Volume 5, Number 2, April 2014
p. 103 - 230
Issue online since Friday, April 11, 2014

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

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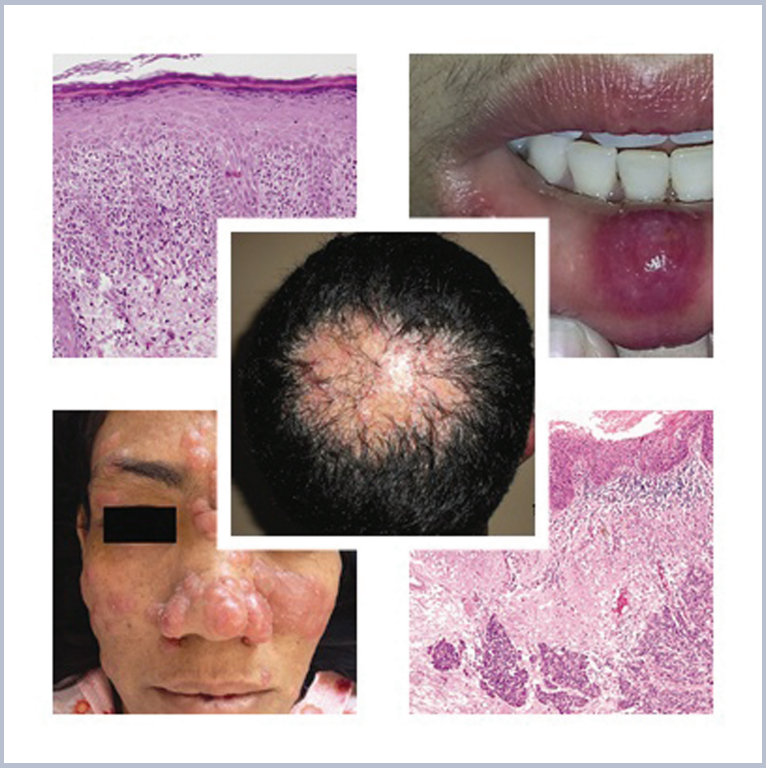

2 / 2014

Editorial Pages

NASZA DERMATOLOGIA Online
OUR DERMATOLOGY Online

e-ISSN: 2081-9390

DOI: 10.7241/ourd

Quarterly

published since 01/06/2010 years

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DOI: 10.7241/ourd.20142.27

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ESTIMATION OF PEROXISOME PROLIFERATORS - ACTIVATED RECEPTOR γ GENE EXPRESSION IN INFLAMMATORY SKIN DISEASES: *ATOPIC DERMATITIS* AND *PSORIASIS*

Doaa Mahgoub[1], Amira M. El Tawdy[1], Dina Metwally[1], Amin Manar[1], Laila Rashed[2]

[1]*Department of Dermatology, Kasr Aini Hospital, Cairo University, Egypt*
[2]*Department of Biochemistry, Kasr Aini Hospital, Cairo University, Egypt*

Corresponding author: Dr. Amira El Tawdy *amiratawdy@gmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 107-112 Date of submission: 03.02.2014 / acceptance: 21.03.2014

Abstract
Introduction: Peroxisome proliferators- activated receptors (PPARs) represent a major research target for the understanding and treatment of many skin diseases, such as benign epidermal tumors, psoriasis and atopic dermatitis.
Aim: Estimate and analyze the PPAR gamma expression and its pathological role in psoriasis and atopic dermatitis.
Materials and Methods: Fifteen patients with atopic dermatitis, fifteen patients with psoriasis and twenty apparently healthy subjects as controls,were included in the current study. We estimate the PPARgamma gene expression in the lesional skin of atopic and psoriatic patients and control, by quantitative real-time RT-PCR.
Results: Our data showed a significant decreased PPARgamma expression in lesional skin of atopic dermatitis patients and psoriatic patients (P value<0.001) compared to the control group, and the decrease was more marked in the psoriatic patients (P value<0.001).
Conclusion: Abberent PPAR γ expression has an important role in the pathogenesis of psoriasis and atopic dermatitis through the affection of cell proliferation, differentiation and inflammation.

Key words: PPAR γ; psoriasis; atopic dermatitis

Cite this article:
Mahgoub D, El Tawdy AM, Metwally D, Manar A, Rashed L. Estimation of peroxisome proliferators - activated receptor γ gene expression in inflammatory skin diseases: atopic dermatitis and psoriasis. Our Dermatol Online. 2014; 5(2): 107-112.

Introduction

The peroxisome proliferators - activated receptors (PPAR) belong to a subfamily of nuclear hormone receptors compromising three different isoforms of PPARs termed PPARα, PPARβ/δ and PPARγ. These subtypes are encoded by separate genes, exhibit different tissue distribution, functions and, to some extent, different ligand specificities. After ligand binding, PPARs can regulate gene expression by binding to peroxisome proliferator response elements (PPRE) in target genes as heterodimers with the retinoid X receptors (RXR) [1].
PPARs and corresponding ligands have been shown in skin and other organs to regulate important cellular functions, including cell proliferation and differentiation, as well as inflammatory responses [2].
PPARγ is the target ligand for thiazolidinediones (TZDs). Within the skin PPAR γ is present in sebaceous glands, inner root sheath epithelium, epidermis, and adipocytes. Also, melanocytes in benign nevi, primary melanomas, and melanoma metastases have all been shown to produce this protein. Staining for PPARγ in keratinocytes has been demonstrated in the nucleus and paranuclear region [3].
A gradual increase in expression of PPARγ from basal to granular layer has been observed in keratinocytes, and PPARγ ligands have been shown to induce the expression of genes associated with keratinocyte differentiation in vitro [2].
PPARγ plays a critical role in the regulation of genes that are involved in cellular proliferation, specific components of the T helper 2 (TH2) inflammatory pathway and maintenance of the skin barrier. This suggestion was supported by the observation that the PPARγ ligand ciglitazone inhibits allergic immune response by inhibiting TH2-driven IgE production and also production of (pro) inflammatory cytokines of the TH response in vitro and in vivo [4].

Based on the previous data showing the suggested important physiological role of PPARγ in cellular proliferation, differentiation and its possible association with inflammatory responses, the aim of the current study was to assess the tissue expression of PPAR gamma gene in psoriatic and atopic patients in an attempt to assess its suggested role in the aetiopathogenesis of these diseases which accordingly will introduce new future therapeutic strategies for both diseases.

