (17.8%) and urban (34.3%) areas. OR confirmed an association between residence and HSV 2 seroprevalence. This findings were not agreed to that reported by others [15,41], however, it was consistent with that reported by Chawla et al [58]. Acute HSV -2 infections also was more in urban areas than in rural, but such difference not reach a significant level. The higher primary infection and seroprevalence may be attributed to sexual behavior in urban areas which is more complicated than in rural areas.

HSV 2 IgG seroprevalence was significantly (X^2=4.11, P=0.03) higher in working women (42.2%) as compared to housewife (27.9%) women, however, OR not confirm such association. This findings agreed to that reported by others [40,41,42,46], and a recent one for Kirkuk [15] while one study from Saudi Arabia [52] reported an association, but when the data grouped as we do, no such significant association was achieved.

HSV 2 IgG seroprevalence was significantly (X^2=5.05, P=0.025) varies according to women education levels in our study and this association was confirmed by OR using bivariate analysis (OR= 1.7, P=0.02). This finding agreed to that reported for Kirkuk population [15]. The seroprevalence was steady increased with education, same to that reported by Chawla et al [58] and Xu et al [59], while other studies show high seroprevalence in less educated women [52,54,60]. However, Biswas et al [42] reported higher incidence in women with secondary school education. Page et al [61], showed the highest prevalence of HSV 2 in women with the lowest education level residing in the highest socioeconomic status area. Rathore et al [41] and Agabi et al [62] not found a significant association between HSV seroprevalence and education levels.

Study		Value or rate
Present study		29.1%
Kirkuk study		34.2%
Iraqi studies		36.9%
Global studies		28.49%
X^2		2.01
P value		NS
Present versus Kirkuk study	**X^2**	2.36
	P value	NS
Present versus Iraqi	**X^2**	1.45
	P value	NS
Present versus Global studies	**X^2**	0.025
	P value	NS

Table IX. Comparison of HSV-2 serprevalence rate with other studies.

In this study, HSV IgG seroprevalence was higher in small size families (crowding index) as compared to large size families and this association was not confirmed by OR calculation. However, Aljumaili et al [15] suggest significant association between small family size and HSV infection. HSV infection is increased with the increase in sexual activity and thus small size families may provide comfortable environment that encourage sex performance. In addition, young women receiving family planning services are at risk for herpes simplex virus type 2 (HSV-2) infection [63].

The literature indicated a paradox in association between HSV 2 seropositivity and lower income and this could be due to differences in risk behavior among the different income groups [15]. It was seen in a study performed for India [42], that majority of Muslims subjects (84.9%; 0/106) were from low income group. It was also observed that Muslims subjects had the lowest HSV 2 seroprevalence (3.8%) compared to Hindu (5.8%) and Christians (12.6%), which may explain that disparity. The suggested risk factors that lead to high HSV 2 seropositivity in developed and some undeveloped countries are not applicable in our society due to religious and social reasons [15].Thus other risk factors are to be speculated in our society, one of these is the male circumcision, as it lowers the prevalence of HSV 2 [64]. Recently reported study [41], higher HSV 2 seroprevalence was found among Christians versus Muslims and this differences in prevalence with religions, may be due to practice of male circumcision at infancy or early childhood by the spouses of the pregnant women among Muslims.

Low socioeconomic status observed in some studies to be associated with HSV 2 seroprevalence [41,42,56,58,61]. However, Germany as a country with high socioeconomic status, the HSV 2 seroprevalence was 82% in pregnant women, while the corresponding value in Arab countries ranged from 6.5% to 27.1%. Thus Islamic legislation concerning faithful family relations and personal hygiene are an important factors that reduce HSV 2 infection [15].

Smoking was associated with significantly higher (X^2=19.42, p=0.000) HSV-2 seroprevalence (36.1%) and this high frequency in smoking women was confirmed by OR (OR=2.465, p=0.000). Hemoglobin level was not demonstrated a significant association with development of BOH in women. However, HSV-2 seroprevalence was significantly higher (X^2=13.41, p=0.000) in women with history of animal exposure and this association confirmed by OR (OR=2.018, p=0.0002).

HSV 2 IgM seroprevalence was 2% indicating that current infection of 2% in our study population, and it was significantly higher (X^2=9.23, P=0.002) in women with BOH (3.5%) as compared to women with normal pregnancy (0%), and about the same in pregnant and non pregnant women. This finding agreed to that reported recent for women in Kirkuk [15]. Our HSV IgM (1.9%) seroprevalence in pregnant women was higher than that reported for Turkey (0%) [39], Saudi Arabia (0.5%) [21], Croatia (1.2%) [43], and Bangladesh (1.8%) [28]. Higher seroprevalence was reported for Babylon, Iraq (28.9%) [20], Turkey (13.8%) [46], Qatar (7.6%) [22] and Kirkuk (3.1%) [15]. In women with BOH, HSV IgM seroprevalence (3.1%) was lower than that reported for India [48,50,68,69], Baghdad, Iraq [16], Waset, Iraq [14], Mosul, Iraq [17], Kirkuk, Iraq [15]. Thus current infection with HSV 2 was lower to that reported in other Iraqi Governorates including Kirkuk [15].

The present study shows a significant variation in current HSV 2 infection between age groups (X^2=7.93, P=0.048), the highest incidence in women with age of 20-29 years (5.5%) old, while the lowest rate in women of <19 years old. Using Bivariate analysis, OR confirmed an association between HSV 2 current infection and age of <30 or > 30 years old (OR=3.083, p=0.041). Furthermore, residence, family size, smoking, hemoglobin level, animal exposure, congenital anomalies and occupation were not show association with HSV-2 IgM seroprevalence. However, current infection of HSV 2 was significantly higher in women with 1 to 2 abortion and OR confirmed such association (OR=3.473, p=0.01).

Conclusion

The present study indicated a significant association between HSV 2 IgG and IgM and bad obstetric history. The overall HSV 2 seroprevalence in our study population was 29.9%, with no significant difference between women with BOH and women with normal pregnancy. Significant association was found between HSV 2 seroprevalence and urban residence, education levels, smoking, and animal exposure. However, HSV 2 seroprevalence was different due to occupation, family size, hemoglobin level, abortion number, congenital anomalies, and age of < 30 years, but OR not confirmed significant association. Furthermore, presence of pregnancy with HSV-2 IgG was a risk factor for development of BOH.

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DOI: 10.7241/ourd.20141.05

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PROPOSAL OF EMPLOY OF EXTRACT OF DESMODIUM ADSCENDENS AS ANTI-HISTAMINIC DRUG: TRIALS OF EFFICACY BY REFLECTANCE SPECTROPHOTOMETRY

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 29-32 Date of submission: 29.10.2013 / acceptance: 06.12.2013

Abstract
Introduction: Aim of our study is to propose the ancient plant Desmodium adscendens, that is hitherto known for combating, when orally administered, a plethora of other ailments and diseases and considered even an anti-histaminic, for external use. An inhibition of histamine depot by inhibiting the enzymatic activity of histidine decarboxylase can be suspected, since biological principles contained in D.A. belong to the same pharmacological class of natural derivatives that elicit the same effects (nicotinic acid, cyanides and quercetine) and of synthetic alkylammines (e.g contained in bubble baths). Desmodium adscendens is a perennial plant, growing wild in Africa, especially in Camerun and Ivory Coast as well as in South and Central America and the continent of Asia. Aborigines were accustomed to employ the entire plant for rites of initiation and other shamanistic ceremonies. Notwithstanding, it has been used for thousands of years by peoples native to those areas where it grows for a variety of health issues. This plant has been studied in France, Italy, India and Canada and appreciable are the results with regard to bronchial dilation, relaxation of smooth muscles, antihistamine effects, when orally administered, albeit there is a neat evidence of an extreme paucity of references about its ability to act as a completely natural anti-histaminic herb for external use.
Material and Methods: To conduct our study we have recruited 24 volunteers out from 4 categories of employees generally suffering from Type I Contact Dermatities. They were prayed to spread the hydroglyceric extract of Desmodium adscendens every morning at 10.00 a.m. and every afternoon at 03.00 p.m onto the skin of forearms and cheeks, where an artificial rash was evoked by the use of a mix made up with allergenic herbs. As far as the evaluation of the degree of severity of skin inflammation is concerned we have used the Reflectance Spectrophotoscopy, to measure the erythematous manifestation twice a day for one week: at 09.00 a.m. (to check the gravity of erythema induced in each single case) and at 04.30 p.m., to check the real efficacy of the D.A. hydroglyceric extract. We have to keep seriously on account that Reflectance Spectrophotoscopy can't evaluate histamine concentration and its characteristic effects and that the 40–50% of cases of erythematous manifestations are not rigorously ascribable to the phenomenon of the histamine release.
Results and Conclussions: Results are amazingly encouraging, since it has been observed that the mean value of the blanching effect of the electuary on erythema is of 48.8%.

Key words: Desmodium; anti-histaminic; Spectrophotometry; Erythema; Skin rash

Cite this article:
Lorenzo Martini, Roberto Solimé. Proposal of employ of extract of Desmodium adscendens as anti-histaminic natural drug: trials of efficacy by Reflectance Spectrophotometry. Our Dermatol Online. 2014; 5(1):29-32.

Introduction

Desmodium adscendens var. ceruleum (Lindl) (synonymous: *Desmodium strangulatum* Thwaites od *Desmodium Twaitesii* Baker) is a perennial plant, growing wild in Asia, especially in India, Java, Malaysia, Sarawaki and Philippines, Indian Ocean (Madagascar, Mauritius and Seyscelles) [1-7]. Africa (Angola, Cameroun,Ivory Coast,Swaziland). In ancient times aborigines were accustomed to employ the entire plant for rites of initiation and other shamanistic ceremonies. It has been used for thousands of years by peoples native to those areas where it grows for a variety of health issues: asthma, bronchitis, jaundice, hepatitis, muscle cramps and backache. This plant has been studied in France, Italy, India and Canada and appreciable are the results with regard to bronchial dilation, relaxation of smooth muscles, anti-histamine effects, when orally administered, albeit there is a neat evidence of an extreme paucity of references about its ability to act as a completely natural antihistaminic herb for external use [4-7].

Effectively, only Rastogi & Pandey [8] referred that different concentrations of a hot water extract of *Desmodium adscendens* showed that the extract's inhibition of histamine-induced reactions is largely competitive and that its effect of reducing histamine content is dose-dependent, and that this entire process takes 10-30 s.

Besides, Mitsuma & De Hengs [9] assert that the same extract causes a dose-dependent increase of the amount of beta-endorphines in the pituitary gland, competitively with the same histamine and that this complementary contingency occurs in 20min.

Phytochemical investigations on hydroglyceric extract of Desmodium adscendens has led to the isolation of several alkaloids and triterpenoid saponins although there is evidence of a valuable percentage of indole-3-alkyl amines and alpha and beta phenylethylamines that play an agonistic role of paramount importance in the physiological pathway of histaminic induced reactions on safe or scarified skin [8,9].

A pharmacological theory flourished at the half of the XX century, about indole-alkylamines that may be useful in the control of histamine-release, especially as mimetics and/ or direct inhibitors with regards to receptors for histamine. MacIntosh was the first in 1949 [10] to disclose that histamine can be liberated by certain organic bases (aromatic amines) and successively Feldberg et al. [11] and Erspamer [12] in 1954 deepened this argument, discovering that these amines could be useful to reduce the phenomenon of the histamine release.

Aim of our study is to propose the external use of a plant as an anti-histaminic drug: the *Desmodium adscendens*, that is known and employed for combating, when orally administered, manifold ailments and diseases and already considered an anti-histaminic drug when taken orally.

In this study we focus our attention on the time necessary to observe the blanching effect of the hydrogliceric extract of *Desmodium adscendens* on the skin rash, that has previously been artificially evoked by the aids of an herbal electuary and on the blanching degree of the same extract.

In future we will provide to study how long the effect of blanching on the skin rash can last.

Material and Methods

To conduct our study we have recruited 24 volunteers out from 4 cathegories of employees generally suffering from Type I Contact Dermatities:

- 6 (six) seasonal sunflower pickers (in their specific case the peculiar noxa was represented by the sesquiterpenic lactones contained in the flowers);
- 6 (six) hairdressers (in their specific case the peculiar noxa was represented by the Brandowky bases for hair dyes);
- 6 (six) tawers (in their case the peculiar noxa was represented by the Potassium dichromate contained in leather dyes);
- 6 (six) workers at quick frozen fish processes in food industry (in their specific case the peculiar noxa was represented by the hemocyanines contained especially in lobsters and crabs).

We have aprioristically excluded from the experiments:

Pregnant women.

Women or men which generally use cosmetic products that are referred to induce dermatitis or eczemas.

Individuals that declared a certain personal hypersensitivity to chocolate.

Individuals that denounced their participation to another clinical trial during present trial.

Subjects taking antibiotic, anti-viral, anti-fungal drugs or corticosteroids within 3 days of inclusion. The trials were conducted in accordance with the good clinical practices (GCP) after having dispatched the plans of study to the competence of the Department of Work, Health and Social Politics in Rome, since trials deal with herbal therapy, only an informed consent was required from each volunteer prior to participate to the experiment.

An electuary was made up with roots of Pastinaca sativa (CAS 90082-39-6 EINECS/ELINCS 290-129-0), fruits and leaves of Ficus Carica (CAS 90028-74-3 EINECS/ELINCS 289-868-1) and leaves and roots of Angelica Archangelica (CAS 84775-41-7 EINECS/ELINCS 283-871-1) and diluted in a solution of water and glycerine.

This electuary, once applied to safe skin, is capable to induce a quasi-sudden (9-23 min) rash, itching/swelling (especially of the face/throat/armpit areas), and for, all the 24 volunteers are gently requested to spread this electuary onto their forearms and cheeks once a day for 7 days, every morning 8.00 a.m.

Afterwards they are required to spread the hydroglyceric extract of Desmodium every morning at 10.00 a.m. and every afternoon 03.00 p.m, that is respectively two and seven hours after the application of the herbal electuary.

As far as the evaluation of the degree of severity of skin inflammation is concerned we have decided to use the Reflectance Spectrophotoscopy [13] albeit Skin rash status and Erythema must be regarded as a mere descriptive observation with regards to the severity of skin inflammation, so we measured the erythematous manifestation twice a day for one week, at 09.00 a.m. (to check the gravity of erythema induced in each single case) and at 04.30 p.m., to check the real efficacy of the *Desmodium adscendens* hydroglyceric extract.

We have to punctuate that Reflectance Spectrophotoscopy can't evaluate at all the histamine concentration and its characteristic effects and that the 40–50% of cases of erythematous manifestations are not rigorously ascribable to the phenomenon of the histamine release.

For this, we have decided to administer the herbal electuary that induces skin rashes onto skins of subjects already compromised by conclamated contact dermatities, exorcizing by this way the statistical gap provided by the fact that 40-50% of cases of erythemata may arise from other aetiologies.

Besides we have decided to evaluate the blanching effect of the extract of *Desmodium adscendens* even by the use of a magnifying glass, albeit we can assure that results are really encouraging (without debating these values in this seat).

Redness is calculated by subtracting the absorbance due to hemoglobin from the absorbance of the green filter, using Color Meter II (Cortex Technology, Hadsund, Denmark). Three independent measurements were made at an interval of 30 s, on the basis of which the average value was determined. Instrumental assessments were performed in the same room conditions (temperature 20-22°C, humidity 20-40%) after 15 min acclimatization by the same physician.

Reflectance spectrophotoscopy [14] provides a useful adjunct to the current subjective method for the evaluation of irritation. This method provides an objective measure of erythema (one of the hallmarks of cutaneous irritation) and provides a continuous grading scale for this parameter. This is in contrast to the current subjective evaluations by a trained observer. Using a continuous scale provides several advantages, the most obvious of which is the ease of statistical analysis of the data.

The difficulty of discriminating between grades is removed and the influence of background skin colour is reduced. Spectrophotometric readings were taken between the wavelengths of 510 and 650 nm.
The absorbance maximum for hemoglobinis in the green region of the spectrum. Thus, the relative absorbance for the green and red regions is related to the degree of erythema [7]. The values used for the correlation were calculated as follows:

Adjusted absorbance = (Gt – Rt) – (Gc – Rc)

Where G is the absorbance in the green region (570-580 nm), R is the absorbance in the red region (645-650 nm), t is the treated site, and c is the control site. The data were analyzed using Spearman's rank correlation procedure.

Results and Discussion

Table I refers the mean values of E-indices (Erythema indices) recorded each of every 7 morning of trial and the mean values of E-indices recorded each of every 7 afternoon.
Normal values of E-indices (that is the value recorded by Reflectance Spectophotometry spectra measured on safe skin) depend strictly on the phenotype and especially as far as the presence of haemoglobin and melanin (that are the major responsible of the spectrophotometric spectra) are concerned, we have to stress to keep in account the range of E-indices that goes from Finnish subject (5.8) to Russian (8.41), from Chinese (13.90) to Iranian (21.65), from Kazakhs (13.90) to Nepalese (46.09) and finally to African subject (49.06).
For Caucasians the mean value generally accepted is 8.41 [15]. We desire to emphasize that volunteer 404 was mulatto, for this, E-indexes resulted higher than the standard ones.
The mean value of the results recorded as blanching effect onto erythema afforded by the hydroglyceric extract of D.A. is 48.8%.

Volunteer	Mean of Initial E-index (measurement at 09.30 a.m.)	Mean Final E-index (measurement at 04.40 p.m.)
101	17.7	12.1
102	16.1	9.9
103	15.4	8.5
104	18.2	9.7
105	15.6	8.2
106	16.9	7.4
201	18.1	9.1
202	17.4	6.6
203	18.8	7.4
204	14.9	5.7
205	15.8	9.1
206	16.2	8.8
301	19.1	7.9
302	15.7	9.6
303	18.7	8.3
304	15.7	7.7
305	16.4	9.8
306	17.5	6.1
401	18.6	8.4
402	19.2	7.8
403	18.3	8.9
404	27.9	19.6
405	18.5	9.0
406	16.9	8.5

Table I. Changes of E-indices's values during the day.

Conclusion

It is noteworthy to stress that a perennial, redundant and infesting vine, native to tropical and equatorial areas, could elegantly replace, in certain cases, some synthetic drugs for topical use, apt to interfere with the phenomenon of histamine release, generally chemical remedies that act inhibiting the enzymatic functionality of histidine decarboxylase, catalyzing the transformation of histidine into histamine (atypical antihistaminics), inhibiting the action of histamine by blocking its attachment to histamine receptors (H1-H4 histamine receptors) or acting as mastzellen stabilizers.

The anti-erythematous effect of the herb is guaranteed almost for 7 hours.

We must apologize that, even if results appear satisfactory, the real congeries of causes that evoke erythematous manifestations in human skin is not precisely predictable, for, we attempted to resolve this dilemma, by inducing skin inflammations to volunteers which are already compromised from dermatological diseases.

In future we will provide to make additional measures of E-indices after 7 hours the final measurement at 4.30 p.m., to validate the chance that *Desmodium adscendens* could be long-lasting effective.

Effectively all the volunteers assure they did not need to scrape the inflamed area during the night.

Acknowledgement

We are proud to declare that we have not received any funding or financial support from anybody: raw materials and herbs have been furnished by the Firm that has co-worked in this study (Solimé Srl.) and the Department of Pharmaceutical biotechnologies has permitted to use without limits all the instruments and tools were necessary to conduct the experiments.

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PROPOSAL OF EMPLOY OF EXTRACT OF DESMODIUM ADSCENDENS AS ANTI-HISTAMINIC DRUG: TRIALS OF EFFICACY BY REFLECTANCE SPECTROPHOTOMETRY

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 33 Date of submission: 07.01.2014 / acceptance: 09.01.2014

Cite this article:
Miloš Jeseňák. comment: Proposal of employ of extract of Desmodium adscendens as anti-histaminic natural drug: trials of efficacy by Reflectance Spectrophotometry. Our Dermatol Online. 2014; 5(1): 33.

Complementary and alternative medicine is surviving across the decades and also in the medicine of 21st century. The physicians are meeting different preparations during their praxis and the challenge for them is to find the right way how to navigate the patients in the middle of thousands of preparations and methods.

Complementary and alternative medicine is considered to be the therapeutic approaches and methods which are not involved in the standard conventional treatment schema. This medicine should not be alternative to the standard therapy but should be used complementary. Many studies have confirmed that the patients suffering from chronic allergic diseases (respiratory, skin) are very prone to use various methods of alternative medicine [1]. In general these preparations are considered to be safe, but in reality, they can worsen the allergic diseases and can be in conflicts with standardly applied therapy [2]. Therefore it is very necessary to provide the studies such as the study by Martini & Solimé [3] which are able to show the proposed efficacy of the selected modality of alternative therapy along with the confirmation of their safety. Today, many preparations of complementary medicine possess the relevant studies which are able to fulfil the strict criteria of evidence based medicine. Many widely used natural immunomodulators, e.g. beta-glucans, have shown the anti-allergic characteristics [4]. They have also the positive effects on the skin physiology [5]. Another widely studied group of natural preparations and different phytopharmacs. The study of Martini & Solimé [3] objectively showed that the extract of *Desmodium adscendens* possesses antihistaminic and antiallergic effect on the skin erythema. The plant *Desmodium adscendens* used for decades in the traditional medicine in many pathological conditions. The current study can support its topical used in the complex management of atopic eczema and other skin diseases which are accompanied with erythema and pruritus. The topical complementary therapy and other modalities are highly required by the desperate eczematic patients [6]. This study enlarges the possibilities of complementary topical therapy of chronic skin diseases in the context of "integrative medicine", which combines the successes of standard, conventional and complementary therapy. There is an urgent need also to perform the studies with other widely used and recommended preparation for eczema just to create some system in this broad group of natural products.

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DOI: 10.7241/ourd.20141.06

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LUPUS TUMIDUS: UNDERREPORTED VARIANT OF *LUPUS ERYTHEMATOSUS* (A CASE REPORT AND REVIEW OF THE LITERATURE)

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Source of Support:
Nil
Competing Interests:
None

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Our Dermatol Online. 2011; 5(1): 34-36 Date of submission: 23.10.2013 / acceptance: 20.11.2013

Abstract
Introduction: Lupus erythematosus tumidus (LET) is an underreported variant of lupus erythematosus (LE) that is characterized by soft urticarial-like elements usually located on the sun exposed skin. LET is featured with high photosensitivity. Lesions of LET resolve without scarring and do not cause disfigurement as seen in the discoid LE variants. Lesions of LET may co-exist with other variants of LE: discoid or systemic.
Main observations: The case presents a female patient with LET localized on the lateral infraorbital areas of her face and cheeks. Histopathological evaluation showed a lymphocytic infiltrate in the middle and deeper parts of the dermis. This article also presents a contemporary review of the clinical variants of LET, histopathological features and approaches to the treatment of LET.
Conclusions: LET should be considered in urticarial-like lesions on the skin of the face and other skin exposed areas. Histopathological examination is needed to make a definitive diagnosis of the condition and helps in cases when the clinical presentation is subtle or non-specific.

Key words: lupus erythematosus; lupus tumidus; tacrolimus

Cite this article:
Viktoryia Kazlouskaya, Karan Lal, Alena Khaikova. Lupus Tumidus: underreported variant of lupus erythematosus (a case report and review of the literature). Our Dermatol Online. 2014; 5(1): 34-36..

Introduction

Lupus erythematosus tumidus (LET) is an underreported variant of lupus erythematosus (LE) that is characterized soft urticarial-like elements usually located on the sun-exposed skin. LET is featured by high photosensitivity. Lesions of LET resolve without scarring and do not cause disfigurement as seen in discoid LE variants. Lesions of LET may co-exist with other variants of LE: discoid or systemic.

Case Report

A 41 year old otherwise healthy female presented with asymptomatic lesions on both sides of her face. The lesions were present for several weeks and had first appeared at the beginning of the summer season. Scaling of the skin and atrophy were absent in the lesions. The patient noticed exacerbation of lesions after increased sun exposure. She denied a family history of similar conditions. On physical examination, poorly differentiated soft urticarial lesions were located on both the right and left sides of her face inferior to the eyes and cheeks (Fig. 1).
Biopsy of the lesions was performed. Histopathological examination revealed an unchanged epidermis without atrophy or desquamation. Periadnexal and perivascular lymphocytic infiltrates were present with concomitant mucin deposition throughout the dermis (Fig. 2).
Clinical presentation along with histopathologic analysis confirmed the diagnosis of lupus erythematosus tumidus (LET). Laboratory tests including erythrocyte sedimentation rate (ESR), anti-nuclear antibodies (ANA), anti-ds DNA antibodies, and anti-Ro antibodies were insignificant. Tacrolimus ointment (0.01%) and sunscreens were administered to the patient with the remission of the elements after 14 days.

Discussion

LET is the uncommon subtype of chronic cutaneous LE that is distinguished from the other chronic forms by absence of skin atrophy. The condition is commonly under-reported, and its incidence according to Kuhn et al, is around 16% [1]. Incidence of LET among women and men is approximately same [2]. The disease usually presents in the 30-40`s age range, but several cases have been reported in kids [3].

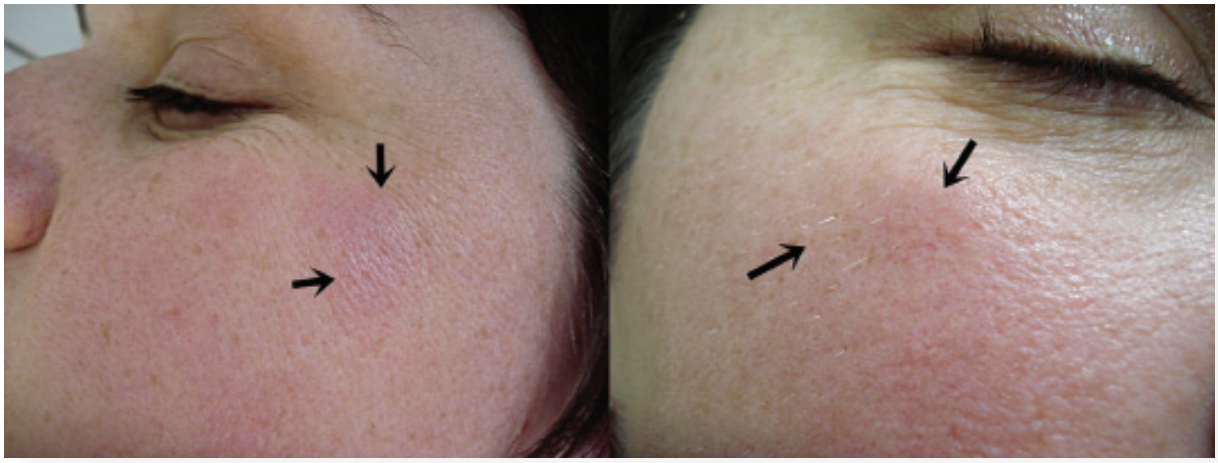

Figure 1. Subtle soft elevated violet patches on the both cheeks.

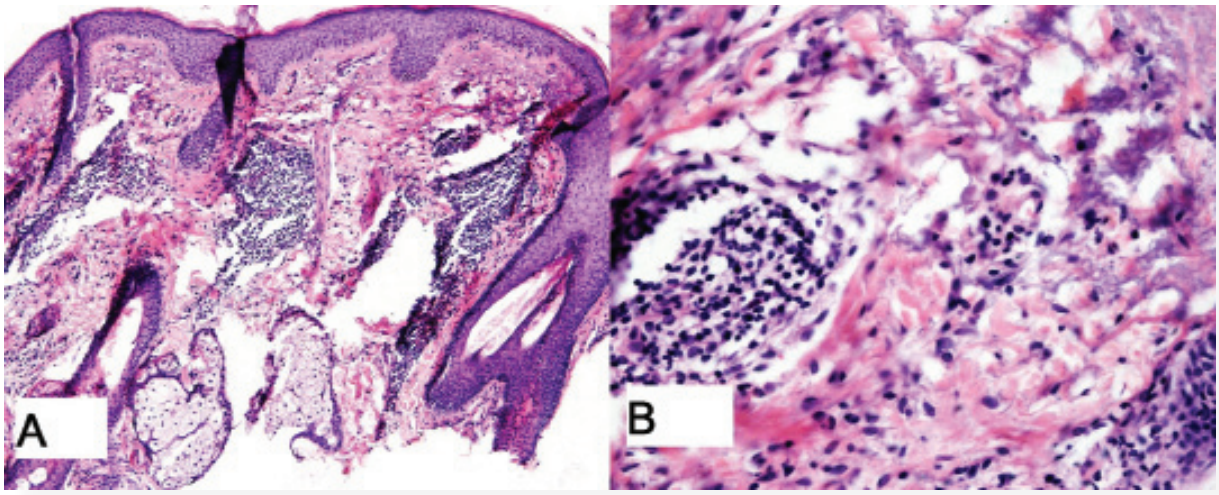

Figure 2. Histopathology of lupus tumidus. A. Deep perivascular and periadnexal lymphocytic infiltrate, Hematoxylin&Eosin, magnification ×40. B. Perivascular lymphocytic infiltrate and mucin deposition in the dermis, hematoxilin eosin, magnification ×400.

Pathogenesis of LET is similar to the other forms of LE, but is featured by high photosensitivity [4]. Photosensitivity is less frequent in LET patients with dark skin [5]. Patients with LET and positive ANA more frequently show signs of photosensitivity [4]. LET may be provoked by the use of certain medications such as antiviral agents [6], bortezomib [7], adalimumab [8], and ACE-inhibitors [9]. A case of LET has been described in a patient who had undergone a sex reassignment operation and was on hormone therapy [10].

Some authors argue the fact that LET should be considered a form of LE on the basis of its indolent course, absence of atrophy and changes of the basal membrane [11]. On the other hand, LET often co-exists with other forms of LE or systemic LE (SLE) and that confirms the common etiology. This has led to the further classification such that LET was classified among other forms of chronic cutaneous LE by a group of dermatologists from Dusseldorf, Germany [12].

LET has a unique clinical presentation. Disease usually manifests during months of maximum sun exposure. Uncovered skin areas (face, neck, upper trunk) are typical between locations. Elements of LET resemble urticaria, in that they are elevated and have no scaling. Their color may vary from pink to violet. Lesions may form annular processes with symmetrical distribution, sometimes resembling targets and scaling is not seen in such lesions. Usually the lesions are asymptomatic, but light pruritis may be present. Rare manifestations of LET include unilateral eyelid edema [13] and linear LET distribution following Blaschko lines [14].

Histopathological examination is essential in the establishing diagnosis of LET. Characteristic features include a deep lymphocytic perivascular and a periadnexal infiltrate and the presence of mucin [15].The epidermis is always intact. LET is identified by the presence of ICAM-1 in the epidermis only ,in comparison to SLE where ICAM-1 expression is predominant throughout all layers of the skin [16]. Data on direct immunofluorescence (DIT) is controversial. Kuhn et al. reports that DIT was negative in all 80 patients with LET from his study with the exception of five that had IgG depositions along the basal membrane [15].

The study by Cozzani et al. in contrary show that DIT was positive in 16 from 19 patients [17]. According to their data patients presented a mixed pattern of positive DIT: deposition of IgA was seen in 2 patients, IgM – in 8 patients, IgG – in one patient and C3 in 9 patients [17]. Only 10% of all patients with LET show positive ANA [4].

Differential diagnosis of LET is extensive and includes dermatoses with the predilection on the open areas of the skin (polymorphous light eruption, rosacea, sarcoidosis, granuloma facilae, porphyria cutanea tarda), annular skin eruptions and erythemas (tinea corporis, subacute LE, superficial form of erythema annulare by Darier, erythema migrans, and erythema marginatum). Urticarial and urticarial vasculitides also should be considered. Several conditions, previously described in medical literature as separate ones, namely Jessner's lymphocytic infiltrate and deep variant of erythema annulare centrifugum of Darier are considered to be variants of LET by some authors based on identical histopathological pictures and very similar clinical presentations [18,19]. The same situation probably concerns reticular erythematous mucinosis as well [20].

Treatment of LET depends on the severity of clinical presentation and presence of other forms of LE. Usually in limited skin eruptions, local therapy and prophylaxis are sufficient for the management. Corticosteroids are traditionally used, but should be carefully monitored for the development of skin atrophy, especially on the face. Several studies as well as our case report suggest the efficacy of local tacrolimus ointment in treatment of LET [21]. In severe cases antimalarials remain the standard of treatment. It should be remembered that lower efficacy may be registered in smoking patients [22]. Prophylaxis of LET is the same as in other forms of LE and includes use of sun screens with SPF 50 or more. The course of LET is usually milder than that other forms of LE, but remission of elements may occur.

Conclusion

LET is a specific variant of LE. It should be suspected in photosensitive urticarial-like lesions on the sun exposed areas. Tacrolimus ointment and prophylaxis serve as safe and sufficient measures for treatment of localized forms of LET.