Material and Methods

Fifty subjects were selected from the dermatology outpatient clinic, at kaser Alainy hospitals. Fifteen patients had atopic dermatitis and fifteen patients had psoriasis in addition to twenty age and sex matched, apparently healthy subjects as a control group. An informed consent was signed by each patient and ethical committee approval was fulfilled before the start of the study. Diagnosis was done on clinical basis and confirmed by skin biopsy.

The atopic patients were eight females and seven males.Their mean age was (21.07+10.6) years. The psoriatic patients were nine females and 6 males. Their mean age was (29.47+8.49) years.

Inclusion criteria:

1. Patients with childhood or adult atopic dermatitis.
2. Patients with any clinical variant of psoriasis.
3. Any age, both sexes.
4. Patients who consent to participate in the study.

Exclusion criteria:

1. Patients who received any systemic medications or phototherapy six months before the study nor topical medications three months prior to the study.
2. Patients with history of any systemic or dermatological diseases affecting the immune system.

Intervention:

All patients and controls were subjected to the following:

1. Informed consent.
2. Full history taking.
3. Full general and dermatological clinical examination.
4. Punch skin biopsy (4mm).
5. Histopathological examination for confirmation of the diagnosis.
6. PCR for the detection of PPAR gamma gene expression.

The history taken from the patients included:

- Personal history.
- History of the present condition.
- Onset of the disease.
- Duration of the disease.
- History of the treatment taken by the patients.
- Past medical history.
- Family history.

A full general examination was performed.

Assessment of disease severity was done by:

- PASI score for the psoriatic patients.

The biological severity of psoriasis at a given point in time is often quantified using the Psoriasis Area and Severity Index (PASI). This is a composite score incorporating a grading of erythema, indurations and scaling of plaques, multiplied by the clinical setting and although it has many shortcomings, it remains the gold standard tool for psoriasis assessment [5].

- Three-Item severity (TIS) score for the severity of atopic dermatitis.

It was developed as a simplified form of SCOR AD score. It is based on the evaluation of erythema, edema/papulation and excoriation, on a scale of 0-3. This score is particularly suitable in general practice, for routine clinical use and for screening purposes in clinical trials [6].

Skin biopsy:

A lesional punch skin biopsy of (4 mm) was taken from the patients and the healthy controls under local anesthetic (1% lidocaine). This procedure was done under aseptic precautions and the patients and controls were given topical antibiotic cream (Terramycin) and systemic antibiotic (Amoxil 500mg) as a treatment for the biopsy site.

Half of the biopsy taken from every patient was for histopathological study to confirm the diagnosis and the other half was kept frozen for PCR.

PCR technique

Detection of PPAR gamma gene expression using real time PCR (RT–PCR)

RNA extraction

Total RNA was isolated from skin tissue homogenates using RNeasy Purification Reagent (Qiagen, Valencia, CA) according to manufacturers instruction. The purity (A260/A280 ratio) and the concentration of RNA were obtained using spectrophotometry (Gene Quant 1300, Uppsala, Sweden). RNA quality was confirmed by gel electrophoresis.

cDNA synthesis

First-strand cDNA was synthesized from 4 μg of total RNA using an Oligo(dT)12-18 primer and Superscript™ II RNase Reverse Transcriptase, This mixture was incubated at 42°C for 1h, the kit was supplied by SuperScript Choice System (Life Technologies, Breda, the Netherlands).

Real-time quantitative polymerase chain reaction (PCR)

Real-time PCR (RT-PCR) amplification was carried out using 10μL amplification mixtures containing Power SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA USA), equivalent to 8ng of reverse-transcribed RNA and 300nM primers, the sequences of PCR primer pairs used for each geneare shown in Table I. Reactions were run on an ABI PRISM 7900 HT detection system (Applied Biosystems) PCR reactions consisting of 95°C for 10min (1 cycle), 94°C for 15s, and 60°C for 1min (40 cycles),Data were analyzed with the ABI Prism sequence detection system software and quantified using the v1·7 Sequence Detection Software from PE Biosystems (Foster City, CA). Relative expression of studied genes was calculated using the comparative threshold cycle method. All values were normalized to housekeeping gene GAPDH (Tabl. I).

Statistical methods:

The data was coded and entered using the statistical package SPSS version 15.

The data was summarized using descriptive statistics: mean, standard deviation, median, minimal and maximum values for quantitative variables and number and percentage for qualitative values. Statistical differences between groups were tested using Chi Square test for qualitative variables, independent sample t test for quantitative normally distributed variables while Nonparametric Mann Whitney test was used for quantitative variables which aren't normally distributed. Correlations were done to test for linear relations between variables. P - Values less than or equal to 0.05 were considered statistically significant [7].

Primer	Sequence
PPAR gamma	Forward: 5' AAAGAAGCCGACACTAAACC 3'Reverse: 5' CTTCCATTACGGAGAGATCC 3' According to gene bank accession number :AB_565476.1
GAPDH	Forward 5' ACCACAGTCCATGCCATCAC 3' Reverse 5' TCCACCACCATGTTGCTGTA3' According to gene bank accession number :XM_005253678.1

Table I. Primer sequences used for RT-PCR.

Results

Demographic data:

This study included 50 subjects of whom 30 were patients and 20 healthy individuals who serve as controls. Patients were divided into two groups (Atopic and psoriatic groups).

Psoriatic group:

The psoriatic group included nine (60%) females and six (40%) male patients. The age of the psoriatic patients ranged between (20-55) with a mean value of (29.47+8.49).

The mean duration of the disease in the psoriatic group was (7.35+5.77) years. The extent of the disease was (33.33%+21.9) and the mean of PASI score was (9.15+6.29) (Tabl. II).

Twelve (80%) patients had psoriasis vulgaris, two (13.3%) had guttate psoriasis and one (6.7%) patient had palmo-planter psoriasis. Ten (70%) patients had(+ve)family history of psoriasis.

Atopic group:

The atopic group included eight (53.3%) females and seven (46.7%) males. The age of the atopic patients ranged between (10-40) years with a mean value of (21.07+10.6).

In the atopic group a positive family history of allergic disease (asthma, allergic rhinitis, food allergy or atopic dermatitis) was reported in all patients (100%).

The mean duration (in years) of the disease was (10.14+9.84) and the extent of the disease was (28.33%+24.03). Eight patients (53.3%) were of the adult type while seven patients (46.7%) were of the child hood type. The mean value of the disease severity was (6.6+1.29) by the TIS (Tabl. III).