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DOI: 10.7241/ourd.20141.07

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CUTANEOUS LEISHMANIASIS: DIAGNOSTIC PITFALL CASE REPORT

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 37-39 Date of submission: 06.10.2013 / acceptance: 21.11.2013

Abstract
Introduction: Cutaneous Leishmaniasis is a parasitic infection encountered in our daily dermatologic practice.
Case report: We present a case of 57 year-old man of Moroccan origin, with erythematous squamous and indurated plaque on the abdomen, treated as sarcoidosis with corticosteroids with no improvement.
Discussion: Cutaneous Leishmaniasis is endemic in 88 countries. Aside from its classical presentation it can manifest in multiple different ways. In our case, the diagnostic of Erysipeloide Leishmaniasis was corrected on the basis of the skin smear and the histopathological examination. Our observation is particular in its clinical presentation and location. To our knowledge it is the first Moroccan case.
Conclusion: Even in endemic countries it is worth reporting unusual forms and locations of Cutaneous Leishmaniasis in order to avoid inappropriate diagnosis and management.

Key words: Leishmaniasis; Leishmaniasis Cutanea; Leishmaniasis types

Cite this article:
Asmae EL Hatimi, Salim Guellouj, Sanae Chehbouni, Kawtar Inani, Hanane Baybay, Fatima Zahra Mernissi. Cutaneous leishmaniasis: diagnostic pitfall. Case report. Our Dermatol Online. 2014; 5(1): 37-39.

Introduction

Cutaneous Leishmaniasis is a widely dispersed parasitic vector-borne disease, caused by the Leishmania's species. Its most common clinical presentation is the "classical" ulcer which starts as a nodule over exposed area of the body after a sand-fly bite, becomes an ulcer with an indurated raised margins and sharply incised central crater and then usually heals over a period of months.

In recent times the number of reports of new and rare variants of Cutaneous Leishmaniasis has been increasing which eludes the diagnosis even in endemic area. We report here a rare and unusual form and localization of Cutaneous Leishmaniasis which was misdiagnosed and treated as Sarcoidosis by dermatologists in an endemic country. To our knowledge, this is the first reported case in Morocco.

Case Report

The case is of a 53 year-old man. In the months preceding the symptoms, he had no past medical history, nor antecedent of trauma or travel. He was referred to our tertiary center for a large, painless erythematous plaque in his abdomen. It had evolved from an initial small plaque noticed 08 months before, which gradually spread. The patient consulted a private dermatologist who performed a skin biopsy revealing granuloma in the histopathologic examination and the patient was treated as sarcoidosis by topical and oral corticosteroids with no improvement. On examination we found an apyretic patient with large erythematous indurated slightly squamous plaque of 20cm at his left hypochondrium (Fig. 1). The diascopy of the lesion did not reveal the lupoidic pattern, and the erythematous color was mitigated. The dermoscopy showed diffuse glomerular vessels (Fig. 2). Our differential diagnosis were mycosis fungoide, sarcoidosis, leishmaniasis, erysipelas and morphea. The patient's skin smear was positive for Leishmania. The histopathologic examination of the lesion showed an epithelioid geant -cell granuloma with Leishmania's bodies in the cytoplasm of histiocytes (Fig. 3). The diagnosis of Erysipeloide Leishmania was retained and the patient was treated by oral Clarithromycine 500mg twice a day for 10 days each month during 3 months with topical Aureomycine; The evolution was good (Fig. 4).

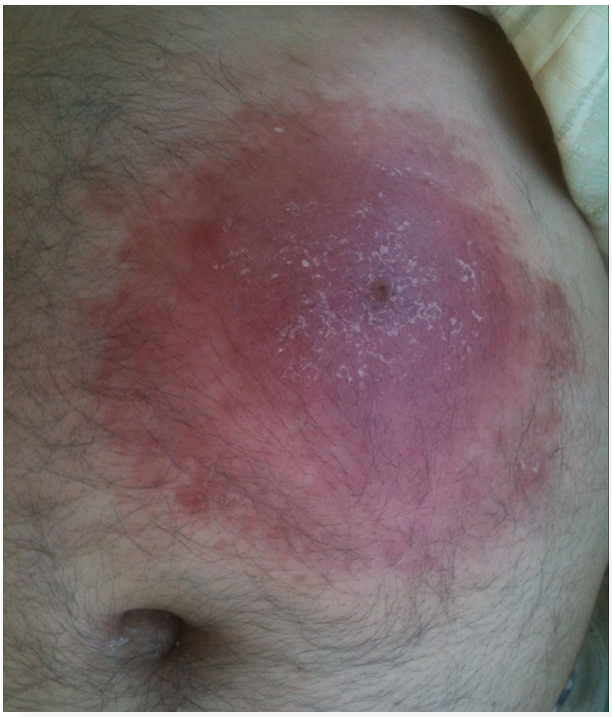

Figure 1. A large erythematous slightly squmous and indurated plaque at the left hypochondrium.

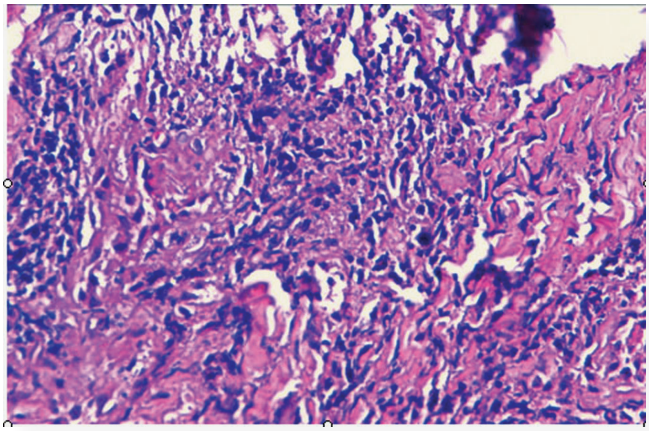

Figure 3. HES x 40 leishmania's bodies in the cytoplasm of histiocytes infiltrating the dermis.

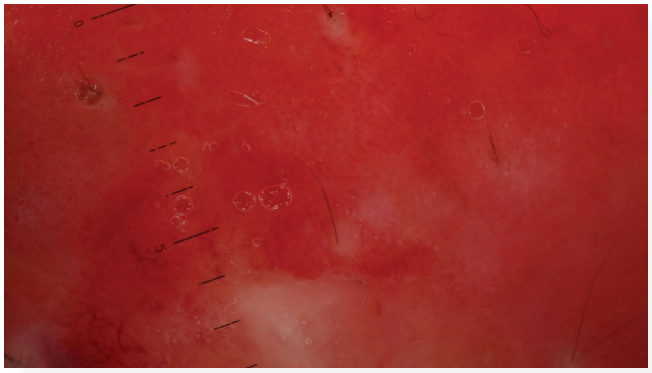

Figure 2. Glomerular vessels.

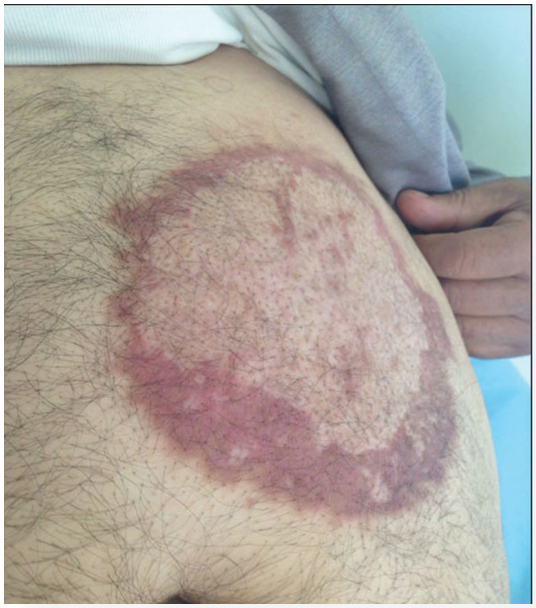

Figure 4. Evolution under treatment at 3 months.

Discussion

Cutaneous Leishmaniasis (CL) is a parasitic vector-borne disease that is well known in the world. WHO stated that Leishmaniasis is endemic in 88 countries with 1.5 to 2 million new cases each year (WHO 1984, 1990).

In Morocco, Leishmaniasis represents a serious health problem. It recognises three epidemiological entities: CL to Leishmania Tropica in the western chain of the Atlas Mountains,represented by a sporadic form with some endemic flare up, CL to Leishmania major in the south and southeast of the Atlas with endemo-epidemic evolution and finally the visceral Leishmaniasis to Leishmania infantum in the Rif and pre-rif area as sporadic form

Curaneous Leishmaniasis has a spectrum of clinical presentations ranging from a single lesion to disseminated form. In the course of its typical presentation, CL starts as a small erythematous papule, which gradually enlarges to 1-2 cm in diameter in about 6 months and then ulcerates. These ulcers are painless with a necrotic base and indurated margins and are frequently covered by a firmly adherent crust. Approximately 85% of skin's lesions are located on the exposed body sites.

Recently there has been an increase in the number of reports for new and rare variants of CL [1,2]. Our case supports this finding. Our patient originated from a region that is known to experience a high prevalence of Leishmaniasis. On the eco-epidemiological level this region corresponds with a sporadic cluster of visceral Leishmaniasis to Leishmania infantum and not with Cutaneous Leishmaniasis. Clinically he presented with a slightly squamous, erythematous, indurated plaque of 20cm in diameter at his left hypochondrium. In the literature, this form corresponds with the erysipeloide form of leishmaniasis which is a very rare and unusual presentation of CL.

Its frequency was estimated to less than 5% in the literature [3], and all reported cases were from Iran, Pakistan, Turkey, Italy, Tunisia and Equador [4,5]. To our knowledge, our case is the first case reported from Morocco. In all previous reports erysipeloide cutaneous leishmaniasis (ECL) is described as an erythematous and indurated diffuse plaque of the face covering the nose and cheeks with an evolution's duration of less than 1 year and a good evolution under therapy. It affects predominatly elderly women [6]. Contrasting with all these reported cases, our patient is the first case who manifests the ECL outside the face; on the hypochondrium, but this might be explained by having had increased skin exposure during the summer months. The reasons for this clinical form are poorly understood, but clinical and experimental evidence indicates that vector, parasite and host factors all influence the evolution and outcomes of the broad clinical spectrum of CL. It has been suggested that as with leprosy ,the various atypical lesions of CL are determined by different types of immune response .The granuloma observed in ECL may be explained by the spread of the parasit in the superficial layer of the papillary dermis and the failure of the immune systeme to control parasit replication [7].

Other factors such as skin fragility due to senility, hormonal changes at menopause and trauma were evoked as facilitating factors of ECL given the predilection location to the face, the predominant affection of elderly females and the antecedent of trauma in some reports [4,6]. Our patient was of a male gender, of 53 years old and there were no skin barrier changes. Previously the specie or the strain of leishmania was understood to be the determining factor for the clinical presentation of leishmaniasis. However,currently it is postulated that the interaction between the host immune response and the strain of the parasite influence the clinical presentation of CL and not only the leishmania's strain [5]

In terms of ECL this conjecture is supported by the fact that in all previous reports different species of leishmania were incriminated: *L. infantum* [7], *L. panamensis* [5]. In our context, the identification of the leishmania's species is not a routine test.

The diagnosis of CL is easy in the usual clinical presentations. However, in unusual forms it may give rise to difficulties in diagnosis and appropriate treatments even by dermatologists in endemic areas like our patient who was diagnosed and treated incorrectly by a dermatologist as sarcoidosis with topical and oral corticosteroids. This is why the diagnosis of CL should be confirmed by a direct parasitology test and/or histopathologic examination of skin biopsy or in certain cases by PCR.

There are various treatment options for CL such as pentavalent antimony compounds, cryotherapy, topical paromomycin, local heat, surgical excision, electrodissection, CO2 laser, Clarithromycine and antifungal [8-10].

In our observation, given the extension of the lesion and the age of the patient, we opted for the oral Clarithromycin with topical Aureomycin.

Conclusion

Given the importance and the complexity of the clinical features of CL, it is worth reporting rare and unusual clinical forms and localizations of this disease in order to familiarize and sensitize physicians, in particular dermatologists, with different clinical presentations to avoid inappropriate diagnosis and management.

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DOI: 10.7241/ourd.20141.08

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LICHENOID REACTIONS IN RED TATTOO: REPORT OF 2 CASES

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 40-41 Date of submission: 25.11.2013 / acceptance: 20.12.2013

Abstract
Complications of cosmetic decorative tattoos were uncommon some decades ago. The practice is increasing and more cases are being reported. Red pigments are by far the commonest cause in tattoo reactions. We report two cases of lichenoid reactions limited to red tattoo pigment and review the literature on the subject.

Key words: red tattoo; lichenoid reaction; tattoo reactions

Cite this article:
César Bimbi. Lichenoid reactions in red tattoo: report of 2 cases. Our Dermatol Online. 2014; 5(1): 40-41.

Introduction

Artistic tattoos rely on the use of numerous pigments (including red) which are not all entirely inert once placed in the dermis. Allergic reactions to a particular pigment can manifest in several ways including lichenoid reaction, allergic contact dermatitis and photoallergic dermatitis, granulomatous or pseudolymphoma reactions.
We have described two cases of lichenoid reaction developing to red ink in colored tattoos.

Case Report

Case 1

A healthy 36 -year-old man presented with a 5 month history of plaque lesions inside the tatoo areas of the body (Fig. 1, 2) corresponding specifically to the areas with red pigment. The remainder of the tattoo was unaffected. On examination of the left deltoid area and right leg, indurated plaques involving red coloured areas of the tattoo were shown. These lesions were firm and the edges were warty, bearing clinical similarity to hypertrophic lichen planus.
Incisional biopsy revealed histological features of lichen planus with dense lynphohistiocytic infiltrate in the papillary dermis and no evidence of granulomatous inflammation.

Case 2

A 25-year-old female presented with a complaint of pruritic raised lesion in a tattoo drawn over her upper dorso over the past 3 weeks (Fig. 3a, b). The lesion appeared over the site of a tattoo that was injected one month back. She had no history of cough or weight loss. Biopsy was not taken, corticosteroid cream was indicated first.

Figure 1. Verrrucous plaques over the red ink with sparing of the blue component.

Discussion

Complications of decorative tatoos were considered rare some decades ago [5]. A British report about two cases presented to Clinical Meeting at St John's Hospital Dermatological Society in December 1977 [6], informed that, at that time, a review in the literature made by the authors discovered only four other patients who had lichen restricted to red tattoo áreas. Lichen planus in tattoos was first mentioned by Rook and Thomas in 1952 [1]. With the popularity of tatooing practices worldwide, more adverse skin reactions are being reported. 24% of the US population has tattoos [2].

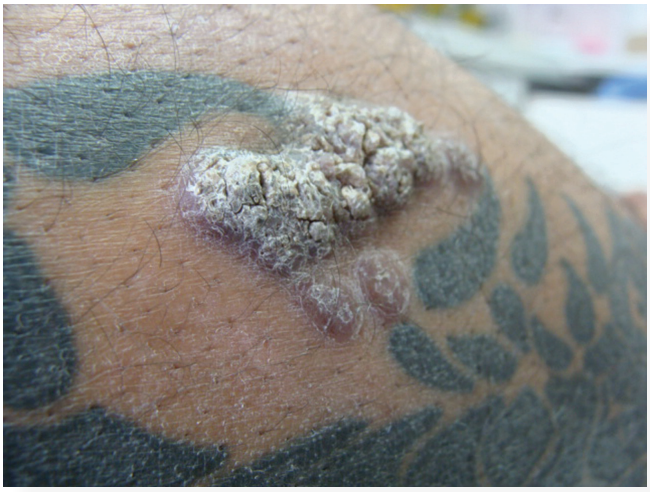

Figure 2. Right leg, same patient. Indurated verrucous nodules over the red component of the tattoo (scorpion tail), blue ink also spared.

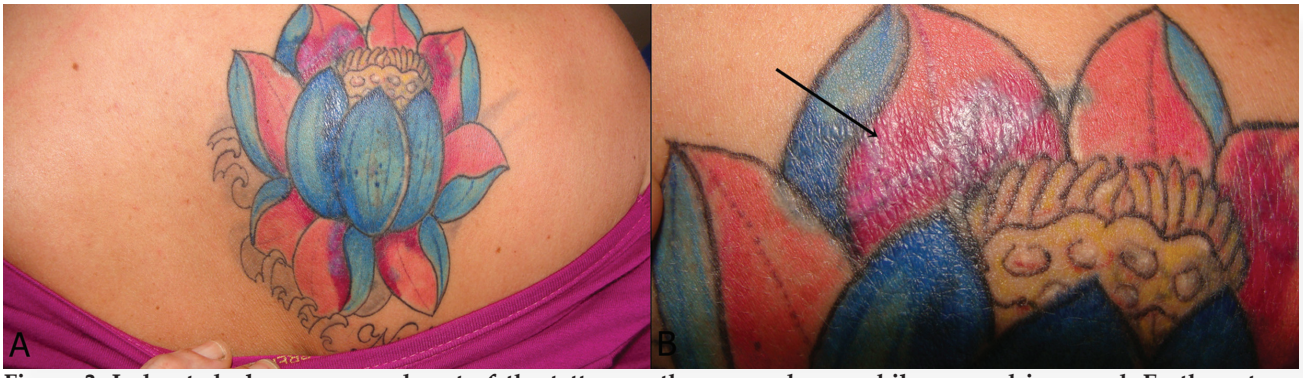

Figure 3. Indurated plaque over red part of the tattoo on the upper dorso, while non-red is spared. Erythematous nodules on petals of the flower.

Reactions in red ink tattoos are increasingly being recorded in current literature.

Red in tattoos has been far more complicated than other colours. Observing the photos among all reports, there is a striking similarity [5]; all show features of elevated nodules or plaques confined to red. Mercury contained in red ink (mercuric sulphide or cinnabar) has been well recognized in the past as the causative agent in reactions associated with red tattoos. Chemical substitutes for mercury are the modern alternatives: sienna-ferric hydrate, cadmium-selenide and organic vegetable dyes, sandalwood and brazilwood, and have largely replaced the use of mercury, but sensitivity to red dyes still occur. Most tattooists do not know the composition of the pigments that they use. It is not easy to define the chemicals involved. In fact, the compositions of many inks have been identified. However, as new mixtures are created, it becomes difficult to identify the specific ingredients in a particular ink. There are also many reports in the literature of reactions to purple, light blue, green, black and yellow pigments. The exact incidence is unknown.

The risk of dangerous chemicals in tattoos seems to be underestimated. Engel et all. [3] adverts the alarming fact that in Europe, the same azo pigments that are forbidden to be used in cosmetics only applied to the skin surface, are "allowed" (no regulations) in tattooing. So, heavy amounts of up to hundreds of milligrams of carcinogenic aromatic amines are directly injected into the skin. Currently data is lacking regarding the safety of tattoo pigment ingredients. Also, none of the tattoo ink or additives are FDA approved [4].

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DOI: 10.7241/ourd.20141.09

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CLASSICAL LICHEN PLANUS AND *LICHEN PLANUS PIGMENTOSUS INVERSUS* OVERLAP WITH DERMOSCOPIC FEATURES

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Source of Support: Nil
Competing Interests: None

Our Dermatol Online. 2013; 5(1): 42-44 Date of submission: 08.10.2013 / acceptance: 02.12.2013

Abstract
A 35-year-old man was referred to our hospital with a 3 months history of itchy cutaneous eruption on the trunk and asymptomatic cutaneous eruption on both groins. Physical examination revealed several, purplish-brown, scaly papules on the trunk and well-circumscribed, brown patchs in a linear distribution, on the bilateral inguinal regions. Dermoscopic examination of papules on the trunk revealed white crossing lines surrounded by brown dots; dermoscopic examination of patchs on groins revealed gray-brown dots and globules. According to histological, dermoscopical and clinical changes, the diagnoses of classical lichen planus (LP) for the lesions on the trunk; and lichen planus pigmentosus inversus (LPPI) for the lesions on the inguinal regions were made. Inhere we have described a rare case of LPPI and classical LP with dermoscopic features; and we suggest that LPPI is a variant of classical LP.

Key words: Lichen planus; lichen planus pigmentosus inversus; dermoscopy

Cite this article:
Şule Güngör, İlteriş Oğuz Topal, Şenay Erdoğan, Deniz Özcan. Classical lichen planus and lichen planus pigmentosus inversus overlap with dermoscopic features. Our Dermatol Online. 2014; 5(1): 42-44.

Introduction

Lichen planus pigmentosus inversus (LPPI) presents with brownish macules and patches in flexural regions and known as a rare variant of lichen planus pigmentosus (LPP) [1]. LPP is an uncommon variant of chronic lichen planus (LP) that is characterized by hyperpigmented, dark-brown macules in sun-exposed areas especially in Indian patients [2]. In here, we present a case of classical LP and LPPI overlap in a man, with dermoscopic features.

Case Report

A 35-year-old man was referred to our hospital with a 3 months history of itchy cutaneous eruption on the trunk and asymptomatic cutaneous eruption on both groins. He had no significant medical history. Physical examination revealed several, purplish-brown, scaly papules on the trunk (Fig. 1) and well-circumscribed, brown patchs in a linear distribution, on the bilateral inguinal regions (Fig. 2). Dermoscopic examination of papules on the trunk revealed white crossing lines surrounded by brown dots (Fig. 3); dermoscopic examination of patchs on groins revealed gray-brown dots and globules (Fig. 4). Oral, nail, scalp or genital lesions were absent. A causal relationship with drugs, recent sun exposure, or trauma could not be identified. Laboratory evaluation, including blood cell count, fasting blood sugar levels, liver function, serum electrolyte levels, serum electrophoresis, urinalysis were within normal limits. Biopsy specimen of the papul on the trunk showed hyperkeratosis, hypergranulosis, bandlike inflammatory lymphocytic infiltrate with basal vacuolar changes and melaninin continence in the upper dermis (Fig. 5), the second biopsy specimen of the macula on the inguinal region showed regressive pattern of lichen planus with prominent melaninin continence (Fig. 6). Histopathological diagnosis of the first biopsy was consistent with classical lichen planus, second biopsy was consistent with melanosis. According to histological, dermoscopical and clinical changes, the diagnoses of classical LP for the lesions on the trunk; and LPPI for the lesions on the inguinal regions were made. Betamethasone dipropionate ointment was applied once daily for 2 weeks. Classical LP lesions were resolved, but LPPI lesions revealed no change after 2 weeks. Tacrolimus ointment was applied twice daily for 4 weeks on the inguinal region and no change was observed in LPPI lesions.

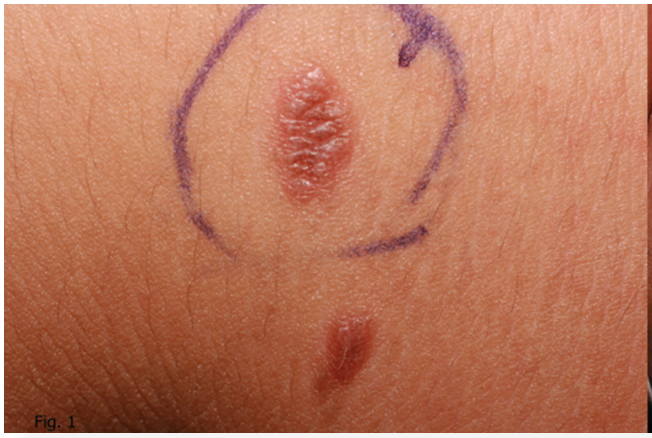


Figure 1. Purplish-brown, scaly papula on the trunk.

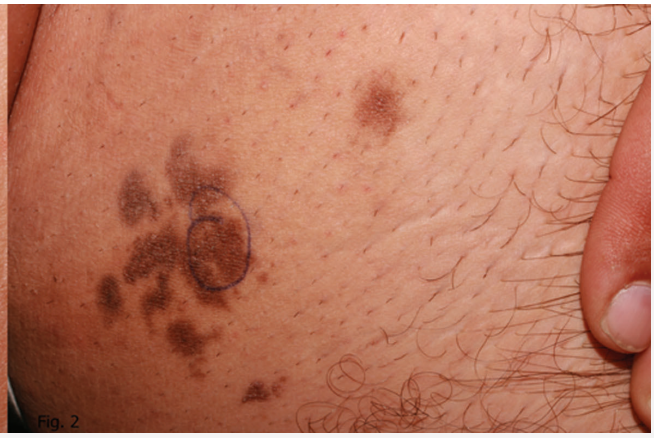
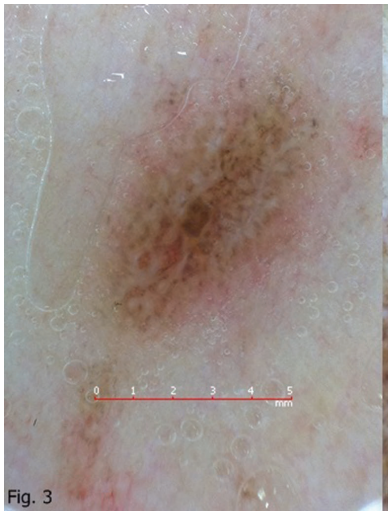


Figure 2. Well-circumscribed, brown patchs in a linear distribution, on the inguinal region.



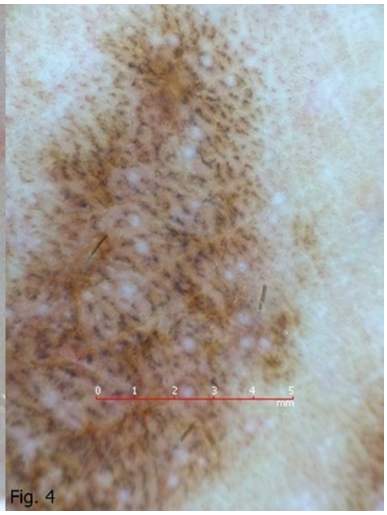
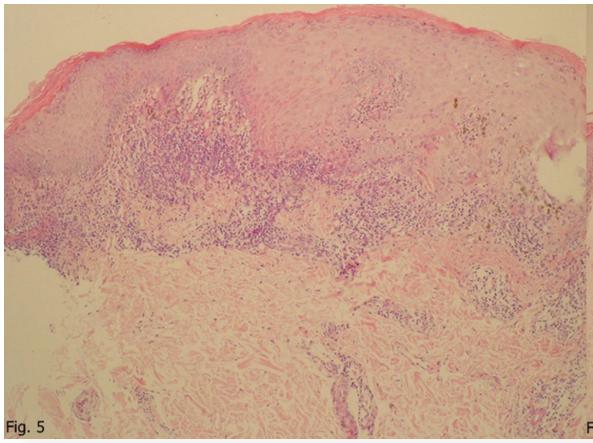


Figure 3. White crossing lines surrounded by brown dots on dermoscopic examination.

Figure 4. Dermoscopic examination of patchs on groins revealed gray-brown dots and globules.



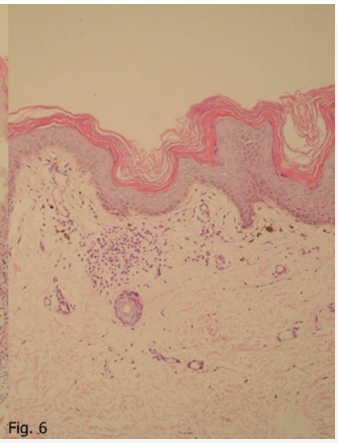


Figure 5. Biopsy specimen of the papul on the trunk showed hyperkeratosis, hypergranulosis, bandlike inflammatory lymphocytic infiltrate with basal vacuolar changes and melaninin continence in the upper dermis.

Figure 6. Biopsy specimen of the macula on the inguinal region showed regressive pattern of lichen planus with prominent melaninin continence.

Discussion

The eruption of LPPI occurs mainly in the flexural regions and presents with brownish macules and patches. It is known as a rare variant of LPP [1].

LPP is an uncommon variant of chronic lichen planus that is characterized by hyperpigmented, dark-brown macules in sun-exposed areas especially in Indian patients [2].

The first literature of classic LP and LPPI coexistence was reported by Saray et al. [3]. Their patient's LPPI lesions were resistant to oral steroid treatment, but classical LP lesions resolved. Similar to that case, our patient's LPPI lesions were resistant to both therapies, while classic LP lesions were resolved by treatment. In our case, dermoscopic examination of the papules on the trunk showed white crossing lines corresponding to the Wickham striae, histopathological examination was consistent with classic LP and resolved by corticosteroid ointment. On the other hand the macules on the groins showed gray-blue dots and globules corresponding with dermal melanophages, and histopathological examination was consistent with LPPI and resistant to treatment. Though our patient states that all lesions (both on the trunk and groins) appeared around the same time, they were clinically and histopathologically different. We consider that it depends on the localization of the lesions, that the course of the lesions on the intertriginous areas alters by friction; showing less lichenoid reaction, more pigment incontinence resulting in asymptomatic brown macules and patches, instead of pruritic purplish papules in classic LP. Due to less inflammation, LPPI lesions are resistant to anti-inflammatory drugs.

Other three cases of LLPI - classical LP relation were reported by Kim and al [4,5]. Their patient's lesions were reported to have emerged on the long standing LP inversus.

Current case is the fifth case in which classic LP and LPPI overlap. In this situation, we doubt whether LPPI is a variant of LPP or it originates from classical LP. Considering this claim, it seems that LPPI is not a variant of LPP, it is rather a variant of classical LP; but the course of the lesions alters by friction.

In conclusion, we have described a rare case of LPPI and classical LP with dermoscopic features; and we suggest that LPPI is a variant of classical LP instead of LPP.

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DOI: 10.7241/ourd.20141.10

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UNUSAL PRESENTATION OF *GRANULOMA ANNULARE* RESTRICTED OVER THE PALMS: A RARE CASE PRESENTATION

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2013; 5(1): 45-47 Date of submission: 26.11.2013 / acceptance: 23.12.2013

Abstract
We report a patient with erythematous firm papules and nodules over palms. Histological examination, which identified epidermis showed marked hyperkeratosis and dermis with perivascular lympho-histiocytic infiltrate which also extended in between the collagen bundles with occasional multinucleated giant cells and mucin deposition. This established the diagnosis of Granuloma Annulare (GA). This is an unusual presentation because of the late onset, uncommon localization, and absence of classical lesions of GA elsewhere.

Key words: Granuloma Annulare; the interstitial pattern of GA; hydroxychloroquine

Cite this article:
Snehal Lunge, Pradeep Mahajan, Neeta Gokhale, Renny Pinto. Unusal presentation of granuloma annulare restricted over the palms: a rare case presentation. Our Dermatol Online. 2014; 5(1): 45-47.

Introduction

Granuloma Annulare (GA) has been described in several morphologic forms i.e. annular disseminated, subcutaneous, papular and perforating. Although GA is primarily a disease of children and young adults, it has been reported in virtually all age groups. Females are affected twice as often as males, and familial occurrence is rare. No associated systemic sequel are present, and laboratory evaluation is usually normal. Disseminated GA is considered a distinct entity from the localised form because of the possible association with diabetes, a later age of onset, and rare spontaneous resolution. Therapy is usually disappointing. Various forms of therapies that have been reported to have a variable response are topical and intralesional steroids, dapsone, retinoids, niacinamide, chloroquine, colchicine, cryotherapy, electrodessication and X-ray therapy [1].

Though GA is a common disorder in dermatologic daily practice, its localization only over palms is uncommon and is infrequently reported in the literature. In most cases it is associated with classical lesions of GA elsewhere, when the diagnosis is relatively easy [2]. In case of isolated lesions a high degree of clinical suspicion of GA is required and histopathology is of vital importance in making the diagnosis. We recently studied an adult patient with lesions of GA at atypical site, absence of classical lesions of GA elsewhere and diagnosis made only on histopathological examination.

Case Report

A 65 years married male patient known stable hypertensive presented with multiple, erythematous, mildly tender, firm papules and nodules on palms of two months duration (Fig. 1). Patient did not have similar lesions or hypoaesthetic patches or any other skin lesion elsewhere. There was no history of drug intake, fever, joint pains, mucosal or genital lesions, sore throat or cough. General and systemic examination of the patient was normal. Various clinical possibilities considered were erythema multiforme, erythema elevatum diutinum, drug reactions, vasculitis / urticarial vasculitis, secondary syphilis, erythromelalgia, sarcoidosis etc.

Routine investigations, VDRL, RA factor and investigations for diabetes, connective tissue disorders and thyroid disorders were all normal. A punch biopsy of one of the papules over left palm showed epidermis with marked hyperkeratosis. The dermis had hypercellularity and inflammation likened to Busy Dermis, perivascular lympho-histiocytic infiltrate with occasional multinucleated giant cells. This lympho-histiocytic infiltrate was extending in between the collagen bundles which appeared to be separated from each other.

Special stain for mucin in the form of alcian blue stain at pH 2.5 showed bluish mucin separating pink collagen bundles in dermis (Fig. 2, 3). There was no frank necrobiosis or vasculitis in the dermis.

These histologic findings made the final diagnosis of Interstitial Granuloma Annulare. The patient was treated with hydroxychloroquine sulphate 400mg/day as the lesions were painful. At the end of 1 month remarkable clinical improvement was observed (Fig. 4) and the patient did not experience any adverse drug reactions. He is being followed till today.