Pt. No	age	sex	duration	extent	PASI	c. variant	f. history
1	26	M	10	10	4.2	PP.Ps	+
2	27	M	15	20	8.6	Ps.vulg	-
3	34	F	19	30	9.8	Ps.vulg	+
4	35	F	2	10	5.2	Ps.vulg	+
5	27	F	10	20	8	Ps.vulg	-
6	22	M	1	10	1.4	Ps.vulg	+
7	20	M	5	60	22.4	Ps.vulg	-
8	25	F	10	10	1.8	Ps.vulg	+
9	30	F	5	50	17	Ps.vulg	+
10	36	F	3m	50	9	guttate.ps	+
11	27	F	9	40	15.2	guttate.ps	-
12	26	F	2	70	17.4	Ps.vulg	+
13	22	M	3	60	8.7	Ps.vulg	+
14	30	F	15	50	4.9	Ps.vulg	+
15	55	M	4	10	3.4	Ps.vul g	-

Table II. Primer sequences used for RT-PCR.

M=male; F=female; f=family; c=clinical; vulg= vulgaris; PP=palmoplanter; m=month

Pt. No	age	sex	duration	extent	TIS	c. variant	f. history
1	12	M	7	20	9	ch.hood	+
2	10	F	9	10	8	ch.hood	+
3	14	F	14	30	8	ch.hood	+
4	14	F	10	30	7	adult.t	+
5	40	M	30	80	7	adult.t	+
6	15	M	7	20	7	ch.hood	+
7	15	F	14	20	6	adult.t	+
8	37	M	32	20	6	adult.t	+
9	16	F	1	30	6	ch.hood	+
10	10	M	2	20	6	ch.hood	+
11	16	F	16	10	5	adult.t	+
12	26	F	4	15	6	adult.t	+
13	40	M	5	90	5	adult.t	+
14	26	F	1	20	5	adult.t	+
15	25	M	2m	10	4	adult.t	+

Table III. Demographic data of atopic patients.

F=female; M=male; m=month; f=family; ch=child; t=type

Control group:
The control group included 11 (55%) females and nine (45%) males. The mean age was (27.50+7.5). All the control subjects had no family history of atopy nor psoriasis.

Analytic data:
Psoriatic group vs. control:
Statistical analysis of the PPARγ gene expression done by Mann--Whitney test revealed that the mean of expression of PPARγ was (0.15+0.05) in the psoriatic patients, and it was (1.20+0.43) in the controls. On comparing both groups (Ps & control) a statistically significant lower PPARγ expression was reported in the psoriatic patients (P.value<0.001) (Fig. 1).

Atopic group vs. control:
The mean value of PPAR γ expression in the atopic patients was (0.36+0.17) compared to (1.20+ 0.43) in the controls.

On comparing both groups there was an evident lower expression in the atopic patients which was statistically significant (P value <0.001) (Fig. 2).

On comparing both atopic and psoriatic groups:
Lower expression of PPARγ gene expression was observed in the psoriatic patients in comparison to the atopic patients with a significant statistical difference (P value <0.001) (Fig. 3).

No significant correlation between:
The mean level of PPARγ gene expression to all of the following parameters in both groups:
· Age of the patient.
· Duration of the disease.
· Extent of the disease.
· Severity of the disease.
· Clinical variant of the disease.

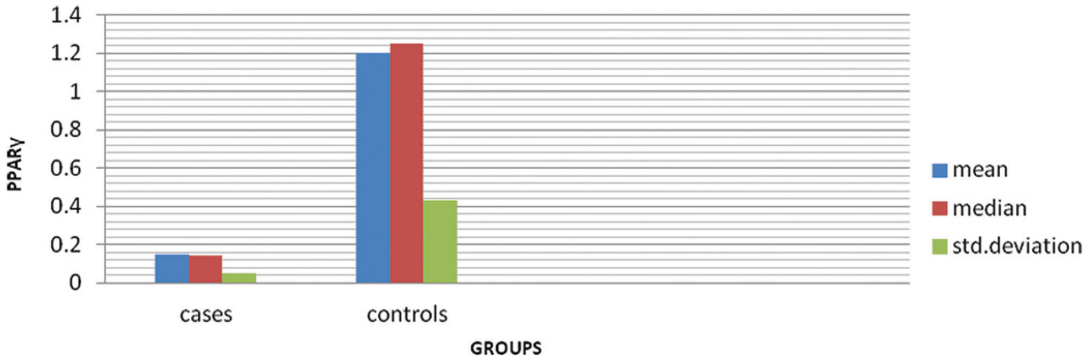

Figure 1. PPARγ gene expression in psoriasis and control.

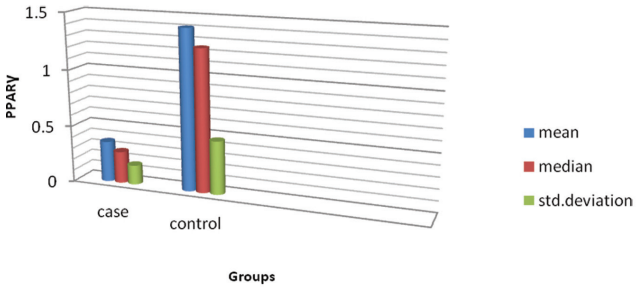

Figure 2. PPARγ gene expression in atopic and control.

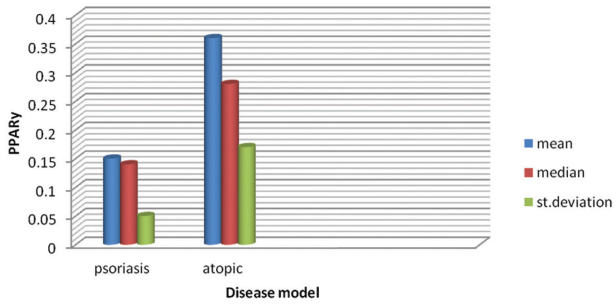

Figure 3. PPARγ expression in AD and psoriasis.

Discussion

The current study revealed reduced expression of PPARγ gene in both atopic and psoriatic patients with a more significant reduction in the psoriatic group.
In agreement with our results, Plager et al. (2007) [8] reported as well decreased PPAR activity and decreased gene expression of both (PPARα and γ) in AD patients. In addition, decreased expression of both PPARα and γ gene expression in psoriasis had been reported before by previous studies [9,10].
Based on those results, other studies investigated the role of PPARγ receptors activators in treatment of different inflammatory diseases. Exogenous ligands for PPARγ include several pharmaceutical products of which TZDs are the most selective ligand. TZDs are potent selective PPARγ agonists [11]. Some studies [2], found that activation of PPARγ receptor, attenuated the allergic immune response via mono- cytes and lymphocytes.
In addition others [12] reported that activation of PPARγ receptors, inhibited the maturation of bone marrow progenitor into connective tissue type mast cells thus giving a good model for therapeutic implications for mast cell-related diseases such as atopic or contact dermatitis.