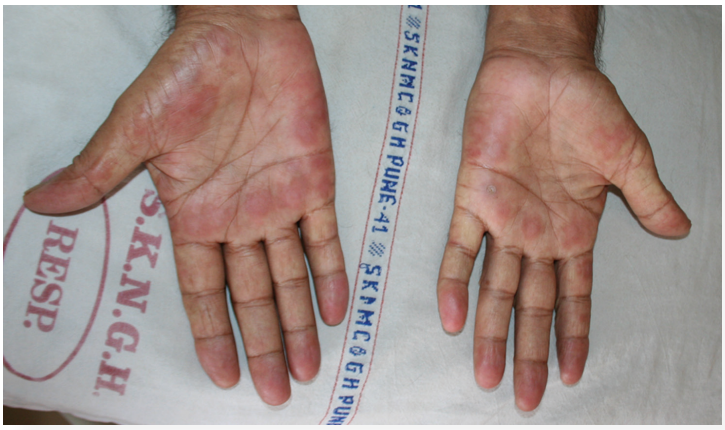

Figure 1. Erythematous papules over palms before treatment.

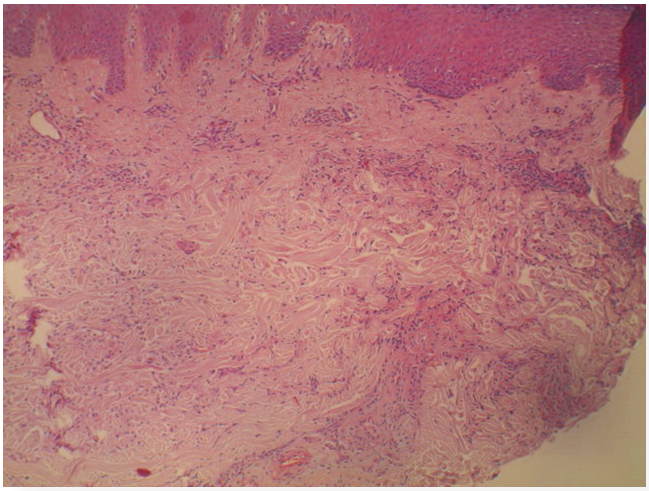

Figure 2. Lympho-histiocytic infiltrate extending in between the collagen bundles which appeared to be separated from each other.

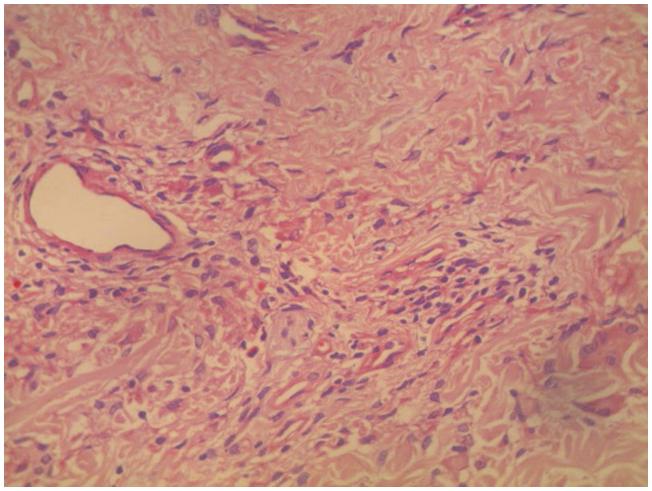

Figure 3. Inflammatory infiltrate composed of lymphocytes, histiocytes and giant cells (H&E original magnification x400).

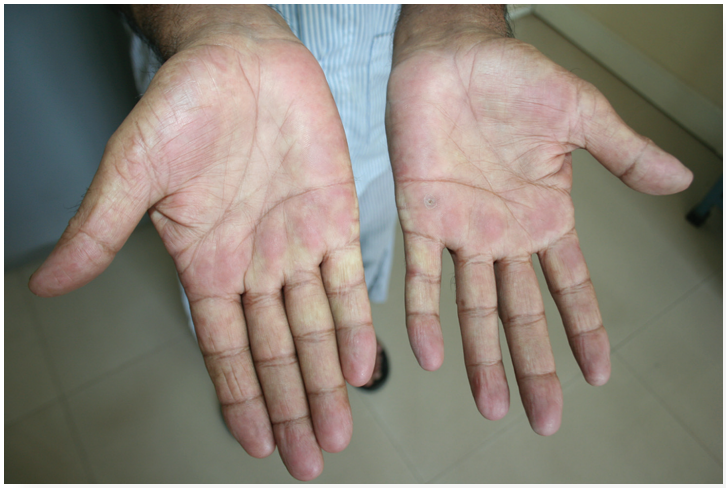

Figure 1. Response after 4 weeks of Hydroxy Chloroquin Sulfate.

Discussion

Papular form of GA has been reported to be familial. None of the family members of our patient was similarly affected. Although the occurrence of GA on the dorsum of the hands is frequent, involvement of the palms appears to be rare. Only a few cases have been previously reported, most often as painful acral papules [2]. Two pediatric cases of the subcutaneous variant of GA also exist [3]. Of the cases of GA on the palms that we reviewed, one case involved a woman with dermatomyositis who developed a solitary lesion of GA on the palm [4]. Brey et al presented 4 patients with acute onset acral papules of GA, 2 of whom had lesions involving the palm. Two of their 4 patients developed concomitant arthralgias and were evaluated extensively for rheumatologic disease, but were found not to meet criteria for any [5]. Painful lesions of GA on the palm and soles were also noted in three of thirteen patients with GA and lymphoma evaluated in a retrospective study by Barksdale et al, leading the authors to conclude that atypical presentations, such as involvement on the palms and soles, may be associated with an underlying hematopoietic malignancy [6]. Whereas GA has not been consistently linked to systemic disease [7], conditions such as interstitial granulomatous dermatitis with arthritis, palisaded neutrophilic and granulomatous dermatitis, rheumatoid papules, and Churg-Strauss granulomas, which all can clinically and histologically overlap with GA, belong to a spectrum of granulomatous diseases thought to be an immune-mediated reaction to a number of underlying conditions, such as rheumatoid arthritis, collagen vascular disease, Wegener granulomatosis, and malignancy. Our patient had no identifiable associated immune-mediated condition at the time of diagnosis or subsequent follow-up. Our patient had slightly tender papules and nodules on palms in contrast to asymptomatic nature of GA elsewhere.

Granulomatous drug reactions have been associated with a number of medications, including calcium channel blockers, ACE inhibitors, beta blockers, antidepressants, and anticonvulsants. These generally manifest with erythematous to violaceous GA-like plaques that characteristically involve the inner aspects of the arms, medial thighs, and intertriginous areas [8] and occur months to years after drug onset [9]. The histologic pattern of interstitial granulomatous drug eruption shares some similarities with that of granuloma annulare. However, interstitial granulomatous drug eruption can be differentiated by the absence of any significant necrobiosis, the presence of vacuolar interface changes, and the variable lymphoid atypia, not seen in granuloma annulare [10]. Our patient was not taking any drugs that had been implicated in granulomatous drug eruptions. In addition clinically & histopathology does not support a diagnosis of interstitial granulomatous drug reaction our patient.

Although GA is regarded as the prototype of a palisading granulomatous dermatoses, the interstitial and mixed patterns predominate [11]. Our patient also had the interstitial pattern of GA. Abundant dermal mucin is a hallmark of GA. Unique histopathological picture clinched the diagnosis of GA in our patient. GA on palms poses a clinical diagnostic challenge because similar clinical features are shared by many a differential diagnoses. Histopathology is of vital importance for correct diagnosis and treatment. GA should be considered in differential diagnosis of papular lesions on palms.

Our patient was unique as regards unusual age of onset, involvement of unusual site like palms, not being associated with classical lesions of GA elsewhere, skin biopsy findings making the diagnosis of interstitial GA and remarkable initial response to hydroxychloroquin sulphate 400mg daily after 1month (Figure 1 and 4 shows pre treatment & post treatment photograph).

Localized granuloma annulare is self-limited and asymptomatic, treatment usually is not necessary. Systemic therapy is required for disseminated GA. Many other treatments proposed are topical, intralesional and systemic corticosteroids, chloroquine, hydroxychloroquine sulphate, potassium iodide, niacinamide, chlorpropamide, cyclosporine, chlorambucil, etretinate etc.

Conclusion

This is an unusual presentation of Granuloma annulare on palms because of the late onset, uncommon localization, and absence of classical lesions of GA elsewhere and was uniquely treated with Hydroxychloroquine which led to remission. On review of literatures on few cases of GA on palms were noted whereas few case of disseminated GA treated with Hydroxychloroquine as been published.

Whenever we come across patient presenting with erythematous papules and nodules over the palm, the diagnosis of granuloma annulare should be rule out with considering all differential diagnosis. erythema multiforme, erythema elevatum diutinum, drug reactions, vasculitis / urticarial vasculitis, secondary syphilis, erythromelalgia, sarcoidosis.

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DOI: 10.7241/ourd.20141.11

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PROGRESSIVE SYMMETRIC ERYTHROKERATODERMA: FIRST CASE REPORTED IN THE DOMINICAN REPUBLIC

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 48-50 Date of submission: 05.09.2013 / acceptance: 18.11.2013

Abstract
Progressive symmetric erythrokeratoderma (PSEK) is an autosomal dominant genodermatosis with incomplete penetrance and variable expressivity. It belongs to the group of erythrokeratodermas where it can be differentiated from erythrokeratoderma variabilis in the absence of migratory erythematous lesions and in a greater incidence of palmoplantar keratoderma. Molecular basis of PSEK has not yet been established although there are reports of mutations in the loricrin gene. We report a 13-year-old boy with symmetrically distributed hyperkeratotic plaques over the dorsum of the hands and the extensor aspect of the forearms, elbows and knees. As far as we are aware, we report the first case of PSEK in the Dominican Republic.

Key words: Erythrokeratoderma; genodermatosis; Dominican Republic

Cite this article:
Manuel Valdebran, Antonio Giraldez, Rafael Isa-Pimentel, Isao Salinas-Hojyo, Bertha Saleta, Raisa Acosta, Fernanda Nanita-Estevez. Progressive Symmetric Erythrokeratoderma. First case reported in the Dominican Republic. Our Dermatol Online. 2014; 5(1): 48-50.

Introduction

Progressive symmetric erythrokeratoderma (PSEK) was first described by Darier in 1911 in his article entitled "Erythroqueratodermie Verruqueuse en Nappes, Symetrique et Progressive" [1]. In 1922 Gottron published an article describing the same entity but this time he calls it as we know it nowadays [2]. Since his initial description less than 50 cases have been published in the literature.

PSEK describes an autosomal dominant mode of inheritance with incomplete penetrance and variable expressivity. It usually develops during early childhood [3] as fixed and slowly progressive erythematous and hyperkeratotic plaques distributed symmetrically over the trunk, knees, elbows, dorsal surfaces of the hands and feet, and sometimes affecting also the face, palms and soles [4,5].

Despite that molecular basis of PSEK has not yet been established, there are reports of mutations in the loricrin gene [4,6]. As far as we are aware we report the first case of PSEK in the Dominican Republic.

Case Report

A 13-year-old male that presented to our institution with the onset of symmetrically distributed hyperkeratotic plaques over the dorsum of the hands and the extensor aspect of the forearms, elbows and knees, from the age of 3, asymptomatic. His past medical history was not relevant, and there were no skin complains in any other family members.

Dermatologic examination revealed, multiple, irregularly-shaped, sharply demarcated and hypopigmented keratotic plaques symmetrically distributed, showing an erythematous border (Fig. 1, 2). Polarized dermoscopy showed white scaly lines over focal areas of hyperpigmentation (Fig. 3).

Skin biopsies were taken from the lesions near the elbows showing epithelial hyperplasia with hyperkeratosis, regular acanthosis, elongation and anastomosis of rete ridges, pigmentation of the basal layer and perivascular lymphohistiocytic infiltrate (Fig. 4) Based on the clinical and hystopathological findings, the patient was diagnosed with progressive symmetric erythrokeratoderma.

Discussion

The dermatological picture of PSEK is considerable similar to erythrokeratoderma variabilis (EKV) with symmetrically distributed, fixed or very slowly progressive erythematous, scaly plaques. It can be differentiated in the absence of migratory erythematous lesions and in a greater incidence of palmoplantar keratoderma.

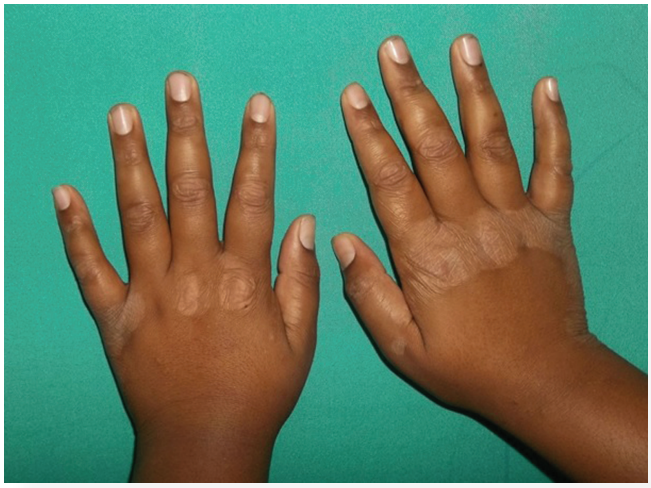

Figure 1. Symmetric hyperkeratotic plaques with well-defined outlines on the dorsum of the hands.

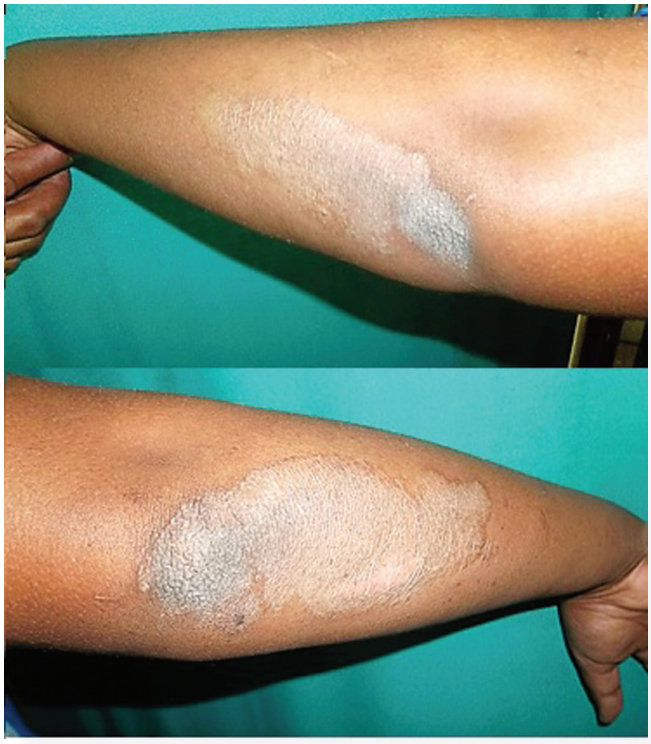

Figure 2. Symmetric hyperkeratotic plaques with erythematous outlines on the elbows and forearms.

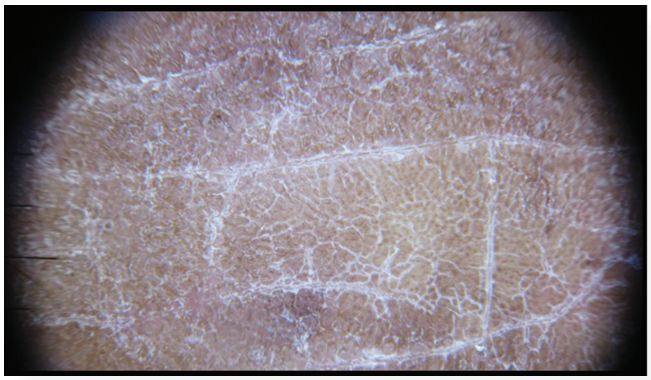

Figure 3. Polarized dermoscopy reveals white scaly lines over focal areas of hyperpigmentation.

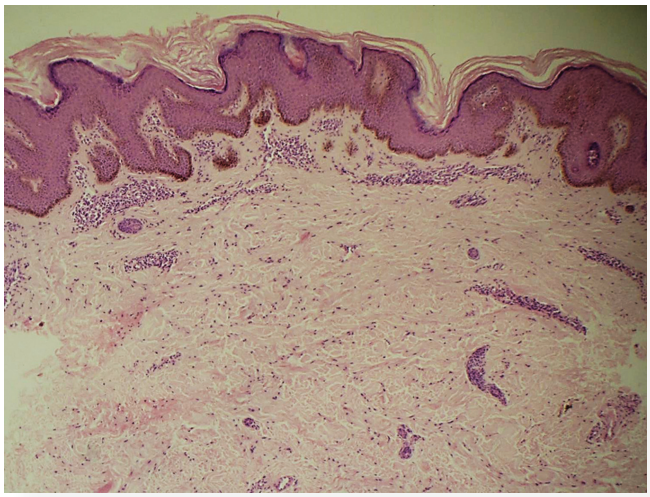

Figure 4. Epithelial hyperplasia observing elongation of the rete ridges, papillomatosis, verrucous hyperplasia and hyperpigmentation of the basal layer. HE 5X.

Also, the symmetry of the lesions in PSEK is more striking than in EKV [5]. These overlapping characteristics have led some authors to propose the alternate term "EKV et progressiva" [7].

The molecular basis of PSE has not been clearly elucidated, Ishida et al reported mutations in the loricrine gene [6] which codifies for loricrin, a major structural component of the cornified cell envelope of the epidermis, which participates in the formation of keratohyalin granules; however similar mutations have not been found by other authors [4]. More studies are needed to clarify the molecular basis of this entity.

It is interesting to observe the presence of white scaly lines on polarized dermoscopy reminding us the Wickham striae that could correlate to the focal hypergranulosis seen on histopathology. Despite histopathology is non-specific it can help us to exclude other conditions such as pityriasis rubra pilaris that shows alternating orthokeratosis and parakeratosis in both vertical and horizontal directions [8], these features were not seen in this case.

Current treatment options for this condition include keratolytics and topical and systemic retinoids, Bilgin et al reported the use of topical calcipotriol with a remarkable improvements [3].

Conclusion

PSEK is an uncommon genodermatosis. Its pathogenesis is poorly understood however advances in molecular biology have identified mutations in genes that codify structural components of the epidermis yet more research must be done to determine the specific molecular and genetic basis of this entity. Diagnosis of PSEK is done clinically and histologically, however physicians can also be aided by dermoscopy, a practical non-invasive diagnostic tool that can help us to inferer histological changes in the epidermis. Patients need to be counseled about the chronicity of their condition and the limitation of temporary improvements with the treatment options available.

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DOI: 10.7241/ourd.20141.12

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MARJOLIN ULCER: A CASE REPORT

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Source of Support: Nil
Competing Interests: None

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Our Dermatol Online. 2011; 5(1): 51-53 Date of submission: 14.11.2013 / acceptance: 17.12.2013

Abstract
Marjolin's ulcer is part of a group of neoplasms arising in chronic skin lesions, whether inflammatory or traumatic. Squamous cell carcinoma is the most frequently reported in the literature, it appears most frequently in burn scars, although also described in other types of lesions. We report a case of Marjolin ulcer in a male, native, 65 years old, from the Paraguayan Chaco, with antecedents of scar post trauma in youth.

Key words: Marjolin ulcer; squamous cell carcinoma; scars

Cite this article:
Beatriz Di Martino Ortiz, Rosalba Riveros, Martinez Braga Gabriela, Raquel Medina de Sosa, Mirtha Rodríguez Masi, Oilda Knopfelmacher, Lourdes Bolla de Lezcano. Marjolin ulcer: a case report. Our Dermatol Online. 2014; 5(1):51-53.

Introduction

In 1828 Jean Nicholas Marjolin described the chronic burn ulcers called chancroid without establishing what this meant. It is because of Da Costa, by the year of 1903, the term Marjolin ulcer was used to describe the malignancy of a chronic ulcer that originates in the scar of a burn, but also described association of this entity with other etiological factors as decubitus ulcers, osteomyelitis and immunization scars [1,2].

Case Report

Male patient, 65 years of age, indigenous, works in a farm, from Bahia Negra, Paraguayan Chaco.

One year of evolution of an injury in the back of left leg over a traumatic scar from youth. Progressive growth and ulceration 6 months ago. Occasional itching. Casual night feverish feeling. Admitted at the Indigenous Hospital with presumptive diagnosis of leishmaniasis.

Personal and family medical history: longtime smoker. No other evidence of value.

Physical exam: Ulcerated tumor composed of irregular and indurated erithematoviolaceous edges, background with foul-smelling discharge, 10 x 7 cm left popliteal settles (Fig. 1), pale skin and tumor of 3 cm in diameter, well defined, consistency elastic solid, not adhered to deep planes in left inguinal region, consistent with lymphadenopathy.

Presumptive clinical diagnosis: squamous cell carcinoma. Cutaneous Leishmaniasis. Chromomycosis. Sporotrichosis fixed plate. Paracoccidioidomycosis.

Auxiliary Diagnosis: Hb 10.6, Hct 32 %, WBC 4500, N 73 %, L 20 %, Eo 7%, platelets 180.000, urea 32, Creat 1.3, simple urine: normal. Montenegro reaction: negative. Leishmaniasis IgM: negative. Sputum for AAR: Negative.

Histopathology: epidermal continuity solution based on which appears a neoplastic proliferation of epithelial origin. The bottom of the sample is formed by fibrous connective tissue devoid of skin appendages and vessels are arranged perpendicularly. There are atypical cells in cords and solid nests with individual keratinization and in the form of corneum pearl shaped. 2/HPF mitotic index (Fig. 2a, b).

Final anatomopathological diagnosis: Squamous cell carcinoma of intermediate grade of differentiation (grade 2), ulcerated, infiltrates lateral margins of resection and respects the deep surgical margin of the biopsy. Not observed vascular invasion, lymphatic or perineural into this sample.

Culture for common germs and fungi: Negative.

Bone radiograph: There was no bone involvement.

Ultrasound of soft tissue was also requested which was not performed.

Based on clinical and histopathological findings is concluded as final diagnosis: *Squamous Cell Carcinoma of Marjolin ulcer type.*

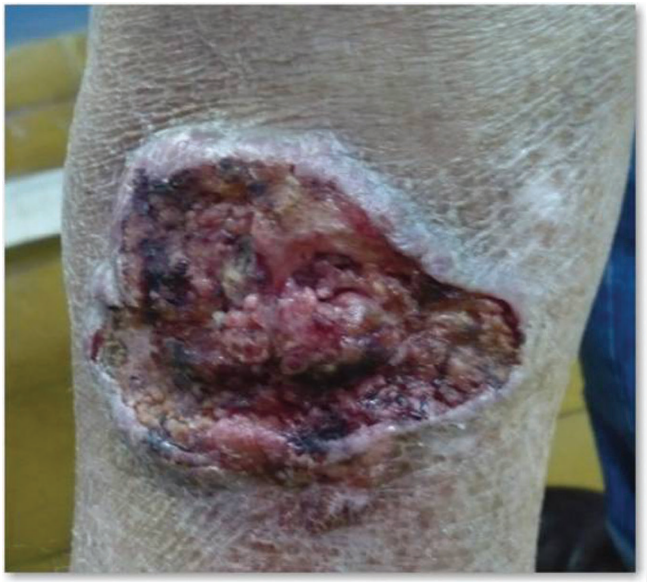

Figure 1. Clinic. Ulcerated tumor with erythematous, irregular and indurated borders, with vegetative looking background with necrotic tissue, granulation tissue areas with foul-smelling discharge, net limits of 10 x 6 cm that sits on a burn scar in left popliteal level. Pale adjacent skin.

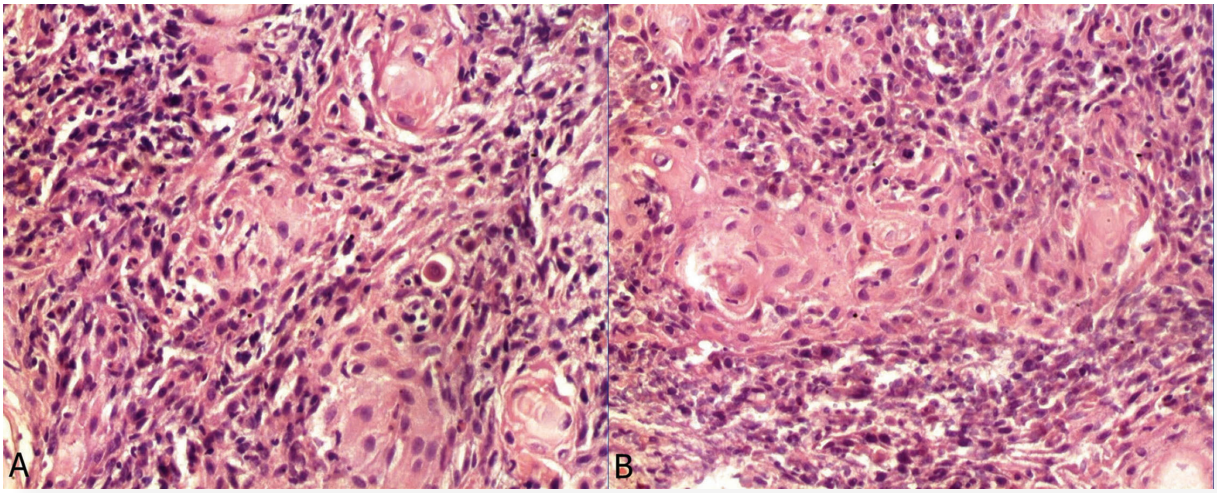

Figure 1. Histopathology. Epidermal ulcer. In the base there is a large proliferation of neoplastic epidermal cells. There is keratinization.

Discussion

In A.D. Celsus was the first to mention, in 1828 Jean Nicholas Marjolin described the chronic ulcers burns, ulcers called chancroid without establishing what this meant. It is because of Da Costa, by the year 1903, the term Marjolin ulcer was used to describe the malignancy of a chronic ulcer that originates in the scar of a burn [1,2].

Carcinomas are developed in chronic wound scarring such as burns (2% incidence), pressure sores (0.5% incidence), venous ulcers and hidroadenitis supurative [1-3].

The mechanism by which malignant transformation occurs is not known, several theories have been postulated, one of which suggests that the toxins released into damaged tissue act as carcinogens, it has been postulated that repeated cycles of irritation, ulceration and tissue repair lead to malignancy. It also has been suggested that chronic damage would lead to a local deficit of nutrients, producing an epithelial carcinogenesis unable to resist the radiation produced in addition to tissue hypoxia, decreased immunity and repeated micro trauma tissue [2,4-8].

The incidence is unknown. 2-3% of squamous cell carcinomas developed in burn scars. The male to female ratio is 3:1, and the age range is from 18-50 years, is most common in the extremities (60 %), especially lower, head and face (30%) and trunk (10%) [2,8,9].

The most common histological type is squamous cell carcinoma (87%), followed by basal cell carcinoma, other histological types, such as melanoma or sarcoma are less frequent [2,6,9].

There are two styles: early malignancy: with a range of 4 months to 1 year of wounding. Slow evolution: with a range of 1-75 years. The malignancy may manifest clinically by increased pain, discharge, or bleeding, and warty appearance of the edges of the lesion.

Epidermoid carcinoma of Marjolin ulcers is more aggressive and more prone to develop metastases through lymphatic pathways. The frequency of metastasis at 5 years is close to 40 % [2,6,7,9,10].

The main diagnostic tool is the histological study. Radiography is used to assess bone involvement, and magnetic resonance imaging to assess commitment to deep parts [2,11].

Treatment consists of surgery with safety margins of 4-6 mm and cures allow up to 90% of the cases. Mohs micrographic ablation has cure rates of 99% in five years. Cure rates down to 70% for tumors larger than 2cm.

When there are palpable nodes is recommended a FNA or excisional biopsy with frozen section to determine behavior.

The recurrence rate after radical surgery is 15%.

Radiation therapy is an alternative to surgery if it cannot be done, does not accept the patient or as adjuvant therapy in cases of large carcinomas, poorly differentiated, deep or recurring [2,4,7,11,12].

Conclusion

Marjolin's ulcer is a rare neoplasm characterized by a long latency period and increased local aggressiveness. The early and aggressive surgical treatment allows better control of this entity and prevent relapse. Early detection of this disease lies in the clinical suspicion.

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DOI: 10.7241/ourd.20141.13

NASZA DERMATOLOGIA Online
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AN UNUSUAL CASE OF *SUPERFICIAL (CUTANEOUS) ANGIOMYXOMAS*

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Source of Support: Nil
Competing Interests: None

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Our Dermatol Online. 2011; 5(1): 54-56 Date of submission: 31.10.2013 / acceptance: 07.12.2013

Abstract
Cutaneous myxomas also called angiomyxomas are rare benign connective tissue tumours, composed of stellate cells, set in a loose mucoid stroma. These lesions have been recognized as part of Carney complex.
We report a 12 year old boy affected by multiple Superficial Angiomyxomas without any other components of Carney complex.

Key words: Superficial Angiomyxomas; Carney complex; Myxoid stroma

Cite this article:
Akshaya Nagaraja, Keerthi Jampani, Srilakshmi Peddireddy, Yugandhar Inakanti, Vijayshankar Metikurke. An unusual case of superficial (Cutaneous) angiomyxomas. Our Dermatol Online. 2014; 5(1): 54-56.

Introduction

In 1988, Allen et al, proposed the disease entity 'superficial angiomyxoma which is a dermal or subcutaneous tumour composed of a mixture of small blood vessels and sparse spindle-shaped cells in a prominent myxoid stroma. Cutaneous myxomas have been well recognized in recent years, especially as part of the autosomal dominant complex of endocrine hyperactivity now known as Carney's complex.
We herein report a case of Cutaneous Angiomyxomas limited to skin and subcutaneous tissue for its rarity.

Case Report

A 12 year old boy presented with asymptomatic multiple swellings of 15 days duration (Fig. 1a - c). The swellings appeared over both the hands and spread to forearms, forehead, chin, nose, and lower back. They were painless, non tender, non reducible, non pulsatile and soft to firm in consistency measuring about 1x1 to 2x2 cm in size. Skin over the swellings appeared normal.
A differential diagnosis of Cysticercosis cellulose cutis, Cutaneous myxomas, and Lipomas was considered.
Physician and Cardiologist were consulted.
Routine blood, urine and stool examination was within normal limits, except raised triglycerides. Serological test for rheumatoid factor, ASLO titer was negative. ECG and ECHO were normal.
Radiological examination of hands, skull and chest was normal. On USG, nodules were found in the subcutaneous plane, hypoechoic with no extension in to the muscular plane. No evidence of Cysticercosis cellulose cutis found.
Fine Needle Aspiration Cytology (FNAC) - aspirates from the lesion showed predominantly many lobules of mature adipocytes, thin capillary channels seen traversing among them. A few ovoid to spindle cells seen encircling and traversing in between adipocytes. Background showed myxoid substance, collagen fibrils and lipid droplets.
Excision biopsy and histopathological examination with H&E, special stains Alcian blue and PAS revealed myxoid matrix in which were noted ovoid to stellate cells with numerous thin walled blood vessels, few of which were arborising in nature, seen punctuating the lesion. Scattered inflammatory cells were noted (Fig. 2a, b).
A diagnosis of Cutaneous Angiomyxomas was made based on clinical and histological picture.

Discussion

In 1957, Herbert Z. Lund classified myxomas of the skin into cutaneous myxoid cysts of the fingers, mucoceles of the lip, and myxomatous reactions associated with epithelial elements [1].
Superficial angiomyxoma was first described as a cutaneous myxoma complex by Carney et al in 1986. Carney's complex is an autosomal dominant syndrome characterized by myxomas of the heart, skin, and breast, spotty pigmentation of the mucous membrane, and endocrine over activity such as Cushing's syndrome and Acromegaly [2].

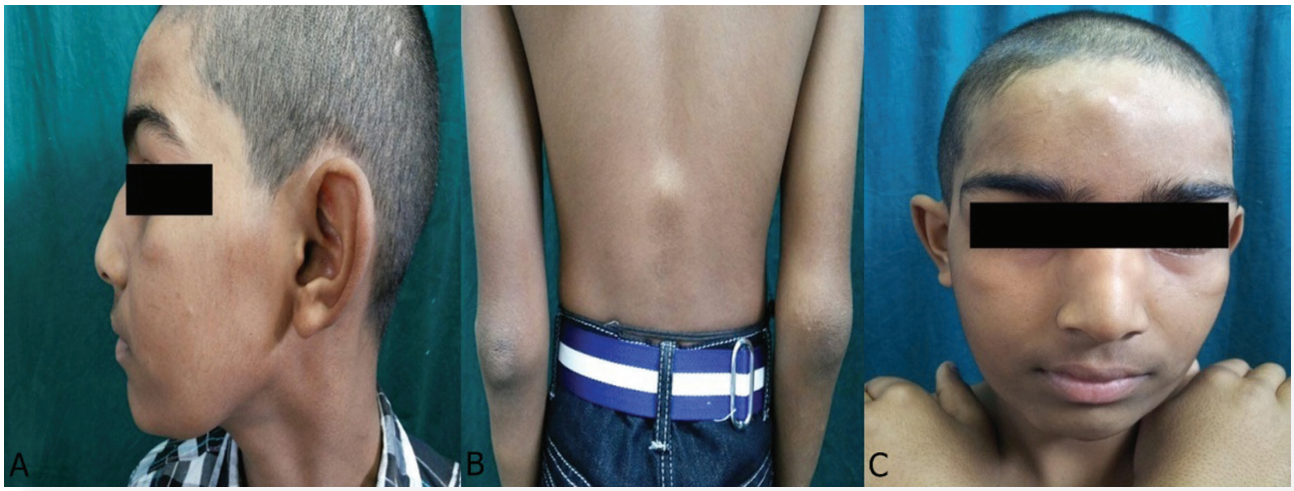

Figure 1A - C. Multiple swellings present over face, back, and upper limbs.