On the same basis, a retrospective review done in 2005 [13], demonstrated the safety &efficacy of rosiglitazone, a PPAR agonist, in 6 cases of severe atopic dermatitis who were unresponsive to first and second line therapies. Moreover, Dahten et al. 2007 [4], stated that PPARγ ligand treatment inhibited not only systemic allergic immune response, but also local allergen-mediated dermatitis. Again it had been reported that activators of peroxisome proliferators-activated receptor (PPAR) α, β/δ, γ regulate epidermal protein and lipid production, leading to superior barrier function. Additionally, some of these activators exhibit potent anti-hyperplasic and anti-inflammatory activity in irritant contact dermatitis and acute allergic contact dermatitis. These results suggest that topical applications of certain activators/ligands of PPARα, β/δ, and γ could be useful for the treatment of AD in humans [14].

Regarding their use in psoriasis, a large ten-year case-control study identified an association between the use of TZDs (specific ligands for PPARγ) and the reduced risk of psoriasis. This association was not present with the use of other anti-diabetic drugs [1,15,16].

Studies in a mouse model of hyperproliferative skin disease have shown that topical administration of PPARγ ligands reduced epidermal hyperplasia and that the treatment had no effect on normal skin [17].

In an attempt to understand the pathogenic role played by the abberrent expression of PPARγ in both AD and psoriasis we reviewed the literature and searched for any previous studies incorporated in the same field.

Concerning AD, the epidermal barrier dysfunction together with the induced inflammatory processes constitute the main scenario for the disease pathogenesis. Activation of PPARγ receptor improves permeability barrier homeostasis by a number of mechanisms, including stimulating epidermal lipid synthesis, increasing lamellar body formation and secretion, and increasing the activity of enzymes required for the extra cellular processing of lipids in the stratum corneum, leading to the formation of lamellar membranes that mediate permeability barrier function [18].

Functional human PPARγ was originally cloned from the human bone marrow, and plays a role in the regulation and development of immune cells like mono-cytes and T-lymphocytes [19].

Several studies support the role of PPAR γ in inflammatory processes as its expression appears to be altered by (pro)-inflammatory cytokines. A different PPARγ expression profile due to the changes of the local inflammatory milieu may result in differential functional effects of the immune response [4]. In a review article published in 2010 [20], stated that peroxisome proliferator-activated receptor (PPAR) transcription factors thus act as connectors between the enzymatic mechanisms of the epidermal barrier and the abnormal immune and inflammatory responses that characterize atopic dermatitis.

The hallmarks of psoriasis are the abnormal differentiation and hyperproliferation of keratinocytes with inflammatory cell infiltration.

Ligand activation of PPARγ can also inhibit proliferation, promote differentiation and induce apoptosis in a variety of malignant and non-malignant tissues. As a reflection to their anti-proliferative property, PPARγ agonists inhibit VEGF-induced angiogenesis. An increasing body of evidence points to an interaction between vitamin D and PPAR-signaling pathways, where the anti-proliferative, differentiation regulatory effects of vitamin D compounds are at least in part mediated by transcriptional regulation done by PPARγ activity [21]. At the molecular level, PPARγ stimulation appears to function in a largely inhibitory fashion. PPARγ diminishes the activity of cytokines including signal transducer and activator of transcription (STAT), interleukin-1, nuclear factor-kappa-beta, and activator protein-1. It also decreases production of interleukin-1β, interleukin-6, and most importantly, TNFα. In general, there appears to be an antagonistic relationship between PPARγ and TNF-α, perhaps explaining its beneficial effects in psoriasis [22].

To the best of our knowledge, the current study was the first done comparing the level of PPARγ gene expression in atopic dermatitis versus psoriasis. We revealed a lower level of the gene expression in the psoriatic group with a significant statistical P value (< 0.001).

Those results point to the evident role played by PPARγ in keratinocyte proliferation and differentiation. Moreover this explains why PPARγ agonists, through their activation, could achieve a great success in psoriasis therapy as stated before by several studies [1,15-17]. Although this study revealed no correlation between the severity of the diseases (in both groups) and the level of PPARγ gene expression. Yet we suggest that the small sample size in each group might explain those findings and a larger sample size in further studies can elaborate more about PPARγ in relation to different clinical parameters in both diseases.

We deduced out of the results of the current study the important role for the PPARγ gene abnormal expression in the pathogenesis of both AD and psoriasis.

Increasing body of evidence out of this study indicates that PPARγ signaling pathways may represent interesting therapeutic targets for a broad variety of skin disorders, including inflammatory skin diseases such as psoriasis and atopic dermatitis.

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DOI: 10.7241/ourd.20142.28

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CD1a, HAM56, CD68 AND S-100 ARE PRESENT IN LESIONAL SKIN BIOPSIES FROM PATIENTS AFFECTED BY AUTOIMMUNE BLISTERING DISEASES

Ana Maria Abreu Velez[1,3], Juliana Calle-Isaza[2], Michael S. Howard[1]

[1]*Georgia Dermatopathology Associates, Atlanta, Georgia, USA*
[2]*Clinic El Poblado, Medellin, Colombia, South America*
[3]*Section of Dermatology, University of Antioquia, Medellin, Colombia, South America*

Corresponding author: Ana Maria Abreu Velez, M.D., Ph.D. *abreuvelez@yahoo.com*

Source of Support:
Georgia Dermatopathology Associates, Atlanta, Georgia, USA (MSH, AMAV); Mineros SA, Medellin, Colombia; the Embassy of Japan in Colombia, Medellin, and University of Antioquia, Medellin (AMAV).
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 113-117 Date of submission: 18.02.2014 / acceptance: 30.03.2014