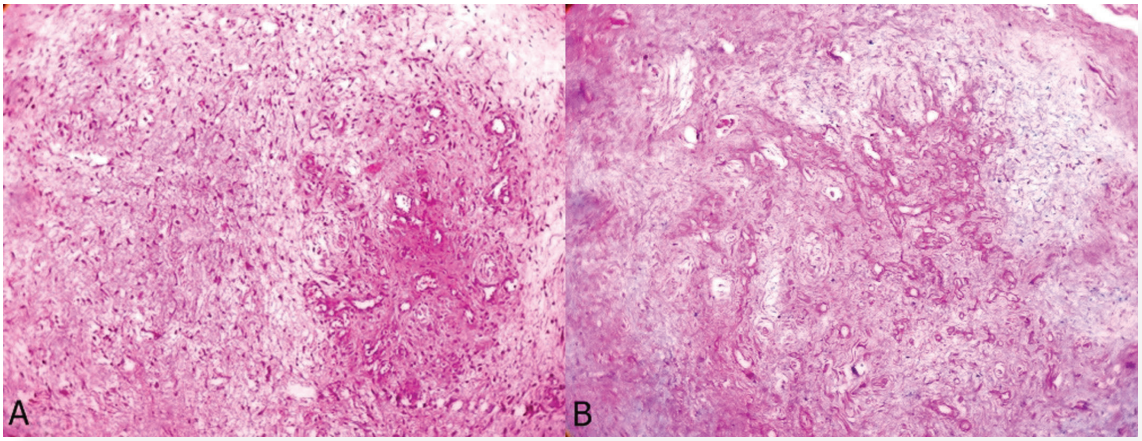

Figure 1A, B. Myxoid matrix with numerous thin walled blood vessels, stellate cells and scattered inflammatory cells.

Carney complex, previously reported as NAME (Nevi, Atrial myxoma, Myxoid neurofibromas, and Ephelides) and LAMB (Lentigines, Atrial myxoma, Mucocutaneous myxoma, and Blue nevi) syndromes, is inherited as either an AD or X-linked disorder as a result of mutations in the PRKAR1A gene [3].

Our patient did not have Carney's complex as his cutaneous tumor was not associated with non-cutaneous myxomas, pigmentation of the skin or mucous membrane, or endocrine disorders.

The skin condition was diagnosed as superficial angiomyxoma based on clinical and histologic findings of the tumor.

In 1988, Allen et al, proposed the disease entity „superficial angiomyxoma", which was a benign myxomatous neoplasm characterized by moderately to sparsely cellular angiomyxoid nodules with scattered small vessels [4].

Most cases occur in adults as an asymptomatic solitary papule or nodule with equal sex incidence. Lesions are usually less than 3 cm and have a wide anatomical distribution with a predilection for the trunk, head and neck and genital skin [5].

In our case age of onset was 12yrs and lesions were measuring about 1-3 cm with predilection for face, forearms, and hands.

Histologically superficial angiomyxoma is a dermal based lesion with frequent extension to the subcutis. Tumours are multilobulated, with copious myxoid

stroma, numerous delicate small blood vessels and spindle-shaped or stellated bland cells, probably representing fibroblasts. Aggregates of inflammatory cells, mainly neutrophils, are frequent [1,5].

Individual nodules are moderately to sparsely cellular with copious basophilic interstitial material that is PAS negative, hyaluronidase sensitive and alcian

blue positive at pH 1-4. Spindle- and stellate-shaped cells are scattered in the myxoid stroma [1,5].

In our case histopathological feature was consistent with the literature except occasional mitotic figure and adipose tissue seen entrapped within the lesion at places.

Conclusion

Contrary to the typical description, the patient here is an adolescent boy. The clinical features, histopathology are consistent with description of superficial angiomyxomas except for the sites of predilection.

Patient is on follow up and there is no new lesion.

Cutaneous Angiomyxomas limited to skin and subcutaneous tissue is presented for its rarity.

Acknowledgement:

We gratefully acknowledge the help of,

1. Principal, pesimsr, kuppam.
2. Dr. Shiva Kumar V. Professor and Hed, Department of DVL, pesimsr, kuppam.
3. Dr. Vishveshwar Reddy Y.J. Professor and Hed, Department of Medicine, pesimsr, kuppam.
4. Dr. Ramaswamy. Professor, Department of Pathology, pesimsr, kuppam.

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DOI: 10.7241/ourd.20141.14

NASZA DERMATOLOGIA Online
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A RARE CASE OF *LEIOMYOMA* OVER THE NOSE

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 57-58 Date of submission: 19.11.2013 / acceptance: 20.12.2013

Abstract
Leiomyoma is an uncommon smooth muscle tumor on the face. Its occurrence is common in the uterus. Though skin lesions have been reported, they are clinically difficult to diagnose as they have features similar to various other swelling. Here we present one such case of leiomyoma over nose that can often be misleading.

Key words: leiomyoma; piloleiomyoma; nose tumor

Cite this article:
Harinatha Sreekar, P Sudarshan, Nithya Raghunath, Vithal Malmande. A rare case of leiomyoma over the nose. Our Dermatol Online. 2014; 5(1): 57-58.

Introduction

A leiomyoma can occur in any part of the body. Since the smooth muscle is ubiquitous in its presence, a leiomyoma can occur in virtually any part of a human body. This common lesion can present in various ways and in often unexpected locations. Leiomyomas over the nose are rare and hence are usually missed by an unwary clinician. Here we present one such case which mimicked many different lesions.

Case Report

A 59 - year - old gentleman presented with a nodular lesion over the tip of his nose. He had the lesion since 20 years and complained of only occasional itching and pain. The area was depressed and scarred from chronic ulceration. (Fig. 1). The lesion was restricted to the skin. The nasal mucosa and the septum were intact clinically. He did not have any co-morbidities or similar lesions elsewhere on his body. The lesion was excised. Since the lesion was restricted to the skin, it was excised in toto and the raw area was covered with a full thickness skin graft. The operated site healed uneventfully.

The histopathologic examination revealed a whorl patterned arrangement of spindle cells. The lesion was well circumscribed into small nodules and was well encapsulated. The nuclei were rod-like and fairly uniform in shape. The stroma was well vascularized with a few areas of hyaline degeneration (Fig. 2a, b). Atypia was mild and mitotic figures were rare. On immunohistochemical analysis, the cytoplasm showed a positive reaction to actin. A diagnosis of leiomyoma was hence reached.

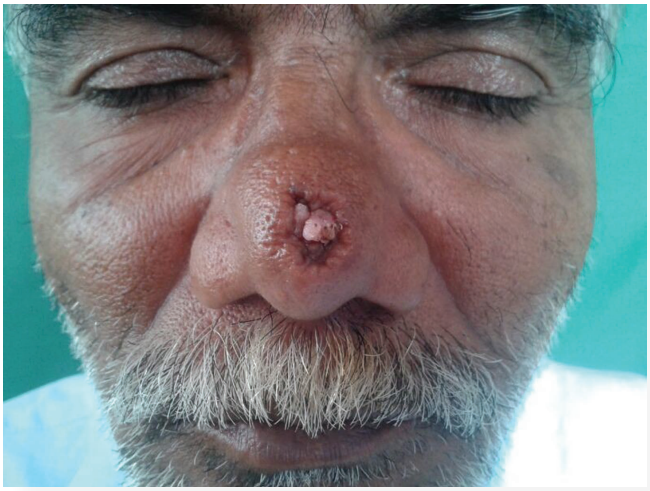

Figure 1. The nodular lesion over nose with surrounding pigmentation and scarring. The edges of the lesion are depressed with nodular pattern in the middle.

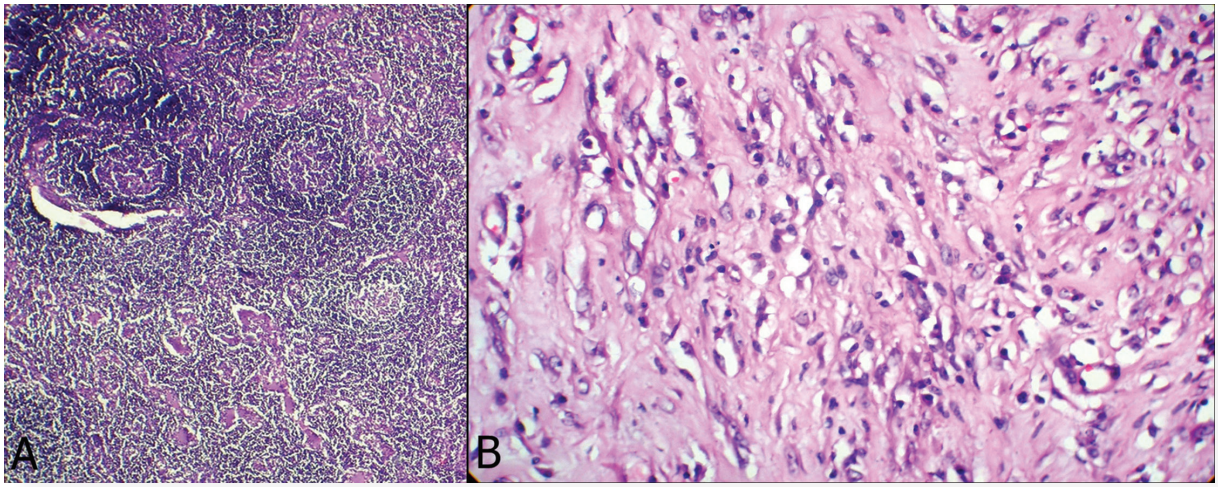

Figure 2A, B. Histopathological: A noticeable whorl patterned arrangement of spindle cells. The nuclei are rod-like and fairly uniform in shape. The stroma is well vascularized with a few areas of hyaline degeneration. Atypia is mild and mitotic figures rare.

Discussion

First description of leiomyoma was given by Virchow in 1854. He described them as benign smooth muscle neoplasms of the skin [1]. The leiomyoma area thought to originate from the smooth muscle of skin, the arector pili muscles and is hence termed piloleiomyoma. Broadly leiomyoma can be classified as:

1. Piloleiomyomas
2. Angioleiomyomas derived from the smooth muscle in the wall of blood vessels
3. Genital leiomyomas that arise from the Dartos muscle of the genitalia [2].

The inheritance patterns of leiomyoma have been the subject of recent genetic research. Unpredictable autosomal dominant patterns have been described in a few families [3]. Multiple syndromes have also been described with group presentation of uterine fibroids, skin lesions, renal cancer etc. The skin lesions however are difficult to diagnose given the simple presentation as skin nodules.

Differential diagnosis of such nodules include:

1. Neurofibromas/Fibromas
2. Myomas
3. Xanthomas
4. Dermatofibroma
5. Mastocytosis
6. Glomus tumor
7. Neurilemmoma etc.

Individual leiomyomas are smooth, firm papules or nodules, usually smaller than 2 cm in diameter, and reddish brown. Many are tender to palpation. Leiomyoma occurs predominantly on the lower extremities, less commonly on the head or trunk, and rarely on the hands or in the mouth [4-6]. Leiomyomas generally are asymptomatic. In our case, the patient had occasional itching and pain which was rare considering the nature of lesion. Such symptoms can hardly be attributed to piloleiomyomas. Pain in the nodules can however be seen in angioleiomyomas.

Asymptomatic lesions can be left untreated. Medical management has a limited role in the management of these lesions. Pharmacologic intervention has been used to alleviate pain. Options include calcium channel blockers, e.g., nifedipine, alpha blockers, e.g, phenoxybenzamine, Gabapentin, BOTOX, etc [4]. Surgical excision can be done for painful lesions or for cosmetic concern. Recurrence is rare in solitary lesions.

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DOI: 10.7241/ourd.20141.15

NASZA DERMATOLOGIA Online
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ERUPTIVE *SYRINGOMAS* OF THE NECK

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 59-60 Date of submission: 20.11.2013 / acceptance: 19.12.2013

Abstract
Syringomas are benign adnexal tumors of eccrine origin. Eruptive syringomas clinically present as multiple, skin colored tiny papules that usually develop during a short period of time and are frequently misdiagnosed with other entities. Histopathological examination is essential in the diagnosis and usually reveals numerous, small ducts in the dermis lined with a double row of epithelial cells. Herein, we present an additional case of multiple eruptive syringomas on the neck in a 25 year old female.

Key words: syringoma; papules; neck

Cite this article:
Liliane Borik, Amy Spizuoco, Viktoryia Kazlouskaya. Eruptive syringomas of the neck. Our Dermatol Online. 2014; 5(1): 59-60.

Introduction

Syringomas are benign adnexal tumors of eccrine origin. The name "syringoma" is derived from the Greek word syrinx, which means pipe or tube, and describes the acrosyringium, the intraepidermal portion of eccrine sweat ducts. Syringomas commonly appear as soft, flesh colored single or multiple dermal papules localized on the eyelids in women during puberty. According to Friedman and Butler´s classification scheme, 4 principal clinical variants of syringoma are recognized: a localized form, a form associated with trisomy 21, a familial form and a generalized form that includes multiple and eruptive syringoma [1]. In 1987 Jacquet and Darier first described eruptive syringoma, a rare variant of syringoma [2]. Clinically, eruptive syringoma may be confused with acne vulgaris, milia, sebaceous hyperplasia, lichen planus, eruptive xanthoma, hidrocystoma, urticarial pigmentosa, trichoepithelioma and xanthelasma on the face, and granuloma annulare on the trunk, therefore, histopathological examination is essential [3,4]. Herein we present a case of multiple syrinogmas of the neck in a 25 years old female patient.

Case Report

A 25 year old female patient was admitted to the dermatologist`s office with the complaint of a rash and itch on the skin on the anterior neck (Fig. 1, left-sided arrows). Patient was otherwise healthy and had no other complaints.
Biopsy was taken from one of the lesions. It showed a well-circumscribed neoplasm in the upper and middle parts of the dermis surrounded by a fibrous stroma (Fig. 2). The neoplasm was composed of small ducts composed of two-layers of cuboidal epithelium. Some ducts were dilated and some had a short "comma-like" tail (Fig. 2, 3). The diagnosis of "eruptive syringoma" was established. The patient refused to undergo treatment.

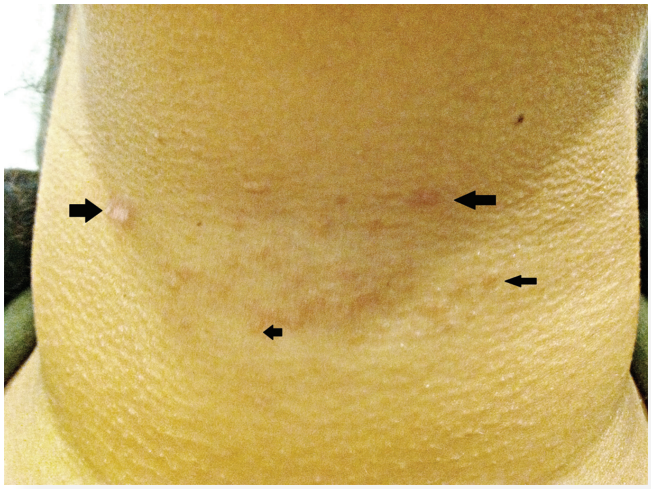

Figure 1. Multiple pink and skin colored papules on the anterior neck. Scar after skin biopsy (right sided arrow).

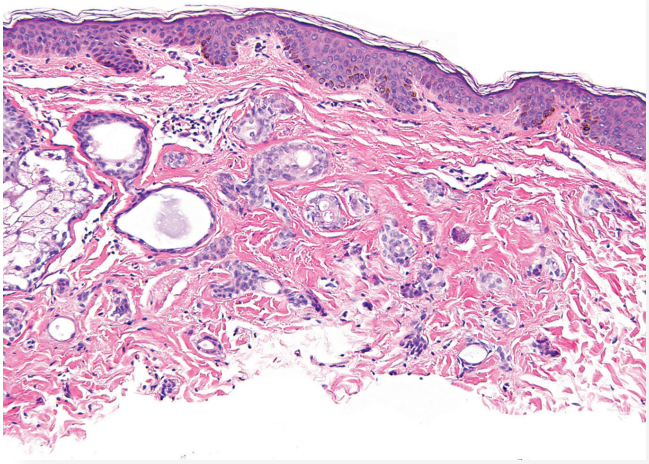

Figure 2. Well-circumscribed eccrine neoplasm in the upper and middle parts of the dermis surrounded by fibrous stroma. Hematoxyllin & Eosin stained sections, ×100.

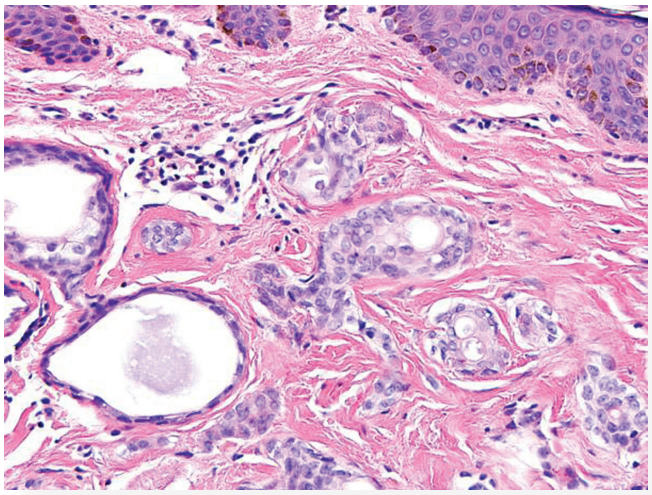

Figure 4. Dilated eccrine ducts lined with two-layers of cuboidal epithelium and short "comma-like" tails, surrounded by fibrotic stroma. Hematoxyllin & Eosin stained sections, ×400.

Discussion

Eruptive syringomas clinically present as multiple, skin colored tiny papules that usually develop during a short period of time. Neck, axillae, pubis and anterior trunk are the most frequent localization. Rare cases with widespread involvement of the body have also been reported [5,6].

The diagnosis is rarely established based on the clinical picture alone, hence, histopathological examination is mandatory. Syringomas are associated with multiple conditions, most frequently with Down syndrome and Nicolau-Balus syndrome (eruptive syringomas, milium cysts and atrophoderma vermiculata) [7].

Histopathologically, eruptive syringoma is characterized by numerous, small ducts in the dermis lined with a double row of epithelial cells. Ductal lumina are filled with an amorphous, periodic acid-Schiff-positive material. Some of the ducts possess small, comma-like tails of epithelial cells, giving them the appearance of tadpoles. Clear cell variant of syringoma and squamous metaplasia were also described [8]. Rarely, especially if located in genital area, syringomas may be located in the deeper areas of the dermis. In such cases differential diagnosis with microcystic adnexal carcinoma is especially difficult.

Absence of follicle differentiation helps to distinguish syringomas from trichoepitheliomas and infundibular-cystic basal cell carcinomas. The differential diagnosis between syringomas and microcystic adnexal carcinoma and reactive eccrine gland metaplasia is more complex and often requires clinico-pathological correlation.

The pathogenesis of eruptive syringoma is unclear. Association with drug intake and variety of inflammatory conditions was described. Guitart et al. propose the term syringomatous dermatitis assuming a hyperplastic response of the eccrine duct to an inflammatory reaction rather than a true adnexal neoplasm [9]. Yoshii et al. reported a case of Syringoma-like eccrine sweat duct proliferation in association with radiation dermatitis [10]. Furthermore, eruptive syringoma may be linked to alopecia areata, prurigo nodularis or lymphocytic inflammatory reactions. Öztürk et al. described a case of post-pubertal eruptive syringoma triggered by anti-epileptic drugs, namely, valproic acid and carbamazepine [11]. In our patient, careful assessment did not reveal any associations.

Treatment of eruptive syringoma includes cryosurgery, dermabrasion, chemical peeling, electrodessication, curettage, CO2 laser and demonstrate variable cosmetic results [12]. Treatment with oral isotretinoin, topical tretinoin, adapalene was also reported. Sánchez et al. suggest the use of topical atropine to alleviate the pruritus in symptomatic eruptive syringoma [13].

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ERUPTIVE SYRINGOMAS OF THE NECK

by Liliane Borik, Amy Spizuoco, Viktoryia Kazlouskaya

comment:

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 61 Date of submission: 26.12.2013 / acceptance: 04.01.2014

Cite this article:
Antonio Chuh, Vijay Zawar. comment: Eruptive syringomas of the neck. Our Dermatol Online. 2014; 5(1): 61.

We read with admiration the article written by Borik L et al on eruptive syringomas (ES) of the neck [1]. We are convinced, from the clinical and histopathological findings, that syringomas is the most likely diagnosis for the patient concerned, and that the authors have provided that highest quality of care to her.

We cast reservations, however, on whether the longitudinal time progression of the lesions warrant the term eruptive to be validly applied here. Specifically, the 25-year-old lady was "admitted to the dermatologist's office with the complaint of a rash and itch on the skin on the anterior neck".

In general usage, eruptive denotes to become active or violent especially suddenly [2]. In dermatology, we might apply eruptive to describe sudden appearance – a crop or several successive crops – of a number of lesions, within a relatively short time frame. From the description by Borik et al [1], we see little substantiation of an eruption.

In other reports of ES, description of the time progression is much more precise. For example, Teixeira M et al [3] described "a few papules on the anterior chest wall and spread to a larger area on her upper body in successive crops (our emphasis)" for a 19-year-old female. Chow C et al [4] reported "new crops (our emphasis) of papules appeared on his axillae, back, and buttocks over several months" for a 19-year-old man. Other reports depict the temporal sequence as "on the forearm first, which was followed by successive eruptions on the face, chest, upper abdomen, thigh and neck respectively" [5], "the papules appeared in crops" [6], "abrupt eruption of small skin-colored or reddish papules on the face, neck and limbs" [7], and "the lesions appeared at the same time" [8] (our emphases).

Review articles also endorse that the chronological progression of ES should be " appearing in successive crops" [9], and "in successive crops of small skin-colored papules" [3] (our emphases).

Whether multiple cutaneous lesions are eruptive or not casts significant impacts on the investigations to unveil the underlying pathogenesis. Eruptions, such as those in ES, lead clinicians to be alerted to infectious or other acute exogenous insults of relative short duration. We suspect several diseases – Gianotti-Crosti syndrome, pityriasis rosea, asymmetric periflexural exanthem, eruptive pseudoangiomatosis, papular-purpuric gloves and socks syndrome – to be paraviral exanthems partly because of the eruptive course for the onset of these rashes. Advanced epidemiological methodologies might then be applied to detect whether the rashes are contagious [10,11]. On the contrary, multiple lesions which are not eruptive would be more compatible with subacute to chronic exogenous insults or longstanding endogenous immunological or other homeostatic upheavals.

Otherwise, we congratulate Borik et al for their review of this interesting cutaneous condition.

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DOI: 10.7241/ourd.20141.16

NASZA DERMATOLOGIA Online
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SUBUNGUAL GLOMUS TUMOR: AN UNCOMMON CAUSE OF MEDIAN CANALIFORM NAIL-DYSTROPHY OF HELLER

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 62-64 Date of submission: 02.10.2013 / acceptance: 02.11.2013

Abstract
Glomus tumor is an uncommon vascular tumor involving mostly subunguum of the thumb or the index finger. It commonly presents as a pink or purplish circumscribed nodule underneath the nail plate. Pain is paroxysmal in nature and precipitated often from exposure to cold or pressure/blunt trauma. Dystrophy of the nail plate occurs rarely. The described case, a 40-year-old woman, had dystrophic thumbnail ascribed to subungual glomus tumor that resembled median canaliform nail-dystrophy of Heller.

Key words: Glomus tumor; Heller's nail dystrophy; Median canaliform dystrophy; Nail dystrophy; Subungual tumor

Cite this article:
Mrinal Gupta, Vikas Sharma, Vikram K. Mahajan, Ravinder Singh: Subungual glomus tumor: an uncommon cause of median canaliform nail-dystrophy of Heller. Our Dermatol Online. 2014; 5(1): 62-64.

Introduction

Glomus tumor (syn - glomangioma, glomangiomyoma) is an uncommon neuromyoarterial tumor of glomus bodies that affects both the genders usually in third or fourth decade and seen rarely in children. It notably involves the subunguum of thumb or the index finger, and occasionally the skin lesions over extremities, head, neck and penis have been described. Extracutaneous involvement of gastrointestinal tract, bones, lungs, liver and cervix may occur sometimes [1]. Pain is paroxysmal in nature and precipitated often from exposure to cold or pressure/blunt trauma. Dystrophy of overlying nail or erosion of underlying phalanx may occur rarely [2]. Median canaliform nail dystrophy of Heller, an uncommon form of nail dystrophy of one or both the thumbnails, is characterized by a midline or paramedian split or canal formation in the midline of nail plate in a characteristic inverted fir tree-like pattern. Most cases remain idiopathic and resolve spontaneously. An intentional trauma from pushing back the cuticle and proximal nail fold as a habitual tic is implicated in most instances. Familial cases of median canaliform nail dystrophy are on record and systemic retinoid therapy too has been a suggested causative factor [3]. However, its pathogenesis mostly remains obscure. The described case, a 40-year-old woman, had dystrophic thumbnail resembling median canaliform nail-dystrophy due to subungual glomus tumor.

Case Report

A 40-year-old woman presented with pain over proximal nail fold of right thumb for 3years. The pain often radiated to forearm and was severe even on mild touch and after exposure to cold. There was no history of prior trauma or drug intake. The nail plate showed a median split that had appeared over proximal nail plate and progressed longitudinally involving the whole nail plate within a year. A localized bluish discoloration over subunguum underneath the nail split was apparent that showed no inflammation (Fig. 1A, B). Direct pressure from pencil tip elicited severe pain (Love test) and tying tourniquet proximally to the arm provided no relief (negative Hildreth's sign). Other finger and toenails, and systemic examination were normal. She was investigated further with a clinical possibility of onychmatricoma and median canaliform dystrophy of Heller. Routine laboratory investigations including hand x-rays were normal. A magnetic resonance imaging (MRI) of right thumb showed a 4mm hyper-intense mass in proximal nail bed suggestive of glomus tumour. A round bluish pink tumor (Fig. 1 inset) was excised after surgical nail avulsion under ring block and it showed histopathologic features of glomus tumor (Fig. 1C, D).

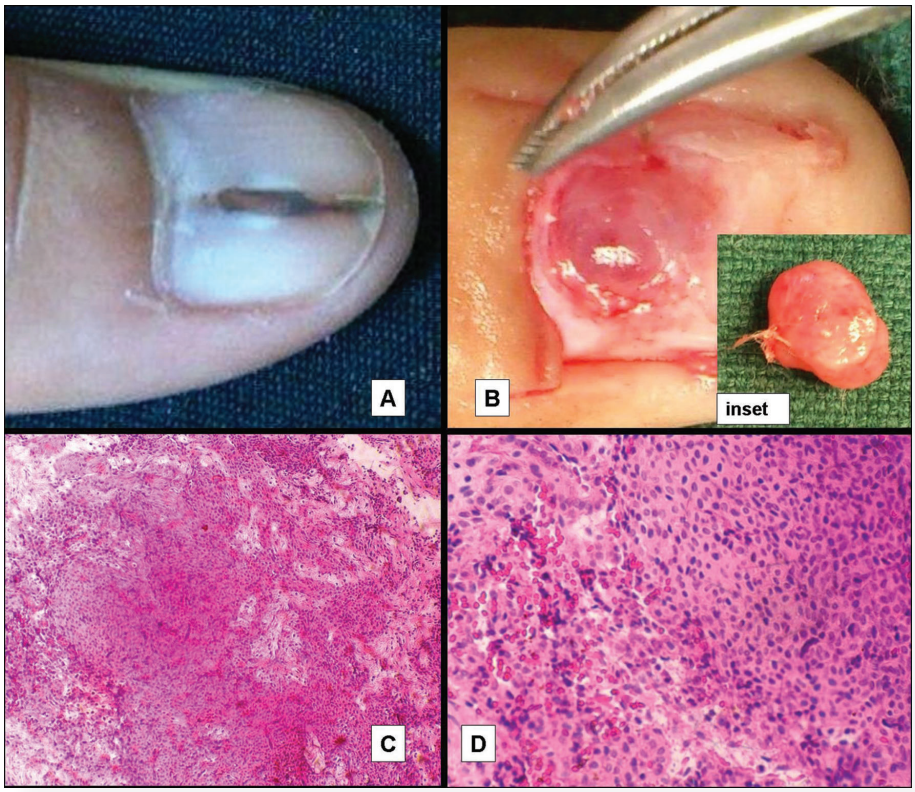

Figure 1. A. Longitudinal splitting of nail plate resembling median canaliform dystrophy. B. Bluish pink glomus tumor of nail bed as seen after surgical nail avulsion Inset shows excised glomus tumor. C. Histopathology of the excised tumor shows numerous dilated vascular spaces, surrounded by clusters of glomus cells (H&E, x 10). D. Single layer of endothelial cells lining the vascular lumina and surrounding tumor cells with scant cytoplasm and pale nucleus (H&E, x 40).

Discussion

Median canaliform dystrophy of Heller is a rare entity of obscure etiology; habitual tic is the most implicated factor in a sizeable majority. Subungual tumors (myxoid cyst, papilloma) have caused a median longitudinal split in a few cases by pushing up the nail plate from beneath or by pressure effects on the underlying nail matrix [4]. Some of the cases have been ascribed to glomus tumors involving the nail matrix or the nail bed [5,6]. Glomus tumor, a rare tumor of the glomus bodies, comprises only about 1-5% of all soft tissue tumors of hands [2]. Glomus bodies are present in reticular dermis at all body sites; most notably the subunguum has them in very high numbers. Nearly 90% patients present with solitary lesion and 25-75% cases have involvement of fingers (subunguum). An autosomal dominant inheritance may occur but most cases occur sporadically. A mutation of a specific gene, glomulin, has been mapped to chromosome 1p21-22 in cases of inherited glomangiomas [7]. Although the tumor may produce visible changes like erythronychia, distal onycholysis, nail dystrophy, discoloration of nail plate and even features of Raynaud's phenomenon, the clinical diagnosis is often delayed for several (0-20) years as no clinically obvious lesion is seen in 1/3rd cases [8,9,2]. Glomus tumor requires differentiation from other painful cutaneous tumors (eccrine spiradnoma, leiomyoma, traumatic neuroma, neuromatoid hyperplasia), schwannoma, mucoid cyst, hemangioma, melanoma, or blue rubber bleb nevus when lesions are multiple. The glomus tumor can be visualized on radio-imaging studies like ultrasonography or MRI while x-ray examination may help in 25-60% cases who develop erosion of the underlying phalanx [10]. Thus, the clinical triad of severe pain, localized tenderness and temperature sensitivity is pathognomic. Surgically excised glomus tumor appears as a 1-20 mm bluish-red nodule. The histopathology of the tumor is characteristic with the presence of vascular lumina surrounded by proliferating glomus cells (identified from scanty eosinophilic cytoplasm and pale nucleus) arising from the arterial end of glomus body. Three distinct histological patterns can be identified:

1) "solid glomus tumor" has sheets of cells resembling glomus cells,

2) "glomangiomas" show dilated vascular channels surrounded by glomus cells, and

3) "glomangiomyomas" have spindle shaped smooth muscle cells mixed with glomus cells.

Laser ablation, sclerotherapy, and surgical excision are available treatment options but recurrence in nearly 50% cases may occur following incomplete excision [5]. This patient had glomus tumor of the nail bed causing unusual form of nail dystrophy due to pressure effect on the growing nail by pushing it up. Surgical excision provided complete relief, and it has not recurred during 1-year follow up.

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DOI: 10.7241/ourd.20141.17

NASZA DERMATOLOGIA Online
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LESCH-NYHAN SYNDROME: A RARE DISORDER OF SELF-MUTILATING BEHAVIOR

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 65-67 Date of submission: 17.09.2013 / acceptance: 16.10.2013

Abstract
This paper describes Lesch-Nyhan syndrome in a 1-year-old boy. This X-linked recessive error of purine metabolism presents in infancy with a constellation of mental and developmental retardation, self-mutilating behavior, neurological features and abnormal urine uric acid: creatinine ratio. The basic defect is deficiency in phosphoribosyl transferase production but exact pathomechanism for clinical symptomatology remains un-elucidated. No specific medical treatment is available.

Key words: Dysarthria; Hyperuricemia; Hypoxanthine-guanine phosphoribosyl transferase; Metabolism, Inborn Errors; Purine metabolism; Self-mutilating behavior

Cite this article:
Mrinal Gupta, Vikram K. Mahajan, Vikas Sharma, Pushpinder S. Chauhan, Karaninder S. Mehta. Lesch-Nyhan Syndrome: a rare disorder of self-mutilating behavior. Our Dermatol Online. 2014; 5(1): 65-67.