Abstract
Introduction: Previous research on autoimmune skin blistering diseases (ABD) has primarily focused on the humoral immune response; moreover, little attention has been given to the potential role of the antigen presenting cells (APCs) in lesional skin.
Aim: The purpose of our study was to immunophenotype selected APC in the lesional skin of ABDs, utilizing immunohistochemistry (IHC) stains.
Materials and Methods: We utilized IHC to stain for dendritic cells (DC), staining with CD1a, CD68, HAM56, and S-100 in lesional skin from 30 patients with endemic pemphigus foliaceus (EPF), 15 controls from the EPF endemic area, and 15 healthy controls from the USA. We also tested archival biopsies from patients with selected ABD, including 30 patients with bullous pemphigoid (BP), 20 with pemphigus vulgaris (PV), 8 with pemphigus foliaceus (PF) and 14 with dermatitis herpetiformis (DH) and 2 with epidermolysis bullosa acquisita (EBA).
Results: Cells stained by CD68, HAM56 and S-100 were present in the majority of the ABD skin biopsies; these cells were located primarily in perivascular infiltrates surrounding dermal vessels subjacent to the blisters. However, these cells were also noted within the blisters, in vessels supplying dermal eccrine glands and ducts, and in areas of dermal endothelial-mesenchymal cell junction-like structures, especially in BP cases. In our CD1a staining, the number and location of positive staining cells varied with each disease, being abundant in most ABD in the epidermis suprajacent to the blisters, or in the epidermis surrounding the blister site if the blister site epidermis was missing. In the control biopsies, most did not display positive IHC staining, with the exception of a few CD1a positive cells in the epidermis
Conclusion: Our findings confirm positive IHC staining for APCs in areas of the skin besides the disease blisters. Our findings suggest that the antigen presentation in ABD proceeds in areas distant from the blister site. Further studies are needed to confirm our findings, and to explore their full significance.

Key words: Autoimmune blistering skin diseases; CD1a; HAM56; CD68

Abbreviations: Bullous pemphigoid (BP), endemic pemphigus foliaceus (EPF), antigen presenting cells (APC), pemphigus vulgaris (PV), pemphigus foliaceus (PF), epidermolysis bullosa acquisita (EBA), immunohistochemistry (IHC), direct and indirect immunofluorescence (DIF and IIF), hematoxylin and eosin (H&E), basement membrane zone (BMZ), pemphigus vulgaris (PV), cicatricial pemphigoid (CP), autoimmune blistering skin diseases (ABD), extracellular matrix (ECM), dendritic cells (DC), intercellular staining between epidermal keratinocytes (ICS), Langerhans' cells (LCs).

Cite this article:
Abreu Velez AM, Calle-Isaza J, Howard MS. CD1a, HAM56, CD68 and S-100 are present in lesional skin biopsies from patients affected by autoimmune blistering diseases. Our Dermatol Online. 2014; 5(2): 113-117.

Introduction

The skin is an integral part of the immune system. Within the skin, there are three classes of antigen presenting cells (APCs); specifically, macrophages, dendritic cells (DC) and B lymphocytes [1-7]. Functional components of the human immune response include antigen recognition, effector cell activation and effector activity. Moreover, antigens are presented by "major histocompatibility complex" (MHC) proteins, on the surfaces of APCs [1-7]. When activated by antigen(s), T cells differentiate into different classes of effector T cells; helper/suppressor (CD4+) T cells produce cytokines and chemokines that direct the immune response.

Cytotoxic/killer (CD8+) T cells kill virus-infected cells, and regulate other cells. DCs are a complex cell population in the skin, consisting of primarily epidermal Langerhans cells (LCs) and dermal DCs; these cells are diverse in their anatomic location, antigen recognition and processing abilities, and migratory capacities. Both the LCs and other DCs function as sentinels, assessing invading agents and conveying information to the immune system by taking up exogenous antigens (and/or autoantigens), then migrating to regional lymph nodes and presenting the processed antigens to T cells. As a result, targeted T cell differentiation and activation occurs. The antigen-specific signal is given by interaction of the T-cell receptor (TCR) with specific MHC/peptide complex(es) [1-7]. Autoimmune blistering skin diseases (ABDs) are a heterogeneous group of diseases associated with autoantibodies that are directed largely against desmosomal proteins, or hemidesmosomal molecules [8-10]. The purpose of our study was the immunophenotypic characterization of APCs in the perilesional and lesional skin of ABD patients, and to compare and contrast our findings with a control group.

Material and Methods

Subjects of study

We performed IHC using antibodies as previously described [11,12]. We utilized multiple monoclonal and polyclonal antibodies, primarily from Dako (Carpinteria, California, USA). For all our IHC testing, we used a dual endogenous peroxidase blockage, with the addition of an Envision dual link (to assist in chromogen attachment). We applied the chromogen 3,3-diaminobenzidine (DAB), and counterstained with hematoxylin. The samples were run in a Dako Autostainer Universal Staining System, as previously described [11,12]. Positive and negative controls were consistently performed. For IHC, we utilized 1) Dako antibodies to monoclonal mouse anti-human CD1a Clone O10. CD1a, a member of the CD1 antigen family, is a non-polymorphic MHC class I related cell surface glycoprotein, expressed in association with ß2-microglobulin. Langerhans cells, lymph node interdigitating dendritic cells and medullary thymocytes are labelled by anti-CD1a. Thus, the antibody is useful for the diagnosis of thymomas, malignancies of T-cell precursors and Langerhans cell disorders. We also utilized 2) CD68; specifically, Dako Catalog No. M3571, monoclonal mouse anti-human CD68, clone KP1. The CD68 antibody labels human monocytes, macrophages and myeloid cells; CD68 is of value in identifying non-Langerhans macrophages in a wide variety of normal and pathological conditions, and for immunophenotyping of myeloid and histiocytic cells. We also utilized 3) myeloid/histoid antigen, Dako Catalog No. IR613, antigen retrieval high pH, monoclonal mouse anti-human Clone MAC 387. This antibody reacts with a human cytoplasmic antigen (L1-antigen or calprotectin) which contains two different subunits (L1H and L1L). The myeloid/histoid protein is a member of the S-100 family, and its subunits in this context are titled S100A8 and S100A9. We utilized 4) mouse monoclonal HAM56 antibody, from Cell Marque Corporation (Rocklin, California), Catalog No. 279M-18, ready to use, antigen retrieval high pH. The HAM56 antibody reacts with tingible body macrophages and interdigitating dendritic cells in lymph nodes, and tissue macrophages. HAM56 also reacts with monocytes, but is not reactive with B and T lymphocytes. We used S100 antibody from Dako, that reacts strongly with human S100B, and weakly or very weakly with S100A1 and S100A6, respectively. S100 from ox brain was used for the antibody immunization. The antibody is a useful tool for the identification of S100-positive neoplasms, such as malignant melanoma (1), chondroblastoma, and schwannoma. Additionally, it is useful for the classification of tumors of suspected histiocytic/dendritic cell type (2). Our direct immunofluorescent studies (DIF) were performed as previously described [8-10]. LC/DC quantification was performed by morphometric analysis, and we estimated the number of LC/DC/mm^2 total epidermis, LC/DC/mm^2 in stratum corneum (SC), LC/DC/mm^2 in the basement membrane zone (BMZ), as well as at other sites. LCs and DCs were also quantified via light microscopy, with a 400X total magnification as previously described [13].

Statistical methods

Differences in staining intensity and positivity were evaluated using a GraphPad Software statistical analysis system, and employing Student's t-test. We considered a statistical significance to be present with a p value of 0.05 or less, assuming a normal distribution of the samples.

Results

We noted that populations of epidermal Langerhans cells were significantly decreased in lesional skin, when compared to perilesional skin in El Bagre-EPF patients. In controls from the El Bagre EPF endemic area, CD1a positive LCs were quantified at ~1-2 cells/mm^2. HAM56 antibody staining was very positive in the EPF cases, especially around dermal neurovascular packages supplying sebaceous glands (a median of 15-18 cells/mm^2), compared to normal controls (~1-2 cells/mm^2; $p = 0.001$). The HAM56 antibody was also positive in the epidermis above the blisters, and in the dermis under the blisters (1-5 cells/mm^2), in comparison to normal skin controls (~1-2 cells/mm^2). In regard to CD68 staining, it was also very positive around dermal eccrine gland coils and ducts, and at the edges of the deep adipose tissue in EPF as well as in PF patients (a median of 15-18 cells/mm^2), in comparison with normal controls (~1-2 cells/mm^2; $p = 0.001$) (Fig. 1 - 4). In BP, we noted a strong presence of CD1a cells above the epidermal blisters (1-5 cells/mm^2) in comparison to normal skin controls (~1-2 cells/mm^2). In the BP patients, increased CD1a cells were seen (a median of 8 cells/mm^2 in the basement membrane and free in the blister; the quantity was similar to that in the epidermis ($p = 0.001$); (Fig. 1 - 4). The numbers of CD1a cells in plastic surgery control tissue specimens was also low, as seen in the normal epidermal samples. In BP patients, significant CD1a staining was seen in the upper dermis in proximity to vessels, as well as vessels around mesenchymal-endothelial cell junction-like structures(especially in the middle dermis) versus low numbers in the controls ($p = 0.001$). Of interest, a few BP cases showed scattered positive CD1a cells, around deep dermal sweat glands (~1-2 cells/mm^2). In regard to HAM56, in BP this was the most positively staining antibody in lesional skin, in comparison to S-100, CD68 and CD1a. In the BP patients, HAM56 positive cells were noted in the floor of the blister, with a median of 15-18 cells/mm^2 in the basement membrane and free in the blister; the rate was similar to that observed in the epidermis ($p = 0.001$) (Fig. 1 - 4). The HAM56 staining in controls was ~1-2 cells/mm^2. Strong staining for HAM56 was noted in the upper dermis in proximity to blood vessels; the staining was accentuated around vessels surrounding mesenchymal-endothelial cell junction-like structures, especially in the central dermis and significantly higher than that observed in the controls ($p = 0.001$).

The HAM56 positive cells were noted in association with dermal lymphatic vessels, including those relatively deep in the dermis. In DH, the rate of CD1a, HAM56, CD68 and S-100 positive cells was similar, with a few cells above the blisters in the epidermis and/or surrounding the blisters and quantified at about 8 cells/mm^2, versus controls at ~1 to 2/mm^2 (p = 0.001). In EPF and PF, positive staining HAM56 and CD68 cells were seen around the upper neurovascular vessels and also around those feeding multiple skin appendices. The Cd1a cells were low in number over the blisters (however most skin biopsies showed thinning of the epidermis). In EBA, the CD1a and the S100 cells were positive over the roof of the blister in the epidermis at (1-5 cells/mm^2) in comparison to normal skin controls (~1-2 cells/mm^2). Ham56 and CD68 were positive mostly under the upper dermal vessels at a similar frequency similar rate.

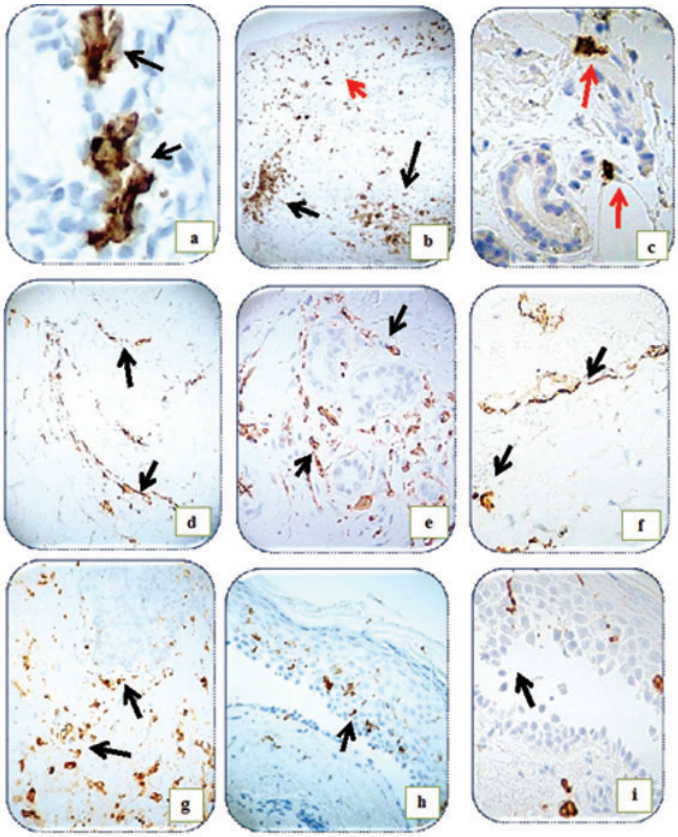

Figure 1. a. A DH case, showing positive IHC staining with CD1a in small upper dermal vessels (brown staining; black arrows) (400X). **b.** A BP case, showing positive IHC staining for CD1a around upper dermal vessels (brown staining; black arrows) (200X). **c.** Same BP case as in **b**, with CD1a cells positive around eccrine glands, which was an unusual presentation of these cells (brown staining; red arrows) (400X). **d.** Same BP case as in **b**, with positive staining for HAM56 around upper dermal vessels (brown staining; black arrows) (100X). **e.** Same BP case as in **b,** but with positive staining with HAM56 around dermal eccrine glands (brown staining; black arrows) (100X). **f.** Same BP case as in **b**, with positive HAM56 staining in lymphatics (brown staining; black arrows)(400X). (Note: lymphatic colocalization confirmed with D2-40; data not shown). **g.** A PV case, with HAM56 positive staining under the epidermis and in the dermal infiltrate around the vessels (brown staining; black arrows). **h.** A PV case, with positive HAM56 staining in the epidermis (brown staining; black arrow) (400X). **i.** A PV case, with positive CD1a staining in the epidermis and dermis (brown staining; black arrow)(400X).