Introduction

Lesch-Nyhan syndrome (LNS) is an extremely rare X-linked recessive error of purine metabolism due to severe inborn deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT) enzyme. This enzyme is normally present in every cell but brain (basal ganglia) has the highest concentration and is essential for normal metabolism of hypoxanthine. The HPRT gene is located on the long arm of the X chromosome at Xq26.1 and the complete amino acid sequence for HPRT is approximately 42 kb and split into 9 exons [1]. Clinically, LNS manifests with consistent and compulsive self-biting behavior that usually begins with the eruption of teeth, hyperuricemia, mental retardation, cerebral palsy, dysarthric speech, choreoathetosis initially and spasticity and dystonia later. The self-mutilating behavior persists and results in partial or total destruction of lower lip and/or amputation of fingers, toes, and sometimes of tongue. Most patients do not survive childhood due to renal or respiratory complications. The survival beyond 20 years of age is an exception but the life span may be normal for patients with partial HPRT deficiency (Kelley-Seegmiller syndrome). The estimated prevalence of LNS is 1 in 380,000 live births in Canada and 1 in 235,000 live births in Spain [2] and it has been rarely reported from India.

Case Report

1-year-old male child was brought for dermatological assessment of failure to thrive and lacerations over lower lip, thumbs and left index finger due to self biting. Historically, the child had developed the habit of self biting at 10 months of age roughly coinciding with eruption of teeth. The ulcers would heal spontaneously after bandaging but recur within a day after its removal. He was the only child born to non-consanguineous parents after a normal gestation/pregnancy. He was unable to hold his head yet. He measured 56cm (50th centile 74.4cm) in height, weighed 6kg (50th centile 9.04kg) and had occipito-frontal circumference of 45.5cm (50th centile 46.5cm) suggestive of severe growth retardation. His bone age was consistent with his chronological age and mental age was 8 months. Cutaneous examination (Fig. 1) showed well-defined ulcers/lacerations with crusting and scarring at places involving both the thumbs and left index finger. Nails of the involved fingers were dystrophic. A single, well-defined, deep ulcer with ragged margins and some scarring was present over lower lip. There was no regional lymphadenopathy. Neurological examination showed chorea, hyper-reflexia and positive Babinski's sign. Other systemic examination and laboratory investigations (blood cell counts, hepatorenal functions, urinalysis and chest radiograph) were normal. The serum uric acid levels were 6.5mg/dl (normal 1.7-5.8 mg/dL) and the urine uric acid: creatinine ratio was 3:4 (normal 2:5-3:5).

HPRT enzyme estimation in erythrocyte lysate or skin fibroblasts was not done for lack of availability/affordability. However, features of self-mutilating behavior, physical and mental retardation, neurological features, and abnormal urine uric acid: creatinine ratio were suggestive of LNS.

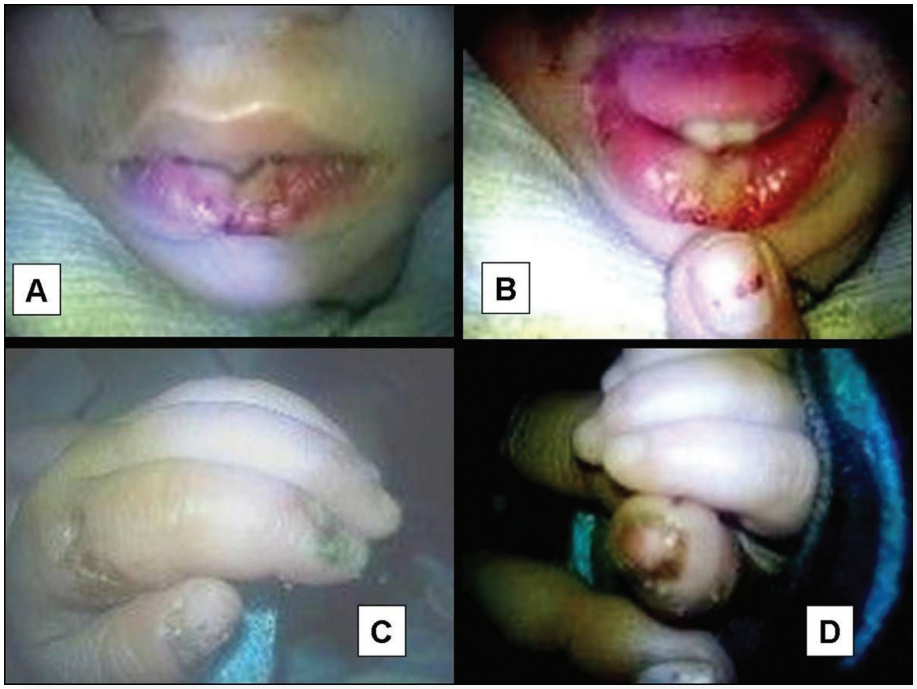

Figure 1. A well defined deep ulcer with ragged margins over lower lip (A & B). Ulcers and lacerations with crusting and scarring over left index finger and thumb (C) and right thumb (D). Note dystrophic nails of the involve digits.

Discussion

Lesch-Nyhan syndrome is extremely rare genodermatosis having developmental, behavioral, neurological, and biochemical abnormalities. Born normally, the infant develops growth retardation and neurologic signs after several months. Extrapyramidal signs (chorea, dystonia) and pyramidal tract signs (hyper-reflexia, sustained ankle clonus, positive Babinski sign, scissoring) become evident usually by 8-12 months. There may be moderate to severe mental retardation along with dysarthric speech. The self-injurious behavior usually begins with self-biting at 1 year or may be delayed until teens. Other patterns of self-injurious behavior emerge over time, albeit, aggressive behavior may decline in few after 10-12 years of age. Self-biting is intense and substantial loss of tissue around the lips and partial or total amputation of fingers/toes may result. The biting pattern can be asymmetric, with preferential mutilation of the left or right side of the body [3]. Interestingly, the pain sensations are intact and the child screams in pain on self-biting. The exact mechanism of neurologic and behavioral symptoms in LNS is poorly understood. The metabolism of both hypoxanthine and guanine is affected; guanine triphosphate and adenosine have substantial effects on neural tissues through dopamine and adenosine systems. Dopamine and adenosine systems are also linked through the neuroprotective role of adenosine in preventing neurotoxicity [4]. The majority of classic LNS patients have low or undetectable levels of the HPRT enzyme while partial deficiency in HPRT with more than 1.5-2.0% enzyme (Kelley-Seegmiller syndrome) is associated with hyperuricemia and variable neurologic dysfunction (neurologic HPRT deficiency) [4]. The deficiency of HPRT leads to accumulation of hypoxanthine, particularly in cerebrospinal fluid, excessive uric acid production, and consequent hyperuricemia. However, the behavior disorder is not due to excess hypoxanthine or hyperuricemia. Depression of dopaminergic neurons due to decreased arborization of terminal neurons too has been implicated as the causative factor but needs substantiation [5].

The diagnosis of LNS is mainly clinical and by serum uric acid estimation. Assay for HPRT enzyme in erythrocyte lysate or demonstration of mosaicism in skin fibroblasts will confirm the diagnosis or carrier state but poor availability and high cost often limit their use in clinical practice. Prenatal diagnosis is possible by amniocentesis or chorionic villous sampling. No drug is effective for preventing neurological dysfunction; prevention of self mutilation by using restraints or protective mouth guard, even tooth extraction, remains the mainstay of management [6]. Treatment with diazepam for anxiety, risperidone for aggressive behavior, and carbamazepine or gabapentin for mood stabilization is advocated. Gabapentin was proved more useful in controlling neuropsychiatric symptoms than carbamazepine or sodium valporate [7]. Conventionally, allopurinol has been used for hyperuricemia to prevent renal complications while fabuxostat remains unstudied. Rasburicase, a recombinant urate oxidase enzyme, effectively reduced plasma urate levels and improved kidney function in a neonate with LNS [8]. Behavioral therapy to manage mood swings has been found successful in selective cases.

There is not enough evidence that bone marrow transplantation is beneficial as no improvement in neurologic or behavioral symptoms has been observed [9]. Gene therapy wherein DNA cloned from HPRT gene transferred to HPRT deficient cells in vitro appears promising [10].

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DOI: 10.7241/ourd.20141.18

NASZA DERMATOLOGIA Online
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CLASSIC *KAPOSI'S SARCOMA*: A RARE CASE WITH UNUSUAL PRESENTATION

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Source of Support: Nil
Competing Interests: None

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Our Dermatol Online. 2011; 5(1): 68-70 Date of submission: 23.07.2013 / acceptance: 10.12.2013

Abstract
A 32 years old female presented with a single asymptomatic lesion on right thigh since 5 years. On examination, a single ill defined, irregular hyperpigmented plaque was present on medial aspect of right thigh. The plaque was firm in consistency and was non-tender. No scaling was evident. Clinically a differential diagnosis of Hansen's disease, lupus vulgaris and deep fungal infection were made. The histopathology interestingly showed features suggestive of Kaposi's sarcoma. The patient was HIV negative and otherwise completely asymptomatic.

Key words: Asymptomatic plaque; Kaposi's sarcoma; Non-HIV

Cite this article:
Sanjay N. Agrawal, Anuprita A. Rawal, Subodhkumar D. Jane. Classic Kaposi's sarcoma: a rare case with unusual presentation. Our Dermatol Online. 2014; 5(1): 68-70.

Introduction

Kaposi's sarcoma (KS) is a multifocal, endothelial proliferation predominantly involving the skin and other organs and is associated with formation of vascular channels and proliferation of spindle-shaped cells [1]. KS is usually linked with HIV. Classic KS occurs sporadically and is seen in immunocompetent individuals and may present as bluish-red or hyperpigmented papules, plaques or nodules over feet or hands with pedal edema. It is more common in male than female having ratio of 15:1 with predilection for elderly males. Four variants are known that is classical (sporadic), endemic (African), iatrogenic (immunosuppressive drugs associated) and AIDS-associated [2,3]. The histopathology depends upon the stage of KS as it progresses from the patch to plaque to nodular stage. The histopathology of plaque stage KS is characteristic with features of spindle-shaped cells arranged between the cleft-like spaces containing red blood cells (RBCs). In India, very few cases of Kaposi's sarcoma have been reported which were associated with HIV infection. We report a case of classic Kaposi sarcoma in an immunocompetent adult female as a very rare presentation.

Case Report

A 32 years old married female having two children presented with single asymptomatic hyperpigmented lesion on right thigh since 5 years. The lesion started as an erythematous macule which gradually increased in size and thickness to form an irregular plaque over right thigh. Throughout its course the lesion was painless and non-pruritic. There was no history of trauma, prior intake of any medication, recurrent fever, chronic cough and weight loss. Local examination showed a single well circumscribed, bluish and hyperpigmented non-scaly plaque measuring around 8-10 cms over inner aspect of right thigh (Fig. 1). With this clinical findings differential diagnosis of lupus vulgaris, Hansen's disease and deep fungal infection were made. The sensations over the lesion were normal, peripheral nerves were not thickened and the slit skin smear test for acid fast bacilli was negative. On diascopy, there was no evidence of apple-jelly nodules with no lymphadenopathy and hepatosplenomegaly. Other systemic examinations were within normal limits. A skin punch biopsy was taken from the lesion and the histopathological examination interestingly and surprisingly showed proliferation of thin walled capillaries along the blood vessels of superficial plexus. The capillaries are arranged in clustered pattern and seen as rounded spaces filled with RBCs extending between collagen bundles (Fig. 2). Moderately dense infiltrate of lymphocytes and occasional neutrophils were present in dermis. Abundant extravasation of RBCs was seen in upper dermis along with some hemosiderin deposits (Fig. 3). Spindle cells arranged loosely in short fascicles are seen with formation of cleft like spaces containing RBCs (Fig. 4). These histopathological features were suggestive of plaque type of Kaposi's sarcoma (KS). With this histopathological diagnosis patient was retrospectively questioned and patient gave no history of chronic diarrhea, blood transfusion or any history of extra-marital sexual exposure. Her husband and both children were not having similar or other complaints.

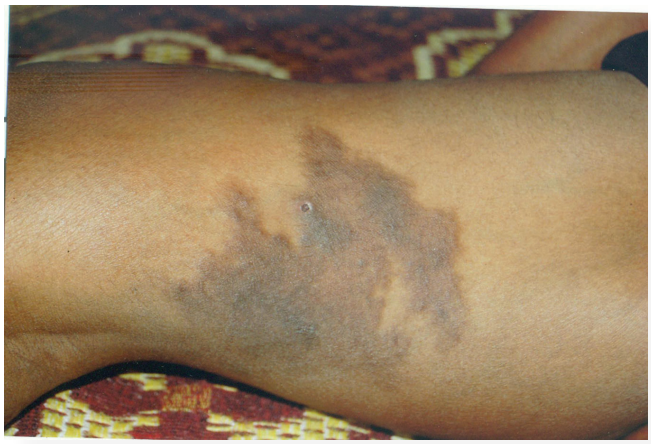

Figure 1. Clinical photograph showing a single well circumscribed, bluish and hyperpigmented plaque over inner aspect of right thigh.

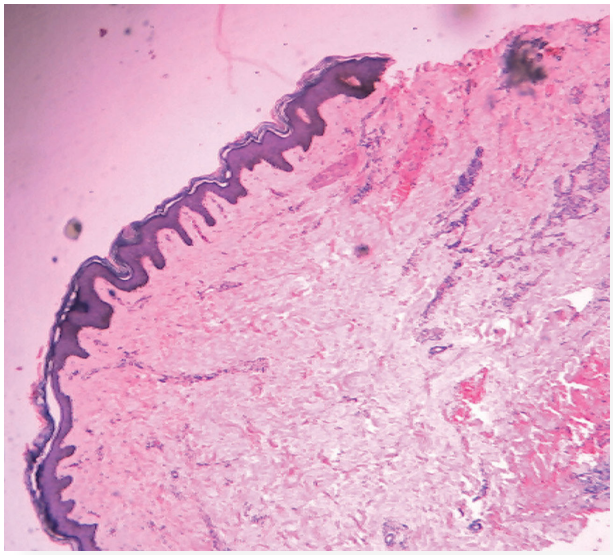

Figure 2. Histopathological features showing capillaries arranged in clustered pattern as rounded spaces filled with RBCs extending between collagen bundles. (H & E, 40x)

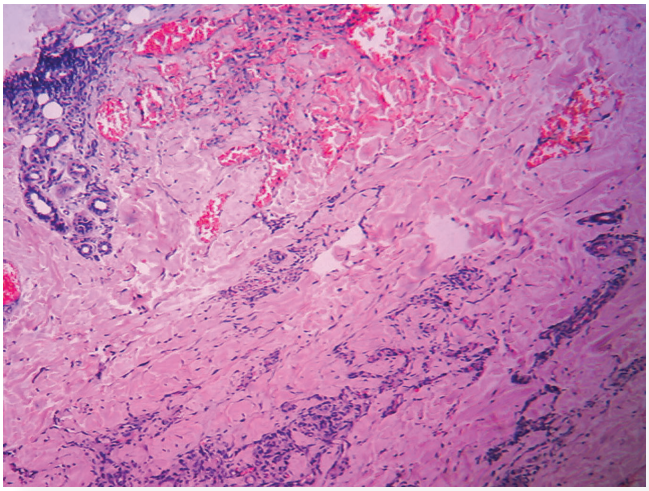

Figure 3. Histopathological features showing infiltrate of lymphocytes and occasional neutrophils and abundant extravasation of RBCs in upper dermis. (H&E, 100x)

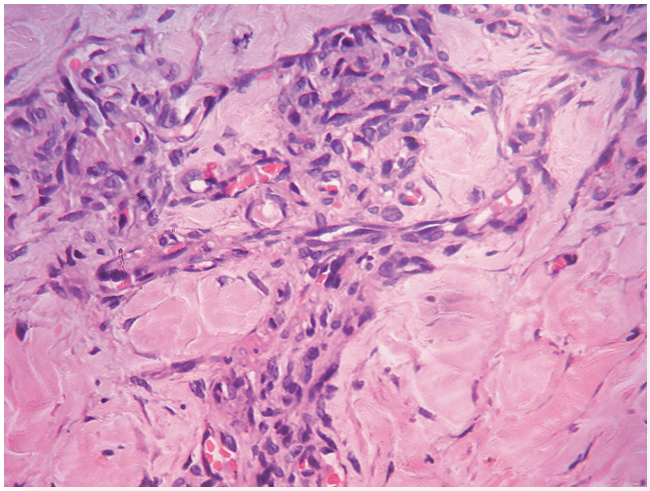

Figure 4. Histopathological features showing Spindle cells arranged loosely in short fascicles with formation of cleft like spaces containing RBCs. (H&E, 400x)

Her laboratory investigations revealed Complete blood count, Liver function test, Renal function test within normal limits. Serology for HBsAg and VDRL and HIV were negative. Because of lack of facilities Polymerase chain reaction (PCR) for human herpesvirus 8 (HHV-8) could not be done. Sputum for Acid Fast Bacilli (AFB) and Mantoux test were negative. Chest radiograph and ultrasonography scan of abdomen were normal.

Thus, a diagnosis of plaque type of Classical (sporadic) KS was made.

Discussion

Classic KS was originally described by Moritz Kaposi in 1872 as an 'idiopathic multipigmented sarcoma of the skin' involving endothelial cells.[4] Classic KS is rare and unassociated with HIV infection. An association with HHV-8 is seen. Its low prevalence in India could be attributed to low prevalence of HHV-8 [4,5]. It most often arises in middle-aged and elderly men of Mediterranean or Jewis descent [6]. Homosexual males are at increased risk for classic KS [7]. It usually presents as multiple firm purple blue or reddish-brown plaques and nodules typically appearing over hands and feet and progress up to arms and thighs. Commonly oedema of legs is present. In 10% of cases visceral or mucosal involvement is seen. A second non-KS hematologic malignancy is often present in as many as 30% cases, typically Non Hodgkin Lymphoma seen. Diagnosis is made by clinical and histopathological correlation. Treatment depends on extent and localization of lesions. It includes non-intervention, cryoablation, surgical excision, laser therapy. Till date very few cases of Classic KS have been reported.

Our patient is a healthy young female presented with a chronic asymptomatic hyperpigmented plaque over thigh with no pedal oedema, HIV antibody negative and the characteristic histopathology of KS. So, in an asymptomatic hyperpigmented chronic plaque one should consider the differential diagnosis of classic KS. Non-HIV Kaposi's sarcoma may not be so uncommon in India and may not be suspected and hence rarely reported.

Ours could be one of the very few cases of classic KS reported from India with unusual presentation of single hyperpigmented plaque in female.

Acknowledgements-

We are grateful to Dr. Uday Khopkar, professor and head of department of dermatology, K.E.M hospital, Mumbai, India for histopathological opinion.

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DOI: 10.7241/ourd.20141.19

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LINEAR IGA BULLOUS DISEASE WITH POSSIBLE IMMUNOREACTIVITY TO THE BASEMENT MEMBRANE ZONE AND DERMAL BLOOD VESSELS

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Source of Support:
Georgia Dermatopathology Associates, Atlanta, Georgia, USA.
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 71-73 Date of submission: 05.09.2013 / acceptance: 18.11.2013

Abstract
Introduction: Linear IgA bullous dermatosis (LAD) is an immunobullous disorder, in which IgA antibodies are deposited along the basement membrane zone (BMZ) of the skin in a linear pattern. The cause of this disease is unknown, but the eruption may occur more commonly in association with certain medications.
Case report: A 61 year old woman presented with blisters in the axillae and legs, with pain, itching and swelling. She was taking many medications for other conditions such diabetes and obesity. Tense blisters were seen, primarily on the legs and accompanied by some ankle swelling.
Methods: Skin biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF), and immunohistochemistry (IHC) studies were performed.
Results: The H&E examination revealed a subepidermal blister, with small numbers of lymphocytes, neutrophils and eosinophils noted within the blister lumen. The dermis also displayed a mild, superficial, perivascular infiltrate of lymphocytes and histiocytes; eosinophils and neutrophils were also noted. DIF and IHC studies confirmed the diagnosis of linear IgA (LAD) at the BMZ. However, in addition to immunoglobulin A, we also observed deposits of IgA, IgM, IgG, IgD, Kappa, Lambda, Complement/C3c, C1q, fibrinogen and albumin around upper dermal blood vessels.
Conclusions: LAD has been most commonly associated with medication intake; the most common DIF immune response is the presence of linear IgA at the BMZ. However, here we found additional reactivity to against dermal blood vessels. Because the patient is affected by diabetes mellitus, it is difficult to know if the observed vascular reactivity was associated with the diabetes or solely an immune reaction to the vessels. Based on our findings, we encourage searching for vascular reactivity in cases of LAD.

Key words: Linear IgA bullous dermatosis; drugs; vessels; autoreactivity

Abbreviations: Linear IgA bullous dermatosis (LAD), basement membrane zone (BMZ), direct immunofluorescence (DIF), hematoxylin and eosin stain (H&E), idiopathic linear IgA blistering disease (LABD).

Cite this article:
Ana Maria Abreu Velez, Vickie M. Brown, Michael S. Howard. Linear IgA bullous disease with possible immunoreactivity to the basement membrane zone and dermal blood vessels. Our Dermatol Online. 2014; 5(1): 71-73.

Introduction

Drug-induced linear IgA (LAD) is a self-limited eruption, characterized by linear deposition of IgA without IgG at the basement membrane zone (BMZ) of the dermal/epidermal junction of the skin. Most patients described with this condition seem to lack circulating antibodies. The distribution of lesions and the course of the disease differ from those of the idiopathic form of linear IgA blistering disease (LABD). LABD is extremely rare, and thus not as well characterized as LAD [1-5].

Case Report

An obese patient presented with inflamed, large blisters on the legs and smaller ones surrounding the large blisters. In addition, the patient presented with edema and some pitting edema, primarily in the legs. The patient was unable to correlate the appearance of these lesions with any specific medication, since she was taking multiple medications simultaneously. The blisters were tender to palpation, and had been present for a week The patient's medications included agents therapeutic for diabetes, arthritis, obesity, venous stasis and vulvovaginal Candadiasis.

The patient had a history of hepatitis B. Specifically, she was taking daily hydrochlorothiazide, (diuretic), Metformin® (antidiabetic; helps reduce LDL cholesterol and triglyceride levels), Symlin® (pramlintide acetate; diabetes treatment, A1c lowering and insulin reducing), Lantus® (insulin glargine subQ), Novolog® subQ (Insulin aspartate) and 1% fluconazole (topical antimycotic). A skin biopsy for histologic studies was obtained, as well as a biopsy for direct immunofluorescence (DIF). After the biopsy, the patient was also prescribed 1) triamcinolone acetonide. 0.1% topical cream twice a day for 30 days, as well as 2) hydrocortisone 2.5%. Because the patient was taking many medications, she was sent to the internist to attempt to consolidate her prescriptions.

Methods

Processing of the H & E biopsy as well as the DIF and immunohistochemistry workups were performed as previously described. For DIF, multiple frozen section sets were cut at four micron thicknesses each, and DIF was performed utilizing antibodies to IgG, IgA, IgM, IgD, IgE, Complement/C1q, Complement/C3, Complement/C4, Kappa light chains, Lambda light chains, albumin and fibrinogen [6-8].

Results

Microscopic Description and DIF findings

Examination of the H&E tissue sections demonstrated diffuse, moderate epidermal spongiosis present. Significant superficial papillary dermal edema was noted (Fig. 1). A subepidermal blister was seen, with small numbers of lymphocytes and eosinophils noted within the blister lumen (Fig. 1). The dermis also displayed a mild, superficial, perivascular infiltrate of lymphocytes and histiocytes; eosinophils and neutrophils that were rare. No definitive vasculitis was present but some inflammation and edema around the upper vessels was observed. DIF and IHC demonstrates the following results: IgG (+, focal dermal perivascular); IgA (+, focal dermal perivascular and faint linear BMZ stain); IgM (+, focal dermal perivascular and focal epidermal anti-cytokeratin); IgD (+, focal dermal perivascular); IgE (-); Complement/C1q (+, focal dermal perivascular); Complement/C3(+, focal dermal perivascular and focal epidermal anti-cytokeratin); Complement/C4 (-); kappa light chains (+, focal dermal perivascular); Lambda light chains (+, focal dermal perivascular and focal epidermal anti-cytokeratin); albumin (+, focal punctate dot epidermal stratum corneum) and fibrinogen(++, focal dermal perivascular, perieccrine and faint linear BMZ). (Fig. 1, 2). The patient was free of lesions within 5 weeks after consolidation of some medicines and the use of topical steroids.

Discussion

LAD is an immunobullous disorder in which IgA antibodies are deposited within the BMZ in a linear pattern. The cause of the disease is unknown, but the eruption has been most commonly associated with selected medications [1-5].

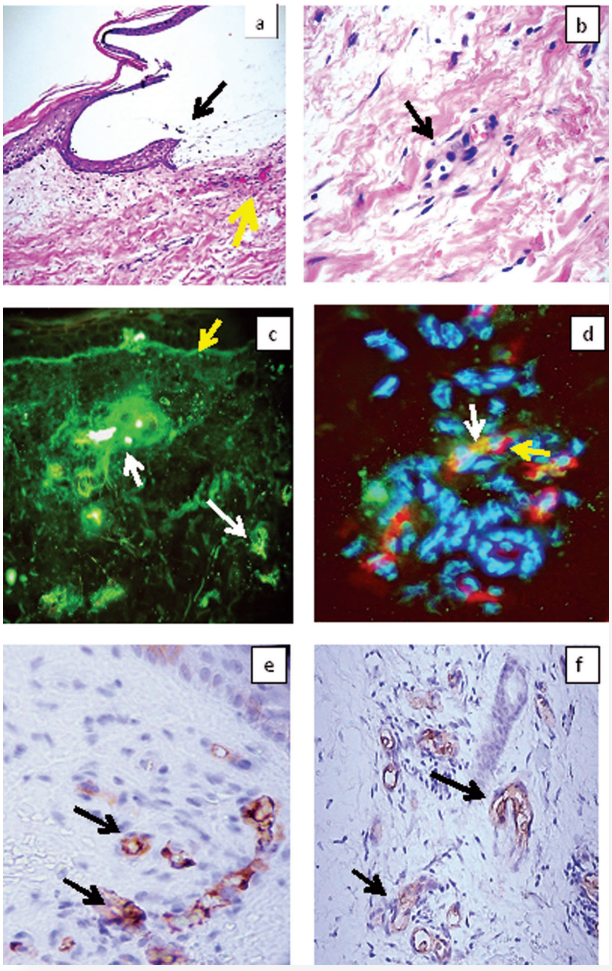

Figure 1. a. H&E section, demonstrating a subepidermal blister with focal re-epithelialization of the blister base (black arrow). Please note the presence of possible erythrocytic rouleaux and pink fibrinous material in the upper dermal blood vessels under the blister (yellow arrow) (100x). **b.** H&E section, demonstrating mild perivascular inflammation around an upper dermal blood vessel(black arrow; 200x). **c.** DIF, utilizing FITC conjugated anti-human IgA and showing positive linear IgA deposits at the BMZ (green staining; yellow arrow), as well simultaneous deposits of IgA on upper dermal blood vessels(green/white staining; white arrows). **d.** DIF, again highlighting FITC conjugated IgA positivity on dermal blood vessels (green/yellow staining; white arrow). Note that the IgA staining colocalizes with a vascular marker, Rhodamine conjugated Ulex europaeus agglutinin I(Vector Labs, Burlingame, California, USA; red staining; yellow arrow). **e.** Positive IHC staining for IgA to upper dermal blood vessels (brown staining; black arrows; 200x); note the IHC colocalization with a von Willebrand factor vascular marker(red staining; black arrows). **f.** IHC staining, showing positive staining for vimentin around inflamed dermal blood vessels and around eccrine sweat duct supply vessels (brown staining; black arrows, 200x).

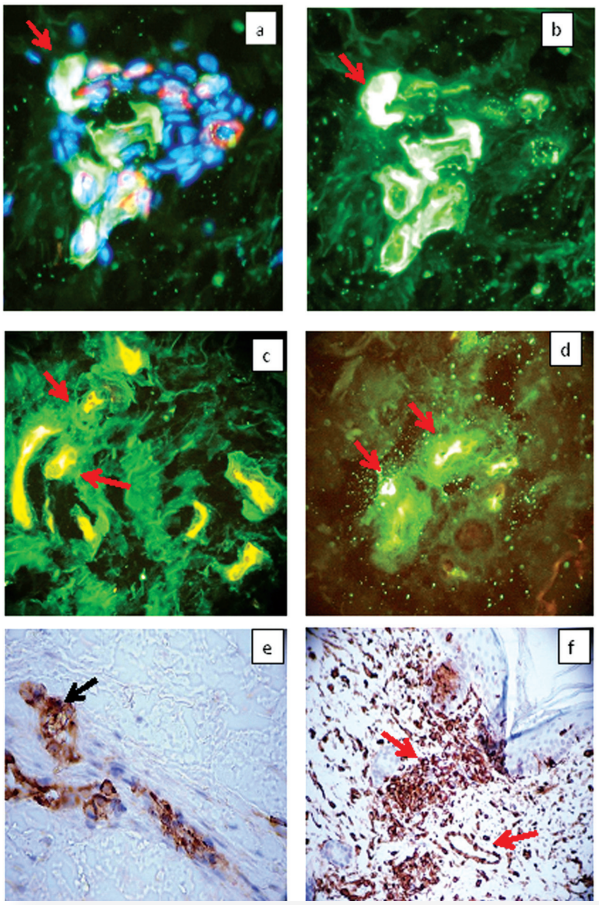

Figure 2. a. DIF, demonstrating FITC conjugated IgA positive staining on upper and intermediate dermal blood vessels (green staining; red arrow). Note the IgA positive reactivity in the vessels colocalizes with Cy5 conjugated ICAM-1/CD54 antibodies(white staining) and Rhodamine conjugated Ulex europaeus agglutinin I antibodies (red staining). The nuclei of endothelial cells were counterstained with Dapi (blue). **b.** Similar to a, but utilizing only FITC conjugated IgA. **c.** DIF, demonstrating positive staining with FITC conjugated IgD on dermal eccrine glands(yellow/white staining; red arrows). **d.** DIF, demonstrating positive staining with FITC conjugated IgA on dermal blood vessels(green/white staining; red arrows). **e.** IHC, demonstrating positive staining for IgA on dermal blood vessels (brown staining; black arrow). **f.** IHC, demonstrating positive staining for Complement/C3c on dermal blood vessels around the sweat glands (brown staining; red arrows).

As previously suggested by Plunkett, et. al. [1], all the cases we have encountered of LAD were associated with a drug reaction. Thus, LAD cases should be confirmed by DIF; a search should be made for any drug eliciting the disorder. Moreover, the majority of the cases reported in the medical literature seem to be drug induced. In contradistinction, idiophatic LAD is rare, and not well immunologically characterized. We have been working for more than 21 years with autoimmune blistering diseases, and have not encountered a single confirmed case of idiopathic LAD. In many countries, physicians may encounter adults taking 3 or more medications simultaneously. Any new medication can induce a drug-drug interaction [9,10]. Based on our current case and others, we advise dermatopathologists to search not only for deposits of immunglobulin A at the BMZ, but also around dermal blood vessels and eccrine glands in suspected cases of LAD.

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DOI: 10.7241/ourd.20141.20

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SEPTAL PANNICULITIS: CLINICO-PATHOLOGICAL REVIEW OF THE LITERATURE AND CASE PRESENTATION

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(1): 74-82 Date of submission: 01.12.2013 / acceptance: 28.12.2013

Abstract
The panniculitides comprise a large and heterogeneous group of diseases, with a high prevalence in the general population, in which the inflammatory process affects the subcutaneous tissue. We briefly review the classification, clinical and histology of the primary panniculitides and present a representative case.

Key words: panniculitis; septal panniculitis; lobular panniculitis; erythema nodosum

Cite this article:
Gabriela Martinez Braga, Beatriz Di Martino Ortiz. Septal panniculitis: Clinico-pathological review of the literature and case presentation. Our Dermatol Online. 2014; 5(1): 74-82.

Introduction

The panniculitides comprise a large and heterogeneous group of diseases, with a high prevalence in the general population, in which the inflammatory process affects the subcutaneous tissue [1,2]. We briefly review the classification, clinical and histology of the primary panniculitides and present a representative case.

The hypodermis or subcutaneous tissue forms the deepest part of the skin, embryologically derived from the mesenchym whose cells give rise to adipocytes. The basic building block of the hypodermis is the fat cell or adipocyte; these represent a special line of connective tissue cells. They are organized into lobules of about one centimeter in diameter.

The lobules are separated and supported by connective tissue through which pass the blood, lymph vessels and nerves [3].

The subcutaneous tissue of the body acts as insulation, energy reservoir, cushion and protector of the skin and allows mobility over adjacent structures [4].

The nutrient artery supplyies the center of the lobe with drainage into venules located in fibrous septa.

Consequently, interference with the arterial supply produces changes in the lobe (lobular panniculitis), while venous disorders are manifested by disturbances in the paraseptal regions (septal panniculitis). Inflammation of small veins will result in a septal panniculitis with localization of the inflammatory process in the lower dermis. Involvement of the arterial blood supply, for example, in vasculitis, produces lobular panniculitis. Other mechanisms are involved in some of the diseases that result in a lobular panniculitis.

From a clinical point of view, panniculitis manifests as more or less well-defined erythematous violaceous nodules or lumps, which coalesce to form indurated erythematous plaques that may be painful.

They are often seen in the lower extremities, but may affect any site where fat tissue is more abundant, as in the mammary regions.