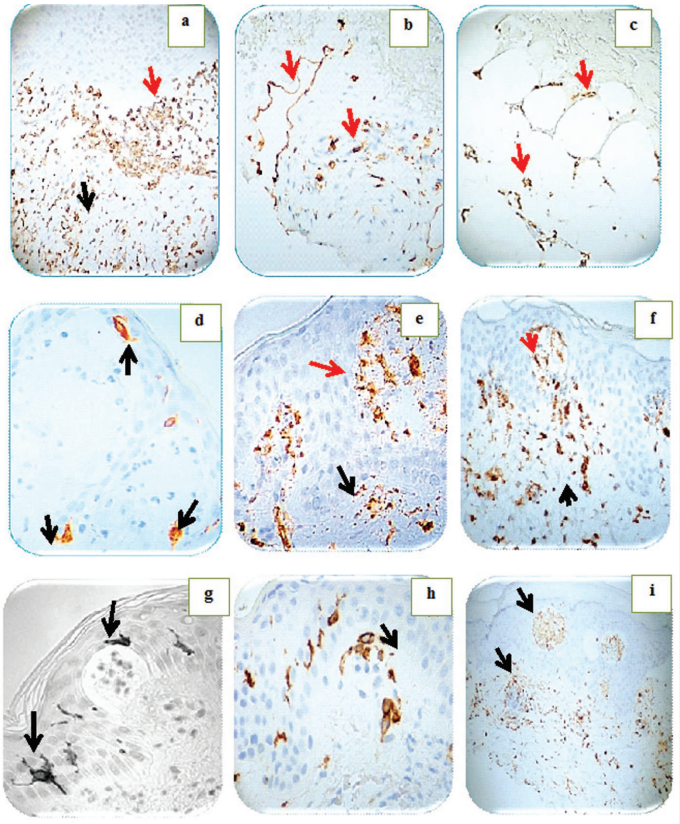

Figure 2. a. A BP case, showing positive IHC staining with HAM56 inside the blister (brown staining; red arrow) as well as in the upper dermal perivascular infiltrate (brown staining; black arrow) (200X). **b.** Same BP case and staining as in **a**, but the stain with HAM56 is in deep dermal vessels (brown staining; red arrows) (200X). **c.** A BP case, with positive HAM56 staining in adipose tissue (brown staining; red arrows) (400X). **d.** A DH case, demonstrating positive CD1a IHC staining around subepidermal blisters (brown staining; black arrows) (400X). **e.** Same DH case as in **d**, with positive IHC staining for HAM56 inside the blister and in the upper dermis subjacent to the blister (brown staining; red and black arrows) (400x). **f.** Same case and staining as in **e**, but at lower magnification (100X) and demonstrating that the HAM56 cells are around the upper dermal vessels (brown staining; black arrow) and in the blister (brown staining; red arrow). **g.** Another case of DH, with positive staining in the sides of blisters with CD1a parenthesis (dark black staining; black arrows). **h.** An EBA case positive for to HAM 56 (brown staining; black arrows) and **i**. A DH case with positive staining for HAM56(brown staining; black arrows).

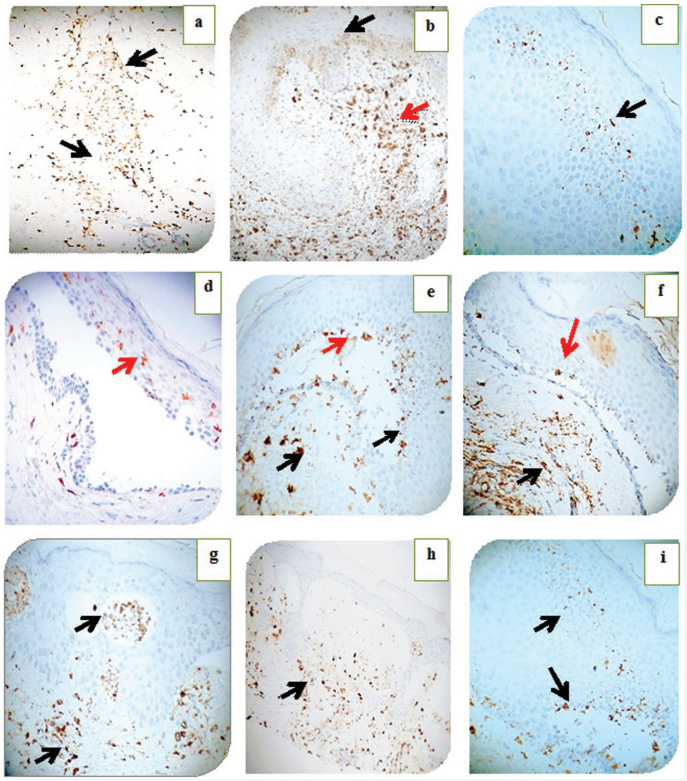

Figure 3. a. A DH case, with positive staining for HAM56 in the deep dermis (brown staining; black arrows) (100x). **b.** A PV case, with positive staining for HAM56 around the dermal papillae (brown staining; black arrow); epidermal basilar keratinocytes seem to be expressing this marker along the cell peripheries (brown staining; red arrow) (200X). **c.** A PV case, positive for HAM56 in the central epidermis (brown staining; black arrow) (200X). **d.** A PV case, positive for CD1a above the blister in the epidermis (brown staining; red arrow). **e.** A PV case, positive for HAM56 above one forming blister in the epidermis (brown staining; red arrow), positive within the blister (brown staining; black arrow), and also in the papillary dermis under the blister (brown staining; black arrow) (200X). **f.** A PV case, with staining for HAM56 above the roof of the blister (brown staining; red arrow) and below the blister in several areas, including dermal vessels and extracellular dermal matrix areas (brown staining; black arrow). **g** and **h.** Positive CD1a cells around the blister in two DH cases (brown staining; black arrows) (400X). **i.** A PV case, with positive HAM56 staining in the middle of the epidermis where blisters are forming (brown staining; black arrows) (200X).