Based on the clinical features, location, inicial lesiones and morphology of injuries, we can perform a diagnostic approach. However to make a firm diagnosis a skin biopsy including subcutaneous tissue should be performed.

Classification

Panniculitis classification is performed in accordance with histological examination, the location of the inflammatory process, involvement or not of the blood vessels and the predominant cell type in the infiltrate.

If the inflammatory process affects mainly the fibrous trabeculae or septa the panniculitis is called septal, and lobular or lobar when lobes are predominantly affected.

The distinction between septal and lobular panniculitis is usually artificial, since there are no purely septal or lobular panniculitides.

It is considered that all panniculitides are mixed because they all have an inflammatory infiltrate able to affect the septum and lobes, but the inflammatory infiltrate is more abundant in one or other of these two components, so the diagnosis should be noted mainly as septal or mostly lobular.

The presence or absence of vasculitis divides panniculitis into four main groups: 1. lobular panniculitis without vasculitis, 2. lobular panniculitis with vasculitis, 3. septal panniculitis without vasculitis and 4. septal panniculitis with vasculitis (Tabl. I) .

Septal panniculitis without vasculitis

Erythema Nodosum

Erythema nodosum was described by Robert Willan in 1798, later by Wilson in 1842, and Strand in 1866. It is the most common form of panniculitis [3].

Erythema nodosum occurs in about 1-5 per 100,000 inhabitants. In adults it is more common in women with a ratio of 1:6 to men. Before puberty the incidence is similar in both sexes and decreases after menopause in women [3,5].

Predominantly septal panniculitis
• No vasculitis Erythema nodosum. Panniculitis of morphea-scleroderma. Necrobiosis lipoidica.
• With vasculitis * Cutaneous polyarteritis nodosa. Surface migratory thrombophlebitis.
Predominance of lobular panniculitis
• No vasculitis Enzymatic: Pancreatic panniculitis Panniculitis in alpha -1 antitrypsin deficiency Immunologic: Panniculitis of lupus erythematosus Panniculitis in dermatomyositis Panniculitis in connective tissue disease With needle-shaped slits in adipocytes: Sclerema neonatorum Subcutaneous fat necrosis of the newborn Post steroid panniculitis Lipodistrophic: Lipoatrophy: partial, full, localized, associated with HIV, gynoid (cellulitis), membranous. Lipohypertrophy Traumatic/Physical: Cold Panniculitis Sclerosing lipogranuloma Panniculitis by injections Panniculitis by blunt trauma Panniculitis factitia, traumatic fat necrosis and encapsulated fat necrosis. Panniculitis induced by infection. Lipodermatosclerosis. Noninfectious neutrophilic and eosinophilic panniculitis. Malignancies: Subcutaneous malignant infiltrates. Histiocytic cytophagic panniculitis. Subcutaneous panniculitis -like T- cell lymphoma.
• With vasculitis Indurated erythema-nodular vasculitis

Table I. Panniculitis classification.

*** The panniculitis associated with the Involvement of large vessels, polyarteritis nodosa and migratory thrombophlebitis, usually are located in the vicinity of the vessel Involved. Often have a mixture of septal and lobular features.**

There seems to be no differences between rural and urban. Some studies have shown a higher incidence in winter-spring, summer-autumn, although this appears to be related more to the cause. The most affected age range is between 20 to 30 years [5].

The intimate mechanism or pathogenesis of erythema nodosum is unknown, it is thought that it is an immune-mediated process (multiple immunological mechanisms) or caused by circulating immune cell delayed hypersensitivity reaction (type III and IV of Gell and Coombs) in response to different antigenic stimuli [3].

There is a wide spectrum of etiologic agents that trigger this reaction, although 30 to 50 % of cases are idiopathic. Tuberculosis in adults is the most frequently related entity, followed by reactions to medications, hormonal changes, inflammatory bowel disease and sarcoidosis. In children streptococcal infections and urinary tract infections are the most often associated pathologies (Tabl. II) [3,4,6].

Idiopatic 30-50 %
Infectious causes
Bacterial: streptococcal infections, tuberculosis and other mycobacteria, yersinia, leprosy, tularemia, syphilis, leptospirosis, gonococcal meningococcal and staphylococcal infections, salmonella, shigella, Helicobacter infections, brucellosis, rickettsiosis: Q fever, chlamydia, mycoplasma, cat scratch disease. Viral: infectious mononucleosis, Hepatitis B and C virus, herpes simplex, cytomegalovirus, HIV (?), Parvovirus B19. Fungal: coccidioidomycosis, blastomycosis, histoplasmosis, aspergillosis, dermatophytosis. Parasitic: toxoplasmosis, amebiasis, giardiasis, hookworm, hidatidosis.
Noninfectious causes
Drugs. Enteropathies: ulcerative colitis, Crohn's disease, diverticulitis, short bowel syndrome. Hormones: pregnancy, thyroid disease. Neoplasms: Hodgkin's disease, lymphomas, leukemias, sarcomas, carcinomas (breast and kidney). Other diseases: sarcoidosis, systemic lupus erythematosus, mixed connective tissue disease, Sjögren's syndrome, Reiter's syndrome, Bechet's disease, giant cell arteritis, Sweet's syndrome, Takayasu arteritis, IgA nephropathy, chronic active hepatitis, Horton's disease (temporal or giant cell arteritis).

Table II. Etiology of erythema nodosum.

Three clinical forms are distinguished:

1. Typical: the acute and multi and bilateral lesions form.
2. Migratory: this is usually a single lesion or multiple but grouped asymmetric, less painful and rarely accompanied by systemic symptoms, has a more chronic course without relapsing but growing eccentrically in the middle.
3. Chronic: it is characterized by the existence of single or multiple persistent nodules recurring for months or years in the legs [6].

In the investigations, should be considered as routine tests complete blood cell count with sedimentation rate, platelets, mean cell volume, simple examination of urine sediment, blood chemistry profile with liver, C-reactive protein, ASO and intradermal tests Mantoux - radiography of the chest and abdomen, throat swab, kidney function test. The rest of the scans will be performed according to suspected etiologies [3,6]. There is no unanimity among authors about whether the diagnosis should be exclusively clinical or if biopsy is necessary in all cases. The prevailing attitude is to base the diagnosis on clinical grounds when the skin lesions are typical and in the rest, take a biopsy. Etiologic diagnosis is based on clinical and analytical data derived from the suspected pathology. Based on the realization of a good history, physical examination and appropriate laboratory tests.

Biopsy is of a septal panniculitis with small foci of inflammatory cells extending into the adjacent lobular fat. In some cases this overflow of cells is marked and includes foam cells, sometimes associated with focal necrosis of fat cells (not a typical feature). The lobe center is unaffected (allows a distinction from lobular panniculitis). There is also a certain degree of inflammatory cells in the adjacent lower dermis.

In most biopsies the infiltrate is predominantly lymphocytic, but there are a variable number of giant cells of foreign body type and a few eosinophils and histiocytes.

Oval small nodules consisting of histiocytes radially around a central grooved crescent (Miescher radial granulomas) are observed. Tuberculoid well formed granulomas are rare.

The summary of findings by time of evolution is:

• Early/Acute: Neutrophils (can be very abundant in the rare variant of erythema nodosum, suppurativa). Septa broadened by edema and fibrinoid changes.

• Intermediate/Established: mononuclear cells predominate. Miescher granulomas.

• Delayed: Increased fibroblast proliferation with obliteration and fibrosis of the septum.

Treatment is essentially symptomatic and includes general and anti-inflammatory actions:
1. General measures: bed rest with elevation of the lower extremities, use of compression bandages with elastic stockings.
2. Anti-inflammatory: non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and potassium iodide:
• NSAIDs. Salicylates are the most commonly used at dose 2-6 g/day, indomethacin, naproxen and ibuprofen.
• Potassium iodide is orally at doses of 0.5-1 g/day in 3 doses for 2-4 weeks produces rapid symptom response.
• Corticosteroids: systemic corticosteroids should be limited to the most serious cases and those that have not responded to other treatments. Prednisone, 30-60 mg/day is used, in descending dose for 2-3 weeks in adults and 0.5 to 2 mg/kg in children. In some recurring or chronic injuries,intralesional corticosteroids have been used.
3. Other treatments: have also been found useful colchicine at doses of 2 mg/day for the first day and then 1mg/day for 2-3 weeks. It quotes the etanercept and infliximab as possible treatments in cases of chronic erythema nodosum [6,7,9]. The main data of this condition are summarized in Table III.

Most common form of panniculitis.
Unknown etiology in most cases.
Painful, symmetrical, erythematous nodules or plaques on the lower limbs.
Septal Panniculitis with paraseptal inflammation.
Neutrophils in the early phase.
Fibrosis in the late phase.
Multinucleated giant cells in septa.
Miescher radial granulomas.
Symptomatic and etiological treatment.

Table III. Summary of findings. Erythema nodosum.

Morphea Scleroderma Panniculitis

Scleroderma is a disease of unknown etiology characterized by excessive deposition of certain components of the connective tissue and structural disorders of the blood vessels. Scleroderma includes two distinct processes: localized scleroderma or morphea and systemic scleroderma [11].
In localized forms, the process may extend into the subcutaneous tissue septum, from the deep dermis and sometimes the process is completely panniculitis, without involvement of the epidermis, dermis and skin appendages. These changes are particularly well developed in deep morphea [3].
Clinically it is characterized by indurated plaques or nodules, steady course or progressive growth, evolving to residual areas of atrophy and hyperpigmentation. The most frequently involved sites are the arms, shoulders and trunk [12]
The most characteristic histopathological finding of deep morphea is the presence of a marked fibrous thickening of the septum of the subcutaneous tissue and thickening of collagen fibers. Collagen replaces the fat normally present around the coils of the eccrine glands and beneath them, giving the impression that amounted eccrine glands within the dermis. The spaces between the collagen bands disappear, with accompanying atrophy, blood vessels and piloerector single muscle fibers remain. When the sclerotic process involves the thickness of the dermis and subcutis, it appears homogeneous eosinophilic. There mucinous changes in the interlobular septa, with particularly striking inflammation at the dermal-subcutaneous interface; lymphocytes surrounded by plasma cells predominate. There may be macrophages and eosinophils and, in some cases, considerable plasma cell numbers [3].
Topical, intralesional or systemic corticosteroids are the most used drugs. You can use alternatives such as penicillamine, topical tacrolimus, nifedipine more urea cream, oral pentoxifylline [3]. Main data of this condition are summarized in Table IV.

Clinical form of localized scleroderma.
Indurated nodules leave residual hyperpigmentation.
Located in arms, shoulders, trunk.
Thickened fibrous septa.
Dermal and fascia thickening.
Collagen arranged parallel.
Treatment with corticosteroids.

Table IV. Summary of findings. Scleroderma panniculitis.

Necrobiosis Lipoidica

Necrobiosis lipoidica (NL) is defined as a process that causes skin collagen degeneration and palisaded granulomas, often associated with systemic diseases, particularly diabetes mellitus [13].

It was first described by Oppenheim in 1929 in a diabetic patient and called „dermatitis atrophicans diabetic lipoidica". In 1932 Urbach also recognized a second case in a diabetic patient and gave him the name „diabetic necrobiosis lipoidica" and suggested that a circulating toxin in these patients was responsible for the skin lesions.

In 1933 Balbi suggests that hyperlipidemia accompanying diabetes would be important in the pathogenesis of this process factor Goldsmith in 1935 reported the first case of necrobiosis lipoidica not associated with diabetes mellitus. Miescher and Leder in 1948 reported a series of non-diabetic patients who had lesions especially scalp, thinking of a new entity named „chronica et progressiva disciformis granulomatosis". Winkelmann and Muller in 1966 established the association between necrobiosis lipoidica with diabetes mellitus in 0.3% of patients and 65% of cases of patients had abnormalities in glucose metabolism. Since then there have been many authors who have described cases in nondiabetic patients so it was decided to call this disease simply necrobiosis lipoidica (NL) [13].

The necrobiosis lipoidica is closely associated with diabetes mellitus, two thirds of these patients suffer and the remaining 1/3 has an impaired glucose tolerance. Despite this, NL is rare and only 0.3 % of diabetics suffer from it.

It affects more women and the female/male ratio is 3:1, the mean age of onset is between 30 and 45, appears at an earlier time when associated with diabetes and in nondiabetic late. Very few studies have been conducted in children. Is frequently observed in type 1 diabetes and in 7-30 % of type 2 diabetics, this gives a prevalence of 6.5% in type 1 diabetics and 0.4 % in type 2 diabetes. The dermatosis can precede, coincide or occur after the diagnosis of diabetes [3]. In one study, preceded the onset of diabetes in 15% of patients , in 25% of patients appeared with the diagnosis of diabetes, and in 60% of patients appeared after diagnosis of diabetes. 66% of patients presenting with NL were diagnosed with diabetes mellitus and the rest showed abnormalities in glucose metabolism [13-15].

The cause of NL remains unknown. It has been reported in patients with various diseases. Many theories have been proposed to try to explain the pathogenic mechanisms of the NL and current theories postulate the following:

a. Microangiopathy. Appears to be the most important in pathogenesis. The vascular damage is preferentially localized in the basement membrane of small vessels, which is due to the combination of multiple factors. We found elevated levels of fibronectin, alpha-2- macroglobulin, ceruloplasmin in LN patients and granuloma annulare and diabetes mellitus and elevated haptoglobin, in patients without diabetes mellitus NL. These protein abnormalities could be responsible for angiopathy.

b. Inheritance. HLA types in 2 groups of diabetic patients with and without NL, in both groups a high frequency of HLA-DR4, B8 and CW3 , and a low incidence of HLA -DR5 and DR7 were studied was observed. In agreement with previous reports of HLA patterns in diabetic patients, it is suggested that genetic factors do not play an important role in NL.

c. Immunological mechanisms. For some authors, the trigger factor for NL can be mediated by immune vasculitis due to evidence of immunoglobulin deposits IgM, IgA and C3 in the walls of the affected vessels, plus IgM, C3 or fibrinogen in the dermo-epidermal junction in some patients. An increase of dendritic cells S -100 positive has been detected in the epidermis [3,17].

d. Alterations of collagen. It is accepted that the granulomatous response may be due to alterations of collagen. It is postulated that hyperglycemia causes increased activity of the aldolase -reducing enzyme, resulting in retention of water in the tissues, and destruction of collagen hyperhydration. Other studies reveal decreased concentration of hydroxyproline in the affected skin, with decreased collagen content and decreased number of fibroblasts. However, this hypothesis does not explain the cases where no hyperglycemia is detected [3,17].

e. Sweat and neural abnormalities. The functioning of sweat glands is altered and the number of nerve endings in biopsies is found to be decreased. However, these changes appear to be the result of the local destruction of these structures by a primary inflammatory process [3,17].

Clinically it is characterized as a chronic disfiguring process. Most lesions are located in the legs, especially in the pretibial region, although lesions on the face, scalp, arms, and trunk may also occur. The lesions are unique but may be multiple.

Initially presents as erythematous papules that increase in size and become plaques with a brownish yellow atrophic center with telangiectasias on the surface. The lesions may resolve spontaneously or become chronic with occasional ulceration. Painful ulcers occur in approximately 15% of cases. The occurrence of squamous cell carcinoma has been reported as a rare complication [13,16,17,19].

Cases with atypical features are outlined, considering both these lesions are located outside of the legs (face, scalp , fingers, penis, nipples, postsurgical scars), as different morphology injuries that may occur as papules, nodules, morphoeic plaques, or ulcerated lesions and piercing injuries. It is clear from the published cases, these atypical forms are more frequently associated with systemic diseases, among which are inflammatory bowel disease (Crohn's disease, ulcerative colitis and intestinal bypass syndrome), sarcoidosis, rheumatic diseases, infectious, hematologic and ataxia-telangiectasia [17].

Histopathology found that the epidermis may be normal, ulcerated or atrophic. There are necrobiotic granulomas in the dermis. The necrobiotic pattern is more common in diabetics and those located in the legs [3].

The granulomatous process in NL extends from the deep dermis to the top of the septum of the subcutaneous tissue, resulting in a septal panniculitis. Necrobiosis in reaction areas of degeneration of collagen is observed. Collagen bundles may be thickened, chipped, or hyalinized amorphous anuclear and extend in different directions. Predominately in the lower third of the dermis and can reach the subcutaneous fat. Necrobiotic areas around lymphocytes, plasma cells, fibroblasts and epithelial cells are observed. In some areas, the inflammatory infiltrate is arranged in palisades surrounding areas of necrobiosis [3].

In the granulomatous reaction, collagen degeneration is moderate. Granulomas composed of histiocytes, epithelioid cells and multinucleated giant cells were observed. Around these granulomas there is no lymphocytic infiltrate. In older lesions, areas of hyalinization of collagen is observed.

Yen Shan et al reported three cases with atypical histopathological features such as prominent tuberculoid granulomas, and the perineural inflammatory infiltrate predominantly lobular panniculitis [20].
Direct immunofluorescence of NL demonstrated in IgM, IgA and fibrinogen in the walls of venous vessels, causing vascular thinning. In nondiabetic vascular changes are not prominent.

Treatment can be divided into 6 categories:

1. Cutaneous blood flow enhancers: In this group the combination of high doses of aspirin with dipyridamole, stanozolol, ticlopidine, perilesional injections of heparin, pentoxifylline and prostagland E1 are cited all with varying results in different studies.

2. Corticosteroids: Topical and intralesional corticosteroids may reduce inflammation in active lesions or lesions on the edges of growth, but has little benefit in stable atrophic lesions, which could worsen atrophy thereof. Intralesional triamcinolone was reported as beneficial in active lesions. In two case reportsthe benefit of clobetasol propionate under occlusion was demonstrated and in two other studies the use of systemic corticosteroids in short pulses was suggested to be beneficial.

3. Surgery: NL tends to exhibit the phenomenon of Koebner so curative surgery can not be guaranteed.

4. Cutaneous healing enhancers: Various reports of efficacy of various topical preparations that act to promote cutaneous healing for ulcerated NL. One case report has described the efficacy of recombinant granulocyte macrophage colony stimulating factor topically to ulcerated NL in young patients with diabetes. Physical modifications of wound background is also beneficial in promoting wound repair. Promogran, a new protease modulating matrix, has been reported to be effective in wound healing. This preparation inactives metalloprotease and other enzymes found in large quantities to have a negative effect on wound healing. The bovine collagen gel applied in a non-diabetic patient under occlusion for 6 weeks, resulted in healing at 24 weeks with no recurrence after 5 months. In two diabetic women with ulcerated NL HBO achieved healing of the lesion after 98 and 113 sessions, this could be related to the correction of tissue hypoxia.

5. Immunomodulators: Within immunomodulatory efficacy in several studies of cyclosporine, mycophenolate mofetil, thalidomide, infliximab and tacrolimus are cited.

6. Miscellaneous: This group includes nicotinamide, clofazimine, chloroquine and topical tretinoin. A study of nicotinamide showed improvement in the lesions of NL in 8 of 15 patients. Clofazomine that has both anti-inflammatory and antimicrobial activity presented an effectiveness of 60%. In two studies with topic tretinoin has reported an improvement of the atrophic component NL. Application NL benzoyl peroxide has been reported to ulcerated beneficial [15,18]. The main findings of this condition are shown in Table V.

Rare process.
More frequently in women.
Associated with Diabetes mellitus and impaired glucose tolerance.
Unknown etiology.
Erythematous plaques with atrophic center on shins.
Thickened fibrous septa.
Necrobiotic dermal granulomas.
Poor therapeutic response.

Table V. Summary of findings. Necrobiosis lipoidica.

Septal panniculitis with vasculitis
Polyarteritis Nodosa

The term polyarteritis nodosa (PAN) includes systemic PAN, cutaneous PAN and microscopic PAN (microscopic polyangiitis) [23].
The limited variety of benign cutaneous polyarteritis nodosa was individualized by Lindberg in 1931 [23]
Both cutaneous and systemic PAN polyarteritis histologically characterized by necrotizing vasculitis of medium-sized arteries, but cutaneous PAN may be clinically differentiated from systemic polyarteritis because they involve organs. Systemic polyarteritis, by contrast, can affect any organ, especially the kidneys , heart and liver , and skin , in 50% of cases. The largest series of cutaneous PAN not demonstrate development of systemic disease in a mean follow up of 7 years [21].
The etiology is so far unknown , although the demonstration of deposits of immune IgM and C3 in lesions of some vessels as well as the detection of circulating immune complexes in others, suggesting immune complex mediation . In some cases there is a high titer of antistreptolysin O (ASO).
Classic polyarteritis nodosa is a systemic necrotizing vasculitis of small and medium caliber arteries with poor prognosis and involvement of various organs, such as kidneys, liver, gastrointestinal tract and nervous system, skin manifestations may occur in 25% to 60% of cases [21].
On the other hand, cutaneous polyarteritis nodosa designates the exclusive skin involvement (deep dermis and panniculus), with a benignchronic course.
Skin lesions were distributed especially in the legs, but can occur in the upper limbs, face, scalp and mucous membranes [22].
Are erythematous and painful nodular lesions, the size will vary between 0.5 and 3 cm, the number can vary, but reports from a few to over 100.
It is commonly found in some patients, lesions and other recent developments, injuries later stages. Nodular lesions may evolve from a few weeks to over a year, with treatment evolve into violet color and may leave some hyperpigmented areas and in some cases leave scars. Nodules usually occur symmetrically, but in some cases the lesions may also be asymmetric. During exacerbations, some nodules can be reactivated in remission. Nodules usually occur singly or in groups [21,22].

According to the classification of Chenen 1989 and Daoud et al three types of skin lesions in PANC described in 1997: a mild form or class I characterized by nodular lesions and livedo reticularis, and between extracutaneous manifestations reported mild polyneuropathy.
Class II is characterized by addition of nodular lesions which may ulcerate and are quite painful, in this group of patients is also described polyneuropathy, fever, malaise and joint pain in the acute phase.
Class III has the characteristics of a PANC but skin lesions are characterized by livedo racemosa and necrotizing gangrene and also have a commitment to progressive musculoskeletal, mononeuritis multiplex, foot drop and some laboratory data autoimmune character. This class III is characteristic of a systemic PAN and is not observed in the cutaneous PAN [21].
The laboratory abnormalities are not too frequent in cutaneous PAN. These deserve mention: elevated ESR, elevated streptococcal enzymes, leukocytosis, I antinucleolar antibody positive, positive cytoplasmic antibodies (ANCA) and elevated C-reactive protein [23].
The most effective treatment of cutaneous PAN is steroids, which are generally used to moderate doses (30-60 mg prednisone daily).
Other drugs used were colchicine (0.5 to 1 mg orally daily) , azathioprine (50 mg daily , oral) , methotrexate (10 mg weekly , orally, fractional) , dapsone (50 mg daily , po) , cyclophosphamide (1 mg/kg/day orally). In cases involving streptococcal infections, penicillin and mycobacterial infection indicates clarithromycin (250 mg twice daily, oral), ciprofloxacin at the same doses. 23 These findings are summarized in Table VI.

Localized form of polyarteritis nodosa.
Exclusive skin involvement.
Unknown etiology.
Painful erythematous nodules on the lower limbs.
Necrotizing vasculitis of small vessels in the dermis and subcutaneous.
Treatment with systemic corticosteroids.

Table VI. Summary of findings. Cutaneous polyarteritis nodosa.

Surface Migratory Thrombophlebitis

It is characterized by recurrent episodes of segmental thrombosis affecting the superficial veins of the lower extremities, trunk or abdomen.
It is characterized by the appearance of painful nodules distributed linearly along the limb and the evolution result in a palpable induration cord. Apart from the superficial veins of the lower limbs may be affected the lateral epigastric, thoracoepigastric or thoracic veins leading to visible or palpable cords in the chest wall. This variety is known as Mondor disease and has also been described in the axilla, groin and penis [24].
This form of septal panniculitis occurs in most patients without evidence of underlying disease. It is usually a complication of varicose veins. It can develop as a result of a primary or secondary hypercoagulable state. Primary hypercoagulable states, such as deficiencies of antithrombin III, heparin cofactor II, protein C, protein S and factor XII. Fibrinolytic system disorders, dysfibrinogenemia and lupus anticoagulant are conditions that may be complicated by the development of this panniculitis. Also, it may be associated with underlying processes, such as venous varices, Behçet's syndrome, Burger's disease, drug abuse, infections, pregnancy or malignancies. When the hypercoagulable state secondary to an underlying malignancy (Trousseau syndrome), the most common places where the primary malignancy sits are the pancreas, stomach, lung, prostate, colon, ovary and gallbladder [3].
Histology notes that recent injuries have an inflammatory infiltrate of polymorphonuclear predominance that affects the entire thickness of the wall of the vein and as the injury evolves polymorphonuclear are replaced by lymphocytes, histiocytes and occasional multinucleated giant cell. During evolution, the thrombus which occludes the lumen initially is replaced by recanalization and fibrosis. Thrombosis of these veins does not alter substantially the lobule oxygenation mode, so you do not find a significant accompanying panniculitis [24].
Treatment can be disappointing, with frequent recurrences. Measures such as relative rest and elastic compression stockings can improve the symptoms. In the case of Mondor ,s disease lesions usually resolve in a few days, with a low recurrence rate. Most clinicians reserve the use of anticoagulants for patients with involvement of the deep venous system. In cases of treatment associated neoplasia addition thereof adjuvantly used anticoagulants, especially heparin [24]. A summary of findings are shown in Table VII.

Surface segmental thrombosis of veins.
Recurrent episodes.
Lower limbs, trunk, abdomen.
Polymorphonuclear infiltrate in early stage.
Recanalization and fibrosis in late stage.
Disappointing treatment.

Table VII. Summary of findings. Surface migratory thrombophlebitis.

Study protocol of septal panniculitis

· Clinical history, especially investigating the possible triggers and the existence of previous similar processes.
· Physical Examination.
· Analytical routine (complete blood count, biochemistry, coagulation).
· Excisional biopsy for histology and direct immunofluorescence.
· Based on histological changes see Figure 1.

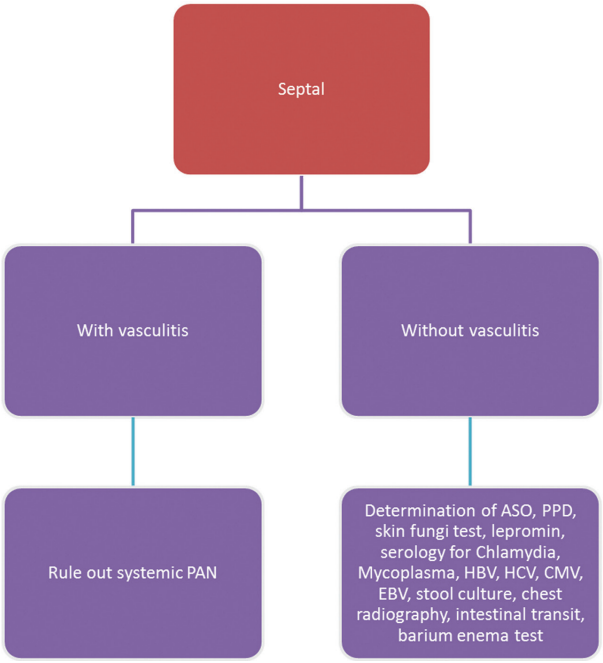

Figure 1. Study protocol of septal panniculitis based on histological findings.

Presentation of a case of septal panniculitis

Female, 67 years, diabetes treated with oral agents, chronic NSAIDs for osteoarthritis. Admitted to the emergency department with upper gastrointestinal bleeding gastric ulcers, drawing attention to physical examination leg ulcers 3 years of evolution. Several treatments used without improvement diagnosed as varicose ulcer.

Physical exam: ulcers, regular margins, net limits, fibrinous center, in lower 1/3 of the lower limbs (Fig. 2a, b). Livedo reticularis in upper and lower limbs.

Histopathology: widening of subcutis septa by presence of abundant numbers of inflammatory cells, including macrophages, foamy predominate. Some neutrophils. Absence of vasculitis. Extension of the infiltrated to the dermis. Ziehl Neelsen for AFB + (fragmented bacilli) (Fig. 3a - c).

Auxiliary Studies: Analytical laboratory data normal except Hb 10.4 g/l. Positive cutaneous lymph for AFB.

Diagnosis: Reactional erythema nodosum.

Evolution: The patient died due to upper gastrointestinal bleeding.

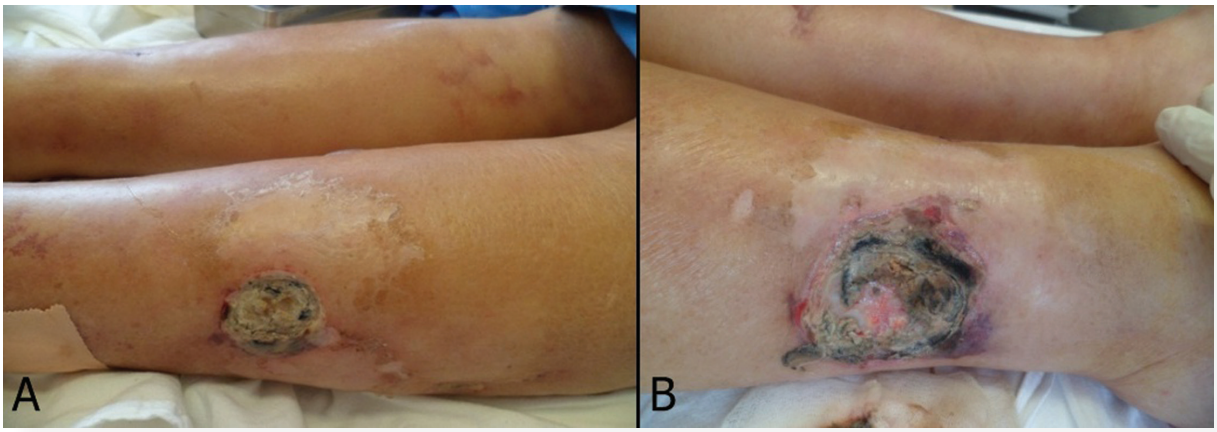

Figure 2A, B. Clinic. Ulcer with necrosis, fair edges, net limits, located in the anterior aspect of Both legs.

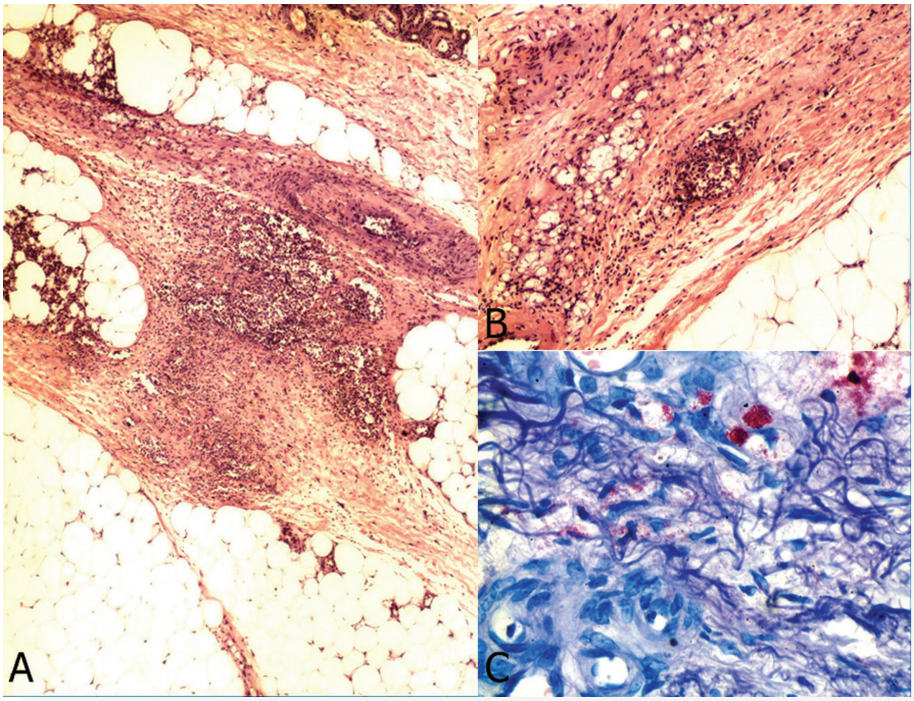

Figure 3A - C. Histopathology. Subcutis septa widening by presence of copious numbers of inflammatory cells, including foamy macrophages. Some neutrophils. Absence of vasculitis. Extension of the infiltrated to the lower dermis. Ziehl Neelsen for AFB + (fragmented bacilli).

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DOI: 10.7241/ourd.20141.21

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HEMATOMA OF THE PROXIMAL NAIL FOLD DUE TO OXIMETER IN A CHILD

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 83-84 Date of submission: 23.08.2013 / acceptance: 14.10.2013

Cite this article:
Patricia Chang, Monica Vanesa Vásquez Acajabón: Hematoma of the proximal nail fold due to oximeter in a child. Our Dermatol Online. 2014; 5(1): 83-84.

Boy 4 years old, hospitalized due to hemorrhagic chickenpox and sepsis during his clinical examination besides hemorrhagic crust, vesicles and bullous he has also a cutaneous red lesion localized at the right proximal nail fold of the big toenail (Fig. 1), dermatoscopic view of the lesion (Fig. 2).

The diagnosis of hematoma of the proximal nail fold due to oximeter was done.

The proximal nail fold hematomas due to oximeter are uncommon dermatoses at this level that are caused for the pressure of the oximeter and it has been seeing in patient in Unit Intensive or Intermediate Unit Care since 2007.

Hematomas are blood collections located at any part of the body. The hematoma of the nail or periungual tissues can be caused by trauma or systemic diseases [1,2]. Usually the proximal nail folds of fingers, are exposed to receive minor and mayor traumas, and it is important to distinguish clinically from other diseases [1,3].

These kinds of hematomas go unnoticed, and are resulted by constant friction caused by the use of oximeter. The proximal nail fold hematoma affects the free edge letting off the cuticle; its appearance has been seen after 1 to 3 days of using the oximeter. One or more folds can be affected according to where the oximeter is placed proximal nail [1,4].

However, it is important to know other hematomas at this level, as those are produced by the oximeter use; their presence in several digits and no history of oximeter use; make us suspect other diseases that can be presented such as repeated collagen diseases or sepsis [5].

Chang and Haneke reported the first 3 cases of proximal nail fold hematoma on 2008, later reported 41 cases of the proximal nail fold hematoma in adult patients from the intermediate and intensive care unit at the Hospital General de Enfermedades on 2011 [4]. Also this pathology has been described in children, 5 cases were reported in children between the ages of 5 months to 4 years old on 2013 [6].

There is no treatment for this affection; prevention of injury is to rotate the oximeter every two or three hours to prevent the formation of hematoma [6].

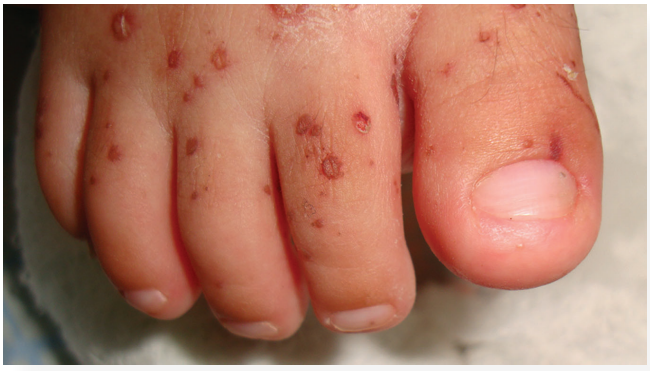

Figure 1. Hematoma of the proximal nail fold on the right big toenail.

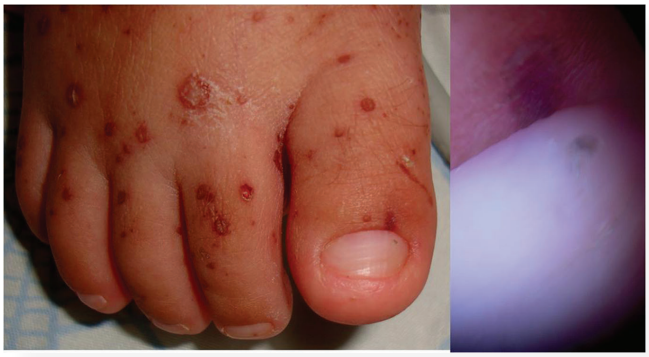

Figure 2. Dermatoscopic view of proximal nail fold due to oximeter.

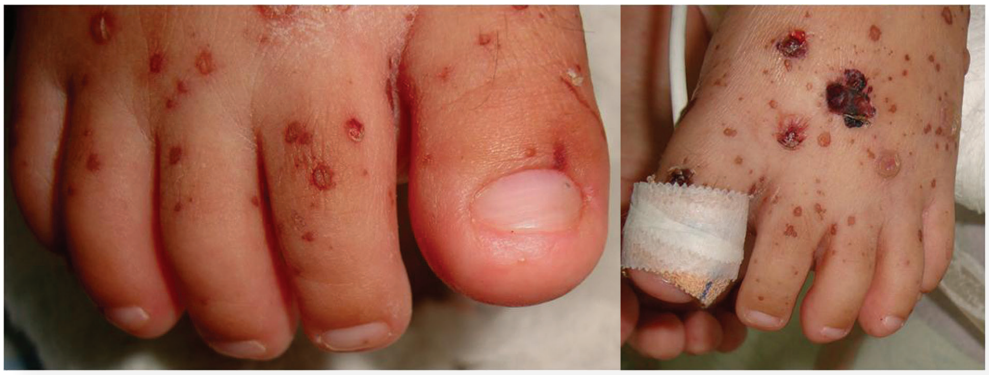

Figure 3. View of the oximeter in children.

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DOI: 10.7241/ourd.20141.22

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ONYCHOMADESIS SECONDARY ERYTHRODERMA EXFOLIATIVE DUE TO CIPROFLOXACIN

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2013; 5(1): 85-87 Date of submission: 09.09.2013 / acceptance: 14.10.2013

Cite this article:
Patricia Chang, Monica Vanesa Vásquez Acajabón: Onychomadesis Secondary Erythroderma Exfoliative due to Ciprofloxacin. Our Dermatol Online. 2013; 5(1): 85-87.

Female patient 63 years old who was hospitalized due to erythroderma exfoliative (Fig. 1) after taking ciprofloxacin by urinary tract infection, 4 weeks later we began to observe the detachment of the finger and toenails from the proximal nail fold predominantly on the thumbs (Fig. 2), and the diagnosis of onychomadesis was done.

Nail diseases are common but no all people and doctors know about nail changes due to drug reaction or systemic diseases.

The present case shows the normal evolution of the nails after an injury due to drug reaction like erythroderma exfoliative.

The study of nail abnormalities is an important research area on actuality, due to they constitute around 5% to 10% of all dermatological diseases [1]. The onychomadesis is an ungual disease which consists in a separation of the nail plate from the matrix [1,2]. It can occur on fingernails or toenails [3]. At first, a cleavage appears under the proximal portion of the nail, followed by the disappearance of the juxtamatricial portion of the nail surface. In latent onychomadesis, the nail plate shows a transverse split (Beau lines) due to the transient complete inhibition of the nail growth, for at least 1-2 weeks [3,4]. Professionals describe onychomadesis like a severe form of Beu lines, and it may result in shedding of the nail [5].

This disease can be hereditary, acquired or traumatic (Fig. 3 a - c) [1,6]. It usually results from serious generalized diseases (Fig. 4), bullous dermatoses (Fig.5), hand, foot and mouth disease, drug reactions (Fig. 6 a, b), severe psychological stress, or it may be idiopathic (Fig. 7 a, b) [4]. Onychomadesis also has been related with pyogenic granuloma and may be consequence of mid nerve injury, It was observed after cast immobilization [2]. Recently, onychomadesis has been associated with the use of valproic acid, azithromycin [4], penicillin, retinoids [7], and carbamazepin [4,7]. Some chemotherapy or X-ray treatments for cancer may also cause this condition [3,4,7].

It is necessary to always take good care to avoid injury or breaking the nail plate and the cuticle. Therapy is intended to treat the underlying disease, this will allow normal nail plate regeneration with eventual growing of the affected areas [3,6]. It is contraindicated apply polish over the defect in the plate, as this will seal in any infective organisms that may be present, thus enhancing the possibility of further infection and injury to the matrix [3].

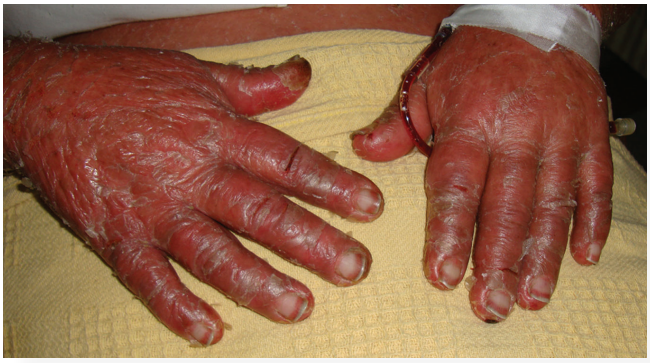

Figure 1. Fingernails at the beginning of the drug reaction.

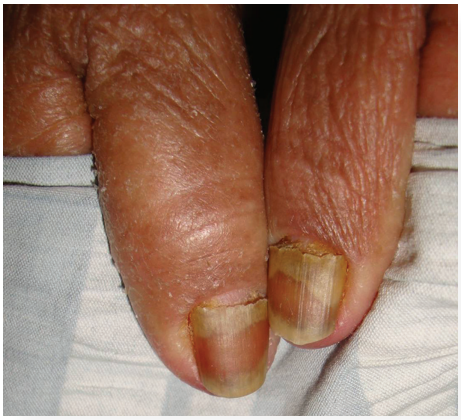

Figure 2. Onychomadesis four weeks after erythroderma.

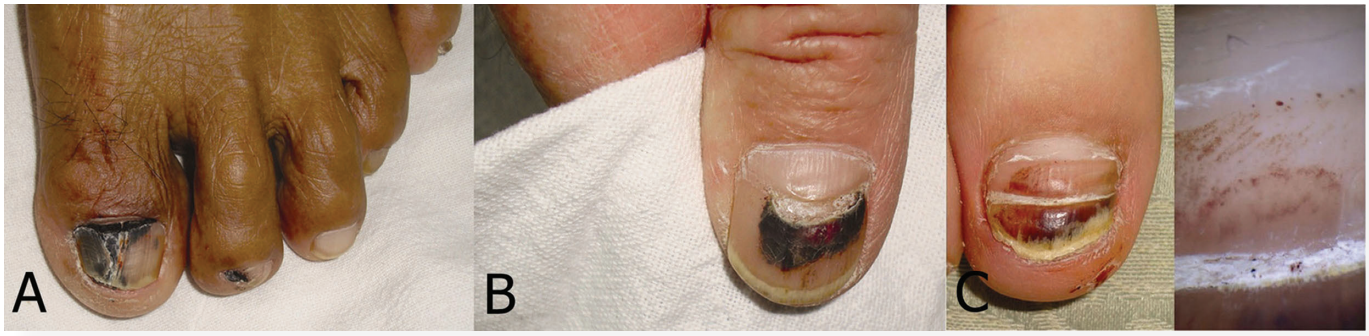

Figure 3 a,b,c. Onychomadesis due to major trauma.

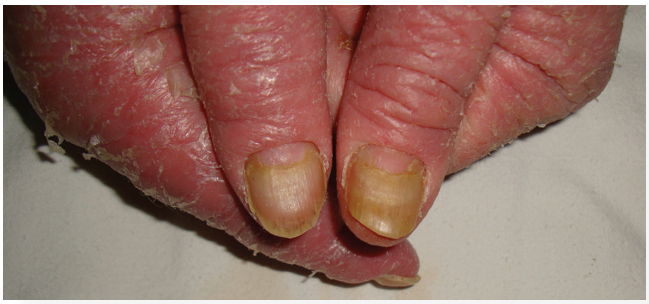

Figure 4. Onychomadesis due to psoriasic erythroderma.

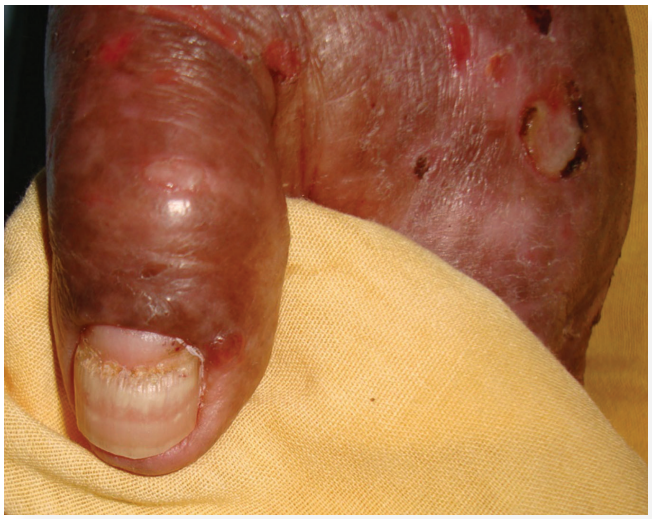

Figure 5. Bullous phemphigoid cause of onychomadesis.

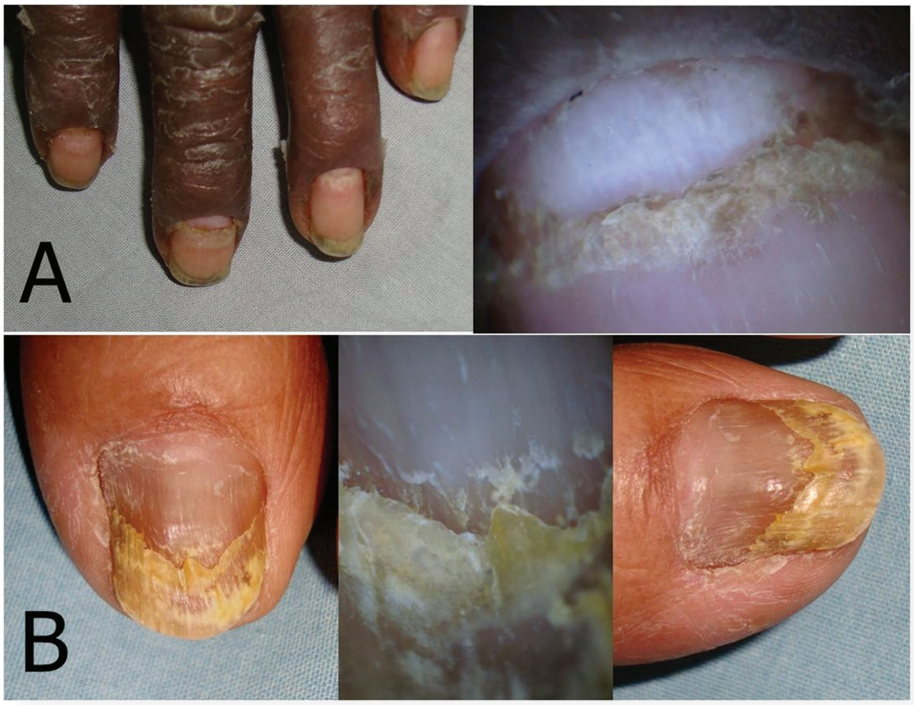

Figure 6 a,b. Onychomadesis due to drug reaction carbamazepin and cytostatics drug.

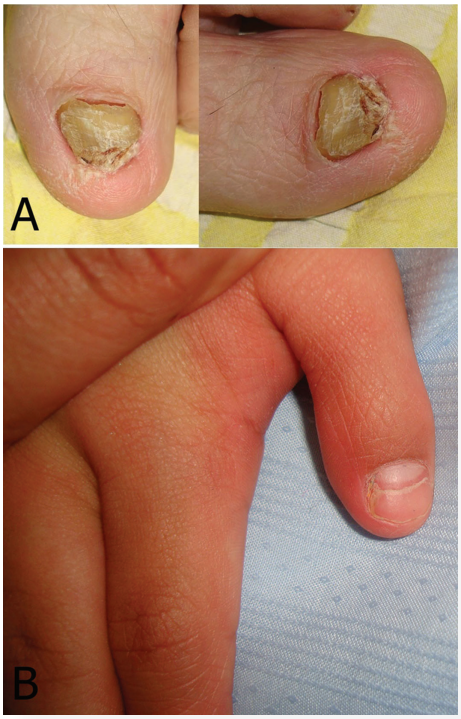

Figure 7. Idiopathic causes of onychomadesis.

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DOI: 10.7241/ourd.20141.23

NASZA DERMATOLOGIA Online
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DISTAL NAIL EMBBEDING

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2013; 5(1): 88-89 Date of submission: 28.09.2013 / acceptance: 30.10.2013

Cite this article:
Patricia Chang, Monica Vanesa Vásquez Acajabón: Distal nail embbeding. Our Dermatol Online. 2013; 5(1):88-89.

Male patient, 35 years old who came to dermatological consultation due to contact dermatitis on back, during his clinical examination alterations of his digits was seen.
Dermatological examination reveals a rim of tissue at the distal edge of the nail of both big toenails and thickened nails (Fig.1a - c, 2a, b). Both big toenails were removed due to ingrown nails two times.
Diagnosis of distal nail embedding was done.
Distal nail embedding is a rim of tissue at the distal edge of the nail. Causes can de acquired or congenital. Although the main cause of distal embedding is total nail avulsion, there are more causes, such as: pincer nails, bad alignment of nail [1], or detachment of the nail caused by a subungual hematoma [1,2].
The hyponychium is the tissue located beneath the free edge of the nail [1]. In the distal nail embedding, the nail plate is blocked by the hyponychium, which cause a distal ring that obstructs the normal nail to grow [3]. Loss of counter-pressure induced by the disappearance of the nail plate allows dorsal expansion of the distal pulp. It promotes distal embedding [2,4] with a subsequent hyperkeratotic reaction facing the impaction of the nail, producing pain and inflammation [1,4].
The distal nail embedding may occur during Infancy. In this case the nail presents a distal edge of tissue and hypertrophy of its lateral edge. This prominent edge of tissue forms an anterior wall that allows the embedding and avoids the normal growing of the free margin of the nail. This congenital deformity may worsen by factors like sleeping in prone. If the nail is aligned normally, the good growth of the nail may reestablish at the age of 6 months [5]. Distal nail embedding may be associated to different causes such as onychomycosis (Fig. 3a - f), bad cut polish (Fig. 4a - c), onychodystrophy (Fig. 5a - e) use steel tip shoe (Fig. 6).
If the patient is asymptomatic or complains of minor discomfort, conservative treatment is indicated: reducing the hyperkeratotic process in front of the distal nail, using 50% urea ointment and debridement with scalpel. Massaging back in a distal-plantar direction is recommended. If there is severe pain, then surgery is mandatory to free the distal edge of the nail plate using the Dubois' procedure resection of a part of the distal wall, from and to each proximal end of the lateral nail fold [2,4].
When possible, partial nail avulsion should always be preferred. If the nail is avulsed for matrix or nail bed surgery, the nail plate should be put back in place and sutured to the lateral nail fold. If the nail is shed afterwards, the patient should be instructed to keep it in place using adhesive tape as long as possible [4].

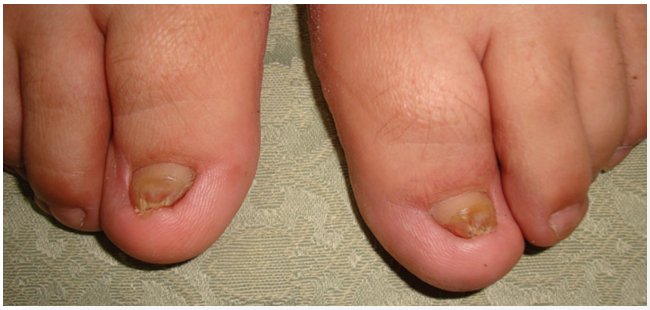

Figure 1a. Panoramic view of distal nail embedding of both toenail.

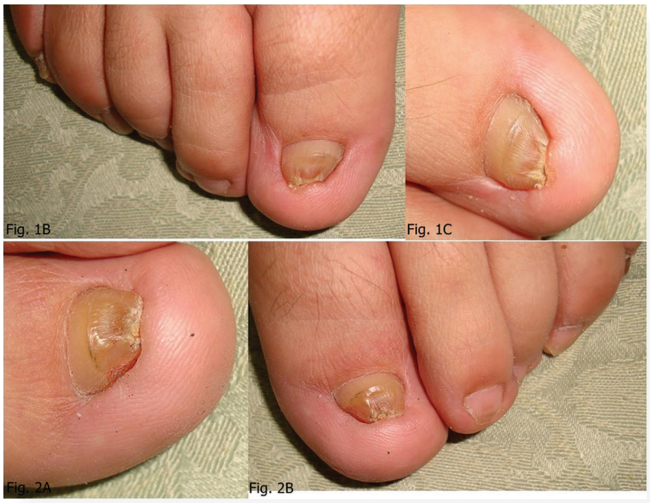

Figure 1 Panoramic view of distal nail embedding of both toenail. Right and left distal nail embedding.

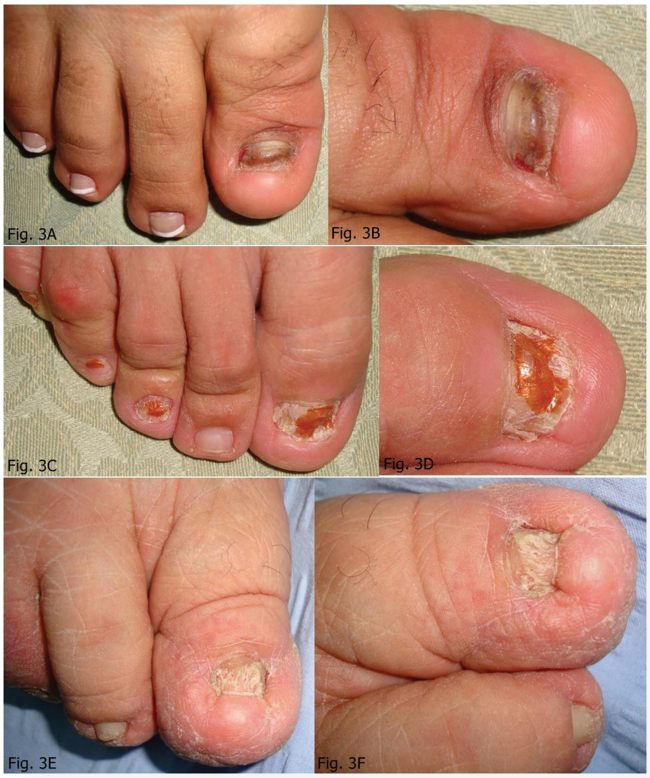

Figure 3 a-f. Distal nail embedding short nail due to onychomycosis.

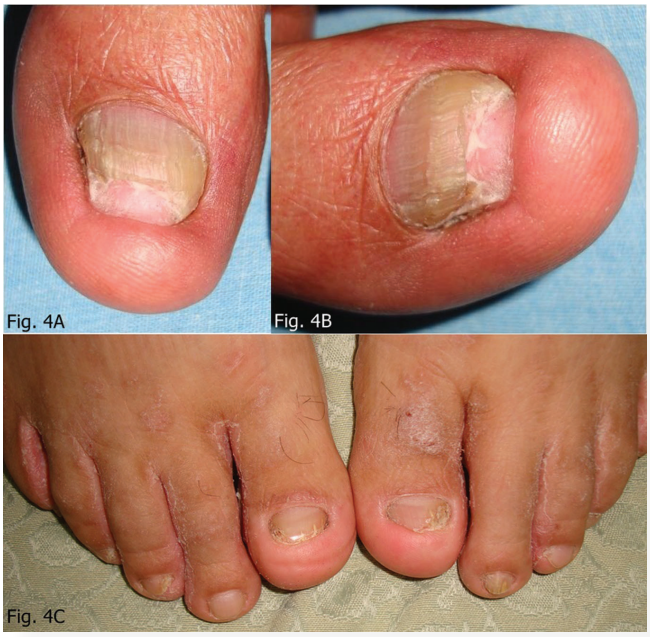

Figure 4 a-c. Distal nail embedding due to bad cut polish.

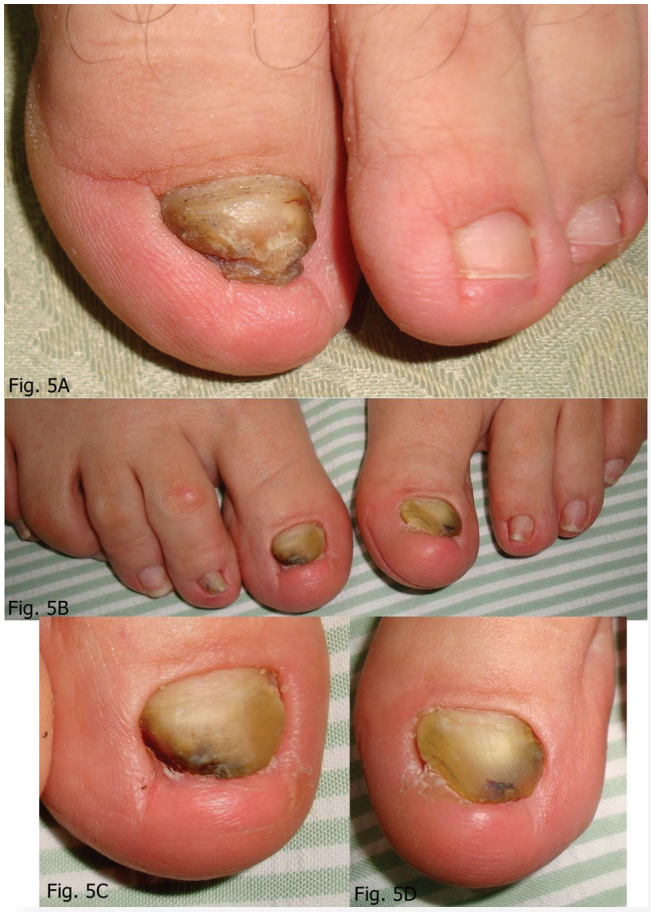

Figure 5 a-d. Distal nail embedding due to onychodystrophy.

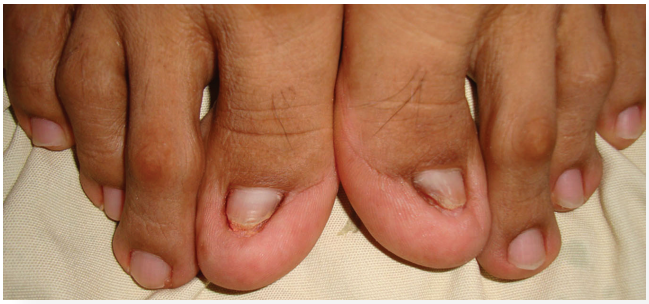

Figure 6. Distal nail embedding due to steel tip shoe.

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DOI: 10.7241/ourd.20141.24

NASZA DERMATOLOGIA Online
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A CASE-CONTROL STUDY OF EPIDEMIOLOGICAL IMPORTANCE RISK OF FAMILY HISTORY OF PSORIASIS

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Source of Support: Nil
Competing Interests: None

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Our Dermatol Online. 2014; 5(1): 90-91 Date of submission: 14.09.2013 / acceptance: 28.10.2013

Cite this article:
Anca Chiriac, Caius Solovan, Anca E Chiriac, Liliana Foia, Piotr Brzezinski. A case-control study of epidemiological importance risk of family history of psoriasis. Our Dermatol Online. 2014; 5(1):90-91.

Sir

We have conducted a case-control study to analyze the epidemiological importance risk of family history of psoriasis. The retrospective study was done on 1236 patients diagnosed with psoriasis on clinical and histopathological grounds, between 2004-2011, in an Out-patient Clinic in North-Eastern part of Romania.The sex ratio of psoriasis was 1.18:1 (male patients 54.13%, female patients 45.87%), median age at the diagnosis was 29.34±15.24SD; family history of psoriasis (by declaration) was 29.53% (Tabl. I).

Family history	Nr. cases	%
Absent	871	70.47%
Present	365	29.53%
First degree	200	16.18%
Children	16	1.29%
Parents	184	14.89%
Second degree	115	9.30%
Grand parents	36	2.91%
Grand children	9	0.73%
Brothers/sisters	70	5.66%
Third degree	36	2.91%
Grand-grand parents	3	0.24%
Uncle/aunt	33	2.67%
Fourth degree	14	1.13%
Cousins	14	1.13%
Total	1236	

Table I. Results of the study.

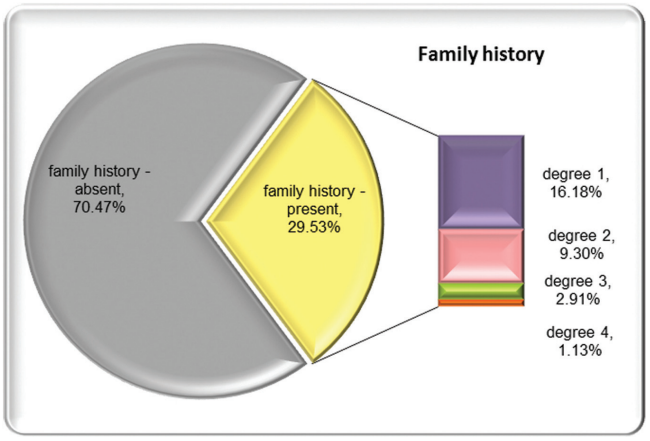

Figure 1. Graphic of the distribution of family history among patients with psoriasis.

The problem of family history of psoriasis is a subject of debate, with great variability of results (Tabl. II), ranging from 7% to 60-70% depending on variable factors.

Our study demonstrated an association of family history of 29.53%: 16.18% -first degree relatives; 9.30% second degree relatives; 2.91% third degree and 1.13% fourth degree relatives.

Study	Family history of psoriasis
Naldi et al[1] 1991	18.8% in parents and 3.25 in siblings
Naldi et al [2] 2001	7% in guttate psoriasis
Bahcetepe et al [3] 2013	56%
Na SJ et al [4] 2013	26%
Brunasso et al [5] 2013	28% in palmo-plantar plaque psoriasis
Clabaut et al [6] 2010	36-64%
Mahé E et al [7] 2004	25% in children with one parent diagnosed with psoriasis and 60-70% if both parents have psoriasis

Table II. Results of the study.

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DOI: 10.7241/ourd.20141.25

NASZA DERMATOLOGIA Online
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THE MEN BEHIND THE EPONYMOUS PHARMACEUTICALS COMPANIES

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 92-93 Date of submission: 29.07.2013 / acceptance:16.09.2013

Cite this article:
Khalid Al Aboud, Daifullah Al Aboud: The men behind the eponymous pharmaceuticals companies. Our Dermatol Online. 2014; 5(1): 90-92.

There are different sources of names in medical field. Similarly, the names given to pharmaceuticals companies are derived from different things.

Selecting a good name is not always easy. In fact, there are now professional companies to help finding proper names for medical organizations and medications [1].

These were of help in naming pharmaceutical companies. For instance; "Zeneca" was an invented name created by the branding consultancy Interbrand. Interbrand had been instructed to find a name which began with a letter from either the top or bottom of the alphabet and was phonetically memorable, of no more than three syllables and did not have an offensive meaning in any language.

However, using the names of the founders (eponyms) is a common type of naming pharmaceuticals companies. In Table I [2-12], we highlighted on selected eponymous pharmaceuticals companies.

We want to stress on the fact that, the men behind pharmaceuticals companies deserve a special attention. Their success stories are educational and a source of inspiration for all the generations. Their histories are worth to be incorporated to medical curriculum.

Patience, perseverance, donations, helping their communities and world as well as many other good things is to be learnt from their stories.

For example; Abbott, in his starts while working in his kitchen, measured his drugs into small pills he called „dosimetric granules", providing a more accurate dosage and a more effective, long-lasting drug than other medicines available at the time [2].

Dr. Upjohn, on the other hand, began experimenting with making better pills in the attic of his home. Eventually he invented his „friable" pill. Friable meant that the pill could easily be crushed to a powder [12].

The most recently lost one of these giants, is Pierre Fabre. He established, Pierre Fabre Foundation which was recognized as a public utility in 1999 and its mission is to help third-world countries to obtain quality drug, ensure better quality control of drugs, use local therapeutic resources and train scientists for the inspection of drugs [11].

Eponymous pharmaceutical companies	Remarks
Abbott Laboratories [2]	It is an American global pharmaceuticals and health care products company. The company headquarters are in Abbott Park, North Chicago, Illinois. The company was founded by Chicago physician Wallace Calvin Abbott (1857–1921), (Fig. 1), in 1888. In 2010, Abbott had over $35 billion in revenue.
Bayer [3,4]	Bayer AG is a German chemical and pharmaceutical company founded in, Germany in 1863. It is headquartered in Leverkusen, North Rhine-Westphalia, and Germany and well known for its original brand of aspirin. The company will be 150 years old on 1 August 2013. In 2011, It had over €36.53 billion in revenue. It was founded by Friedrich Bayer (1825-1880), (Fig. 2). He founded the dyestuff factory Friedrich Bayer along with Johann Friedrich Weskott in 1863 in Elberfeld.

Table I. Selected eponymous pharmaceutical companies.

Figure 1. Wallace C. Abbott (1857-1921).

Figure 2. Friedrich Bayer (1825-1880).

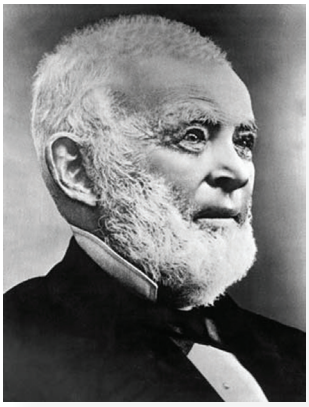

Figure 3. Edward Robinson Squibb (1819-1900).

Eponymous pharmaceutical companies	Remarks
Bristol-Myers Squibb [5,6]	It is, often referred to as BMS, is a pharmaceutical company, headquartered in New York City. The company was formed in 1989, following the merger of its predecessors Bristol-Myers and the Squibb Corporation. In 2009, It had over US$18.8 Billion in revenue. Squibb was founded in 1858 by Edward Robinson Squibb (1819-1900), (Fig. 3), while Bristol--Myers was founded in 1887 by William McLaren Bristol (1860-1935), (Fig. 4), and John Ripley Myers (1864–1899), (Fig. 5).
Eli Lilly and Company [7]	It is an American global pharmaceutical company with headquarters located in Indianapolis, Indiana, in the United States. Their products are sold in approximately 125 countries. In 2011, it had over US$ 24.286 billion in revenue. The company was founded in 1876 by Col. Eli Lilly (1838-1898), (Fig. 6), who was an American soldier, pharmaceutical chemist, and industrialist.
Johnson & Johnson [8,9]	It is a U.S multinational medical devices, pharmaceutical and consumer packaged goods manufacturer founded in 1886. It is headquartered in New Brunswick, New Jersey. Johnson & Johnson had worldwide sales of $65 billion for the calendar year of 2011. It is founded by three American American businessmen; Robert Wood Johnson I (1845-1910), (Fig. 7), James Wood Johnson (1856-1932) and Edward Mead Johnson (1852-1934).
Pfizer [10]	It is an American multinational pharmaceutical corporation headquartered in New York City. Pfizer was founded in New York City in 1849. It is named after the German-American cousins Charles Pfizer (1824-1906), (Fig. 8), and Charles Erhart. Its revenue was estimated to be US$ 58.98 billion (2012).

Table I. Selected eponymous pharmaceutical companies (continued).

Figure 4. William McLaren Bristol (1860-1935).

Figure 5. John Ripley Myers (1864-1899).

Figure 6. Eli Lilly (1838-898).

Figure 7. Robert Wood Johnson I (1845-1910).

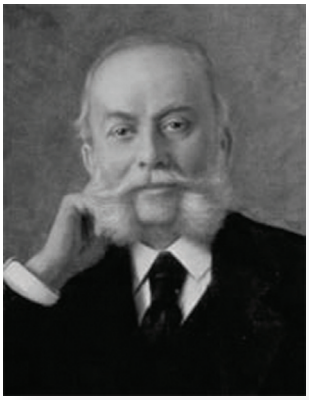

Figure 8. Charles Pfizer (1824-1906).

Figure 9. Pierre Fabre (1926-2013).

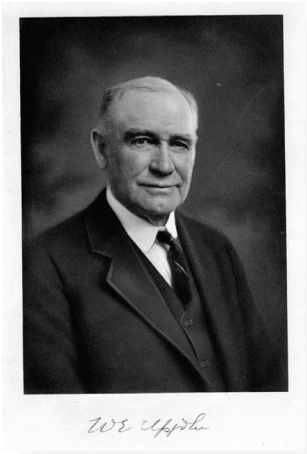

Figure 10. William Erastus Upjohn (1853-1932). A courtesy of Kalamazoo Public Library.

Eponymous pharmaceutical companies	Remarks
Pierre FABRE laboratories [11]	It is a multinational pharmaceutical and cosmetics company based in Castres, France, near Toulouse. The company had a consolidated turnover of 1.978 billion euros in 2012. Founded in 1962 by Pierre Fabre, it is present in over 130 countries and has more than 10,000 employees (in 2012). Pierre Fabre (1926-2013), (Fig. 9), was a French chemist.
Upjohn [12]	The Upjohn Company was a pharmaceutical manufacturing firm founded in 1886 in Kalamazoo, Michigan by Dr. William E. Upjohn. The company was originally formed to make friable pills, which were specifically designed to be easily digested. These could be „reduced to a powder under the thumb", a strong marketing argument for the time. In 1995, Upjohn merged with Pharmacia AB, to form Pharmacia & Upjohn. Later the company merged with Monsanto Company and took the name Pharmacia. William Erastus Upjohn (1853-1932), (Fig. 10), was an American medical doctor, a graduate of the University of Michigan medical school. He was the founder and president of The Upjohn Pharmaceutical Company. He was named Person of the Century by the Kalamazoo, Michigan newspaper.

Table I. Selected eponymous pharmaceutical companies (continued).

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DOI: 10.7241/ourd.20141.26

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DERMATOLOGY EPONYMS – SIGN – LEXICON – (K)

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Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(1): 95-102 Date of submission: 15.09.2013 / acceptance: 20.12.2013

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

Key words: eponyms; skin diseases; sign; phenomenon

Cite this article:
Piotr Brzezinski, David F Fiorentino, Pavai Arunachalam, Ioannis Katafigiotis, Łukasz Matuszewski, Masashi Narita, Yuko Ono, Rahul Shetty, Anca Chiriac, Ahmad Abdilaziz. Dermatology Eponyms – Sign – Lexicon – (K). Our Dermatol Online. 2014; 5(1): 95-102.

KAPOSI'S SIGN

Syn. Xeroderma pigmentosum (Fig. 1) [1].

MORITZ KAPOSI KOHN

Austrian dermatologist (1837-1902) (Fig. 2). Kaposi was an important Hungarian dermatologist, discoverer of the skin tumor that received his name (Kaposi's sarcoma). Born to a Jewish family, originally his surname was Kohn, but with his conversion to the Fig. 22 Moritz Kaposi Catholic faith he changed it to Kaposi. In 1855 Kaposi began to study medicine at the University of Vienna and attained a doctorate in 1859. In his dissertation, titled Dermatologie und Syphilis (1866) he made an important contribution to the field. Kaposi was appointed as professor at the University of Vienna in 1875, and in 1881 he became member of the board of the Vienna General Hospital and director of its clinic of skin diseases. He was authored the book Lehrbuch der Hautkrankheiten (Textbook of Skin Diseases) in 1878. Kaposi's main work, however, was Pathologie und Therapie der Hautkrankheiten in Vorlesungen für praktische Ärzte und Studierende (Pathology and Therapy of the Skin Diseases in Lectures for Practical Physicians and Students), published in 1880, which became one of the most significant books in the history of dermatology.

He is credited with the description of xeroderma . pigmentosum („Ueber Xeroderma pigmentosum. Medizinische. Jahrbücher, Wien, 1882: 619-633"). In all, he published over 150 books and papers [2-5].

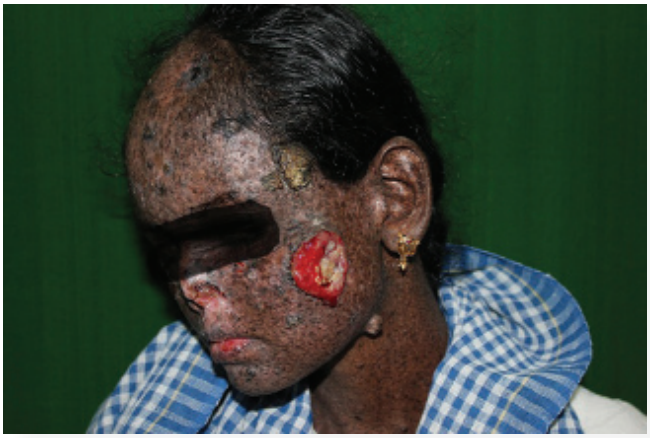

Figure 1. Kaposi's sign. Xeroderma pigmentosum in a 19 years of age female.

Figure 2. Moritz Kaposi Kohn.

THE KASABACH–MERRITT PHENOMENON

Large congenital hemangiomas may result in shunting of blood and high-output cardiac failure or entrapment of platelets and a thrombocytopenic coagulopathy and a potentially life-threatening hemorrhage (the Kasabach–Merritt syndrome or phenomenon) (Fig. 3). The pathogenesis of congenital hemangiomas is poorly understood. There is an association with prematurity. Kasabach-Merritt phenomenon is a rare, life-threatening condition in which either of two specific vascular tumors (tufted angioma or kaposiform hemangioendothelioma) traps and destroys platelets, which are a component of blood that helps clotting. This condition is also associated with other abnormal clotting conditions in which there is excessive consumption of clotting factors. Kasabach-Merritt phenomenon does not occur in children with infantile hemangiomas.

Tumors usually occur shortly after birth and are equally common in males and females. These tumors can involve any area of the body but most commonly involve the extremities. They are usually associated with skin changes. In the area of the lesions, the skin appears firm, warm, and purple.

Tumors also can involve internal organs and can be serious when they occur deep within the retroperitoneum (abdomen). As the tumor grows, it causes more platelet trapping. This is associated with abnormal clotting and utilization of clotting proteins, creating a deficiency in these proteins. Because of this, bleeding can occur and can be fatal [6].

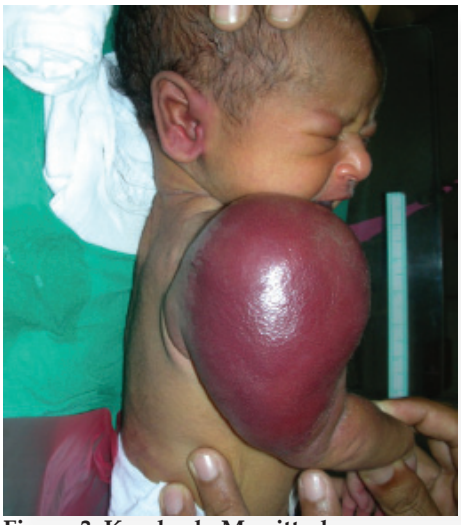

Figure 3. Kasabach–Merritt phenomenon.

KATAYAMA SIGN

Anemia with painful enlargement of the spleen and liver caused by the zoonotic microorganism Schistosoma japonicum [7].

KEDANI SIGN

An epidemic disease of Japan due to a zoonotic proteus implanted by the bite of a mite (kedani). It is marked by fever, swelling of the lymph-glands, and an exanthematous eruption fever [8,9]. Synonym: akamushi disease, flood fever, inundation fever, island disease, island fever, Japanese river fever, kedani fever, mite typhus, scrub typhus (Fig. 4,5), shimamushi disease, tropic typhus, tsutsugamushi.

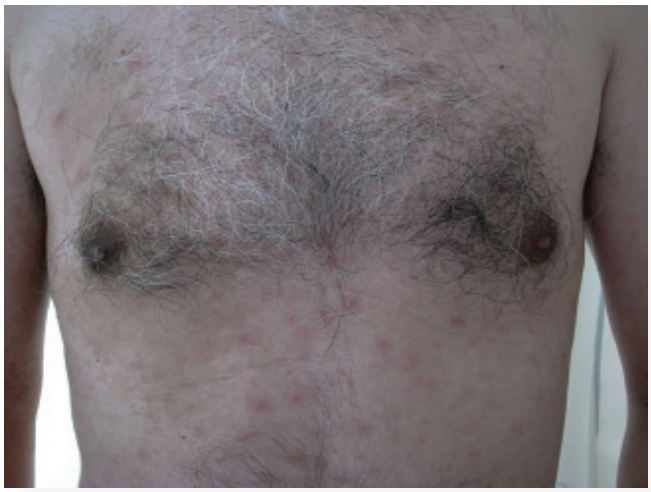

Figure 4. Scrub typhus. Rash on trunk: macular, not popular, without itchiness, pain nor tenderness.

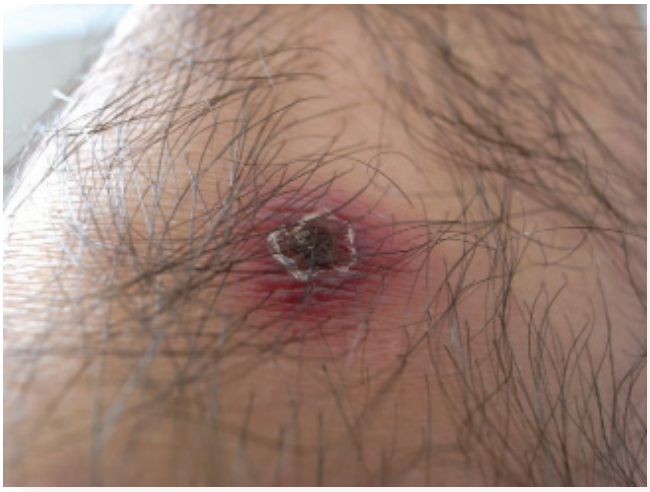

Figure 5. Scrub typhus. Eschar with surround peered scale and erythema inside of the right knee.

KEINING SIGN

bleeding nail fold in dermatomyositis [10] (Fig. 6).

"Classic" DM in adults has various clinical and pathological features, which do not always appear simultaneously or with the same severity. Dermatomyositis is identified by a characteristic rash, which appeared simultaneously or, more commonly, preceded muscle weakness. In addition to manifesting clinical and laboratory evidence of myositis, adult patients with classic DM develop the hallmark cutaneous findings. Cutaneous manifestations of DM could be classified as photosensitive, hyperkeratotic, and vascular. Photosensitive lesions consist of heliotrope rash, a periorbital, dusky, violaceous erythema of one or both eyelids. Heliotrope rash could be a component of a more confluent erythema involving the entire face in many cases associated with edema, and erythematous exanthe-mas on discrete areas of the body: the neck, and anterior chest (in a V-sign) or the nape of the neck and the posterior aspect of the shoulders (shawl-sign), knees, elbows, and malleoli. An erythematous rash may also be found on the face in a limited malar distribution, or more extensively with perioral sparing. This erythema can extend to the ears and scalp. The lesions are pruritic, and can be exacerbated after exposure to the sunlight. Gottron rash is a characteristic feature, with violaceous to dusky, red, flat-topped papules and plaques prominent on dorsal interphalangeal joints, elbows, and knees and, rarely, the malleoli. These papules evolve over time to have depressed, atrophic, porcelain white centers and prominent telangiectasias known as Gottron's sign over bony prominences.

A rare subgroup of patients have follicular hyperkeratosis, which may occur as a pit-yriasis rubra pilaris-like eruption (Wong-type DM). The lateral and palmar areas of the fingers may become rough with cracked, "dirty" horizontal lines, resembling "mechanic's hands", and dilated capillary loops with punctate infarcts at the base of the fingernails with irregular, thickened, and distorted cuticles could be prominent. Scalp involvement is frequently evident as a diffuse, erythematous, scaly, atrophic dermatosis with mild-to-moderate alopecia. Cutaneous vasculitis is seen as palpable purpura and digital or oral ulcerations [11-13].

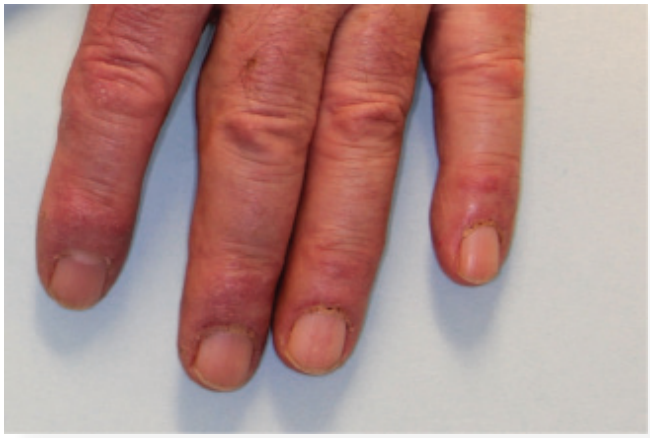

Figure 6. Keining sign.

EGON KEINIG

German dermatologist (1892-1971). [14] (Fig. 7).

Figure 7. Egon Keining.

His interest in medicine woken early by the medical profession of his father. During his medical studies he created through his special study of botany and zoology, and his practical activity in the serological and bacteriological department of the Hygiene Institute of the University of Bonn all requirements for a successful career in the field of Dermato-Venereology. In 1927, he accepted an offer from Mulzer at the Department of Dermatology in Hamburg-Eppendorf, where he worked as a senior physician from 1930 to 1940. This period also fell Habilitation (1929) and the appointment as Adjunct Professor. His unpublished habilitation thesis on „The atypical myxedema of the skin", also known as „Myxoedema circumscriptum basedowianum (Keining)" has entered the literature. In 1940 he was appointed deputy professor of dermatology in Rostock, where he returned for a short time back in its old sphere of influence in Hamburg-Eppendorf to 1944 to take over the chair of dermatology in Greifswald, where he remained until 1946. His particular interest was in clinical morphological issues. Recall the initial recognition of the „Spring perniosis", the description of the nail phenomenon in dermatomyositis, his works, which were concerned with the prominence of the seasonally -bound type of Erythema exsudativum multiforme of the type annuus, also his contributions over Lymphocytoma cutis circumscripta, scleroedema, Scleromyxoedema, Zoster generalisatus, Epidermolysis bullosa hereditaria hyperplastica, Cutis marmorata congenita, Epithelioma calcificans Malherbe, Graham -Little syndrome, miliary Lymphocytome, keratosis verrucosa Weidenfeld, Acrodermatitis continua suppurativa, nail lesions in psoriasis, etc. To him we owe the clear detection of the importance of skin constitutional types (seborrhea, sebostasis) for an adequate dermatotherapy .

He contributed significant contributions, was particularly interested again and again of syphilis therapy to their problems he often remanded position particularly after the introduction of penicillin in publications and presentations and has developed practical guidelines, as well as a look at the textbook by Keining and Braun-Falco reveals (1961).

KERANDEL'S SIGN
Deep hyperesthesia accompanied by pain, often retarded, after some slight blow upon a bony projection of the body; seen in zoonotic African trypanosomatosis [15,16].
Kerandel's sign = Hyperreflexia ± ataxia and unsteadiness ± behavioural abnormalities, psychosis.

JEAN FRANÇOIS KÉRANDEL
French physician in Africa (1873-1934). The author sign of Kerandel and Kerandel's symptom (deep-seated hyperesthesia observed in cases of sleeping sickness).
In 1913 Dr Kerandel, a trainee of the Paseur course on Microbes established a Microbiology laboratory in Phnom Pehn (Cambodia).

KIDNEY WORM SIGN
Renal colic, hematuria, and flank pain, associated with infection from the giant zoonotic roundworm Dioctophyma renale. Caused by the ingestion offrog's liver and infected fish [17] (Fig. 8 a-c). Histologic sections showed a cyst with a fibrous wall, covered focally of a single epithelial layer. The content of the cyst was consistent with hemorrhagic, necrotic elements, containing some "ring" shaped structures, necrotic as well. The outer cover of them was Periodic acid-Schiff (PAS) and Giemsa positive. Within the structures, there was a material, which could not be further evaluated (Fig). These findings were not pathognomonic, but were consistent with the presence of a dead nematodes parasite, likely of Dioctophyma renale type, as it is indicated by the lesion's site.

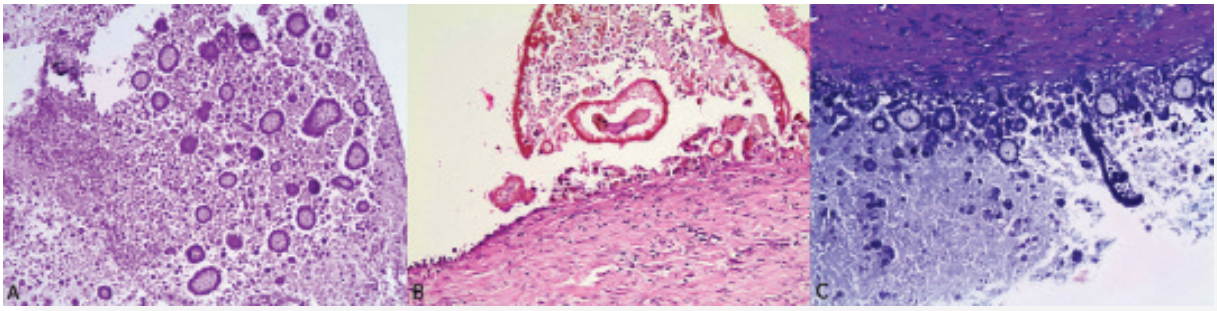

Figure 8 A-C. Fibrous wall of a cyst with necrotic material, which contains small "ring" shaped structures. An almost longitudinal sectioned structure is also seen, filled with a material, not further identified. (H+E, X100).

KILLER X SIGN (c. 1940, South Eastern USA)
A hemorrhagic disease carried by tiny biting gnats commonly called „no-see-ums" or midges that can infect wildlife. Also called blue or black tongue death [18].
Ceratopogonidae (Fig. 9), or biting midges (including what are called, in the United States and Canada, no-see-ums, midgies, sand flies, punkies, and others), are a family of small flies (1–4 mm long) in the order Diptera. In Spain they are referred to as Flying Teeth. They are closely related to the Chironomidae, Simuliidae (or black flies), and Thaumaleidae.


Figure 9. Ceratopogonidae.

KIRMISSON'S SIGN
Transverse striated ecchymoses at the elbow (Fig. 10 a, b). A sign seen in fractures of the humerus with displacement of the proximal fragment [19].

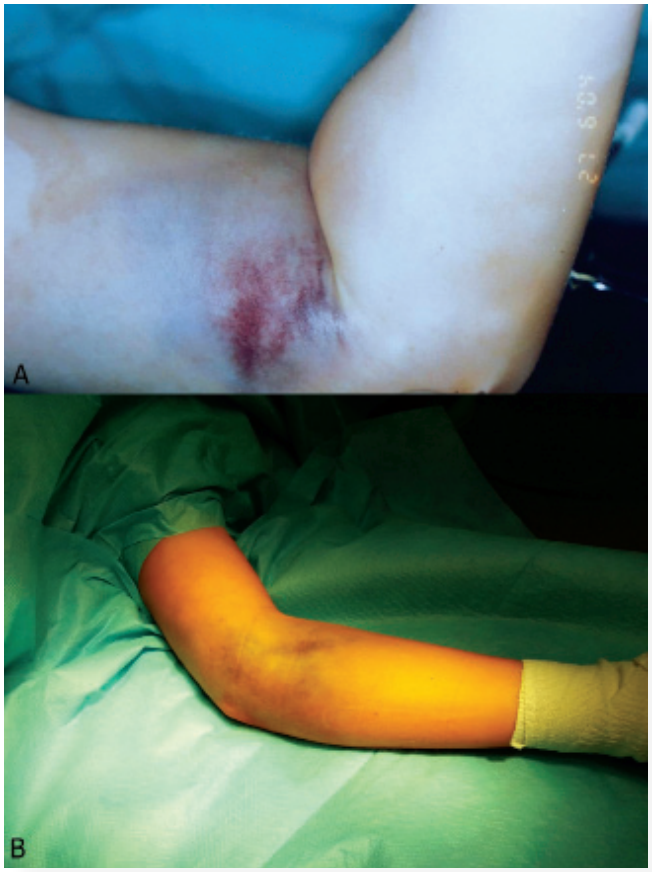

Figure 10 A, B. Kirmisson's sign.

EDOUARD FRANCIS KIRMISSON

French paediatric surgeon (1848-1927) (Fig. 11). He specialized in pediatric and orthopedic surgery. Kirmisson studied medicine at the École de Médecine in Paris, and later worked as an externe under Noël Guéneau de Mussy (1813–1885) at the Hôtel-Dieu. In 1879 he earned his medical doctorate, obtaining his agrégation in 1883. He spent the following years as a surgeon of Parisian hospitals, becoming a professor of pediatric surgery and orthopedics at Hôpital des Enfants-Malades in 1901.

In 1890 Kirmisson founded the journal Revue d'orthopédie. In 1903 he became a member of the Académie de Médecine [20].

Figure 11. Kirmisson's sign.

KOCH'S PHENOMENON SIGN

If a guinea pig which has been previously infected with tuberculosis organisms is reinjected intracutaneously, the skin over the injected area undergoes necrosis and a superficial ulcer develops. The ulcer heals quickly and infection of regional lymph nodes is retarded. The phenomenon demonstrates development of ability to localize tubercle bacilli [21].

Figure 12. Robert Koch.

ROBERT KOCH

German bacteriologist (1843-1910) (Fig. 12). The founder of modern bacteriology, is known for his role in identifying the specific causative agents of tuberculosis, cholera, and anthrax and for giving experimental support for the concept of infectious disease. In addition to his pioneering studies on these diseases, Koch created and improved significant laboratory technologies and techniques in the field of microbiology, and made a number of key discoveries pertaining to public health. His research led to the creation of Koch's postulates, a series of four generalized principles linking specific microorganisms to particular diseases which remain today the "gold standard" in medical microbiology. As a result of his groundbreaking research on tuberculosis, Koch received the Nobel Prize in Physiology or Medicine in 1905 [22].

KOEBNER SIGN

The appearance of isomorphic lesions at the site of an injury in lichen planus, warts, molluscum contagiosum (Fig. 13), psoriasis, or lichen nitidus along a site of injury [23-27].

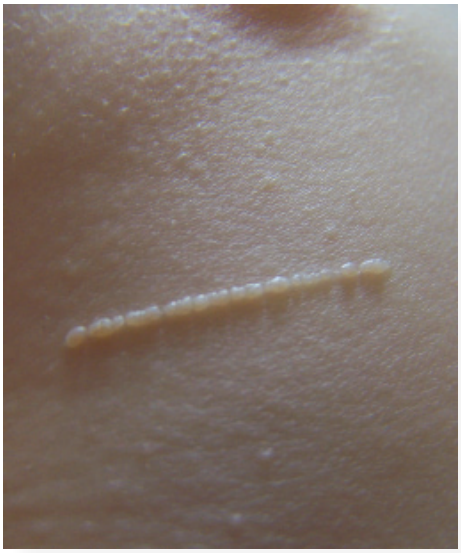

Figure 13. Koebner sign in molluscum contagiosum.

HEINRICH KOEBNER (HEINRICH KÖBNER)

German dermatologist (1838-1904) (Fig. 14). Heinrich Köbner was one of the outstanding dermatologists of the nineteenth century. He studied in Berlin from 1855 to 1859 and obtained his medical doctorate at Breslau in 1859. After hospital service in Vienna with Ferdinand von Hebra (1816-1880) and Paris with Alfred Hardy (1811-1893) he settled in Breslau where he initiated the first policlinic for syphilis and diseases of the skin in 1861.

Köbner received his venia docendi (habilitation) at the University of Breslau in 1869 and in 1872 was appointed to the newly established chair. In 1876 he also became director of the university policlinic for diseases of the skin and syphilis which had been established at his initiative. However, due to health problems, he was forced to make a sustained stay at southern health resorts and to lay down his positions. He then moved to Berlin where in 1884 he built a new policlinic at which ha gave courses for physicians.

His initial observations and studies of the phenomenon that bears his name resulted from having seen patients who had developed psoriasis at sites of excoriations, horse bites, and tattoos.

He presented the phenomenon at a meeting of the Silesian Society for National Culture in 1872.
In 1893 Heinrich Köbner was elected member of the German Academy of Natural Scientists Leopoldina. In 1897 he was appointed Geheimer Medicinalrat [28,29].

Figure 14. Heinrich Köbner.

KONZO SIGN

Irreversible paralysis of the legs, caused by ingesting cassava, a Nigerian fruit containing the glycoside linamarin (Fig. 15) [30].

Figure 15. Manihot esculenta.

KOOL-AID SIGN

Reported sweet fruity grape odor of *Pseudomonas aeruginosa* [31].

KOPLIK'S SIGN

The appearance of a crop of buccal macules consisting of small dark red spots surrounded by minute white specks (Fig. 16). A sign found in the prodromal stage of measles [32].

HENRY KOPLIK

American paediatrician (1858-1927) (Fig. 17). Henry Koplik graduated M.D. from Columbia University, New York in 1881 and then studied in Berlin, Vienna, and Prague. He took a postgraduate course at the universities of Leipzig, Prague, and Vienna, and upon his return to America, established himself as a physician in New York in 1883. There, he became connected with Bellevue Hospital, the Good Samaritan Dispensary, and other medical institutions. In 1899, he was hired as an assistant professor of pediatrics at Bellevue Medical College. He worked for 25 years at the Mount Sinai Hospital, where he established a children's pavilion. He also introduced the free delivery of Pasteurized milk to the needy poor, in which he was followed later by Nathan Straus. Koplik was the first to describe an early diagnostic sign in measles, since known as „Koplik's spots"; and he found, too, the bacillus of whooping-cough. Henry Koplik was one of the founders of the American Paediatric Society. Besides essays in the medical journals, Koplik published his „Diseases of Infancy and Childhood" in 1902 [33].

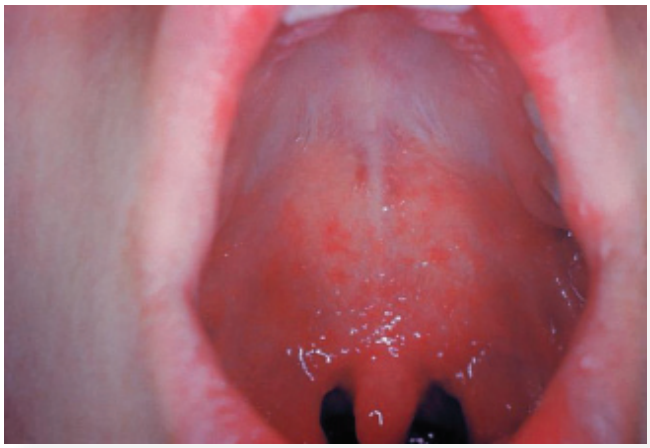

Figure 16. Koplik's sign.

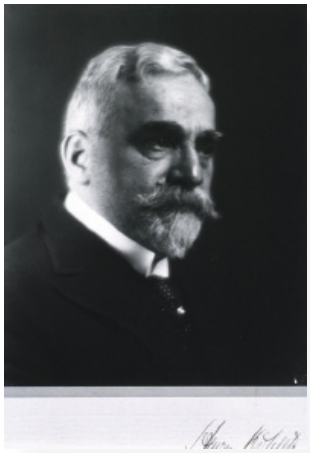

Figure 17. Koplik's sign.

KRISKOWSKY'S SIGN

The presence of cicatrical lines which radiate from the mouth. A sign of inherited syphilis. Also known as Krisovski's sign and Krisowski's sign.

MAX KRISOVSKI

late 19th century German physician.

KRISOVSKI'S SIGN
See - Kriskowsky's sign.

KURU SIGN
Trembling, loss of the ability to walk, talk, and eat. Eventually ending with death. A sign of the fatal brain disease Kuru caused by cannibalism. Kuru means trembling with fear in the Fore language [34,35]. Also known as Laughing Death sign.
Vincent Zigas discovered kuru in 1956, a very rare degenerative brain disorder that occurred primarily among the Fore natives in Papua New Guinea (ZIGAS, 1981). One year later he was joined by Carleton Gajdusek who initiated systematic investigation of kuru and received the Nobel prize of Physiology or Medicine for his work in 1976.
William Hadlow noticed similarities between kuru and scrapie at a neuropathological and clinical level. He recommended transmission experiments to apes in 1959. Gajdusek succeeded in the transmission of kuru via intracerebral inoculation of chimpanzees with kuru infected brain homogenates a few years later
The by far the most investigated form of acquired human prion diseases is kuru which
occurred among the Fore people in the highlands of eastern Papua New Guinea. The spread of disease was based on ritual cannibalism of deceased members of the community and reached epidemic proportions.

DANIEL CALTON GAJDUSEK
Hungarian-Slovak-American physician and medical researcher (virologist and paediatrician) (1923-2008) (Fig. 18). In 1976 won the Nobel Prize for his work on kuru.

Figure 18. Daniel Calton Gajdusek.

MICHAEL PHILIP ALPERS
Australian medical researcher (Fig. 19), and John Curtin distinguished Professor of International Health, at Curtin University. He is an eminent scientist who has spent half a century conducting medical research in Papua New Guinea (PNG). Best known for his research on the brain disease, kuru, Alpers was made a Fellow of the Royal Society in 2008. Alpers graduated from University of Adelaide with a B.Sc. and M.B.B.S. and from University of Cambridge with an M.A. After graduating, he commenced a career, ultimately resulting in investingating kuru disease. He is Honorary Senior Research Associate University College London [36].

Figure 19. Michael Philip Alpers.

KYASANUR SING (India)
Rash, fever, bradycardia, the patient then appears to be getting better and is then attacked by meningoencephalitis. CAused by the bite of a tick infected with the zoonotic Kyasanur forest Flaviviridae virus [37].

Acknowledgement

- for informations about EGON KEINIG:
Prof. Gerd Plewig - Department of Dermatology and Allergology, Ludwig-Maximilian-University, Munich, Germany.
Dr Khalid Al Aboud - Department of Public Health, King Faisal Hospital, Makkah, Saudi Arabia.
- for Figure of Xeroderma pigmentosum:
Dr Aashish Shashidharan, Dr Elvino Barreto and Dr Kingsly Paul M - Department of Plastic and Reconstructive Surgery, Christian Medical College, Vellore, India
- for information about Kirmisson's sign:
Ass. Prof. Julfiqar - Department of Orthopaedics, Teerthanker Mahaveer Medical College & Research Centre (TMMCRC); Moradabad, UP, India

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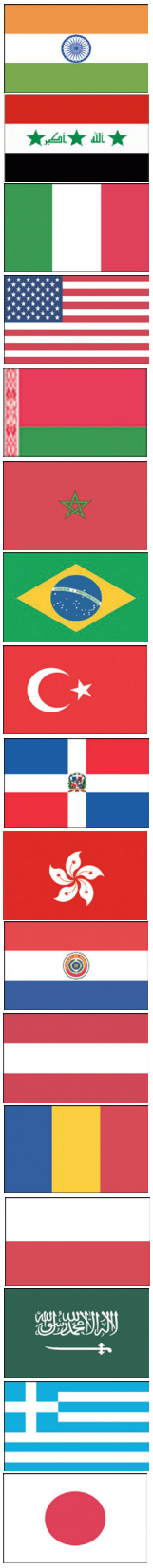

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