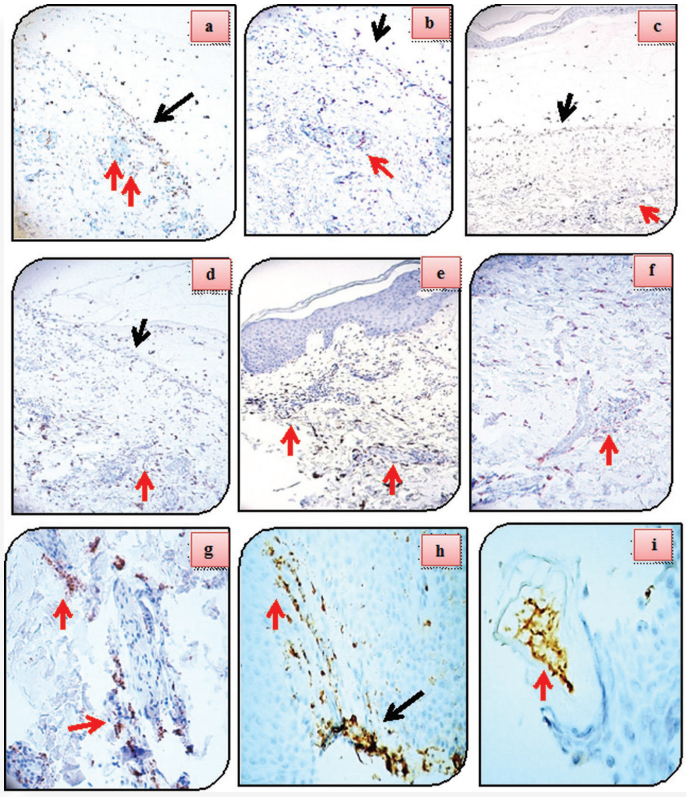

Figure 4. a through c. A case of BP, showing positive staining with S-100 with several patterns: 1) linear at the BMZ (brown staining; black arrow); and 2) several cells in the upper dermis close to inflamed vessels (brown staining; red arrows). **d.** Same BP case as in **a-c**, but in this case the staining was with CD68 antibody, showing positive staining in a pattern similar to that with the S-100 antibody. The black arrow shows the linear pattern at the BMZ, and the red arrow positivity around dermal vessels (brown staining). **e** and **f.** At lower and higher magnification respectively, a BP case staining positive for CD68 around upper dermal vessels as well as around supply vessels of eccrine glands (brown staining; red arrows). **g.** Similar to **e-f,** but at 400X magnification showing CD68 positivity around sweat glands, dermal vessels and mesenchymal–endothelial cell junction-like structures (brown staining; red arrows). **h.** HAM56 positive staining in dermal papilla neurovascular supply structures and upper dermal vessels in a DH patient (brown staining; red arrow and black arrow) (200X). **i.** HAM56 positive staining in a nascent blister of a PV patient (brown staining; red arrow) (400X).

Discussion

In contradistinction to leukocyte migration via blood vessels, transport via lymphatic vessels is the route many of antigen-presenting dendritic cells (DCs), which are crucial for the induction of protective immunity and for conservation of immunologic tolerance [1-7]. Our investigation demonstrated that many of the DCs were found in proximity to lymphatic vessels; thus, we suggest these cells were homing to lesional-draining lymph nodes. The mechanism by which an antigen triggers an adaptive immune response requires multiple steps. Potential antigenic elements must be captured, processed, and presented in a recognizable form to T cells, with suitable associated signals [1-7]. Given that activated DCs are short-lived cells (approximately 1 week), our findings are indicative of ongoing antigen presentations in ABDs in lesional skin biopsies.

Our study indicates that the majority of the ABDs have CD1a positive cells above and below lesional blisters. Notably, HAM56 positive cells were seen in higher numbers in all the ABDs. The presence of CD68 positive staining was significantly less than other markers in the epidermis and/or in the blisters in all the ABDs, but was commonly noted around dermal vessels and in the deep dermis (especially in EPF and PF, present in both in proximity to adipose tissue). The distribution of S-100 positive staining was similar to that observed with CD68.

Cutaneous DCs are involved in several pathologic processes (including infections, non-infectious inflammatory disorders and skin cancers), and play a pivotal role in regulating the balance between immunity and peripheral tolerance. Our staining results indicate that APCs were present around dermal vessels, at dermal endothelial-mesenchymal cell junction-like structures, around dermal eccrine coils and ducts, and in deep adipose tissue. Our findings may be indicative that immune processing and antigen presentation may not be restricted to the areas of the intercellular keratinocytes (as in the case of pemphigus), or to the basement membrane zone (BMZ)(as in cases of subepidermal blistering diseases). Indeed, we have recently reported that HLA Class II antigen (HLA-DPDQDR), ribosomal protein S6-pS240, cyclo-oxygenase 2, IgE, mast cell tryptase, c-kit/CD117, autoantibodies, complement, proteases, protease inhibitors and vimentin positive IHC staining are also present in the same areas of reactivity as reported in our current study with DCs [11,14-18].

A previous study was performed on skin biopsies from 22 endemic pemphigus foliaceus patients, investigating lesional skin and healthy skin from EPF patients and cadaver donors; the study investigated LCs and DCs via anti-CD1a antibody staining, quantified by morphometric analysis as we used in our study [13]. The authors reported that LC numbers in lesional skin and in healthy skin from EPF patients was similar to that of cadaver control groups [4]. The DC numbers in patient lesional skin was higher than that of the cadaver group (median=0.13 DC/mm^2 basement membrane). In the 13 patients with biopsies of both injured and healthy patient skin, LCs and DCs were present in larger numbers within the lesions. There was also a direct correlation between DC numbers in the lesional skin of the EPF group and serum autoantibody titers [13]. The serum correlation was not observed for LCs. The authors concluded that the increased number of DCs in the lesion, as well as their direct correlation with serum autoantibody titers suggested participation of DCs in the pathogenesis of PF [13].

Other authors performed a pilot study in lesional skin of patients with EPF, and found significantly fewer LC and CD1a cells, differing from our results [19]. Could the skin biopsies they examined have been exposed to significant ultraviolet radiation, which can decrease the populations of these cells [20]? Most of our El Bagre EPF patient skin biopsies were taken from the chest, as well as our control biopsies.

Conclusion

Further studies are needed to clarify the precise contribution of each cutaneous APC subpopulation in antigen presentation and cutaneous immune response induction in these ABDs.

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DOI: 10.7241/ourd.20142.29

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EVALUATION OF THERAPEUTIC RESPONSE OF METHOTREXATE AND CALCIPOTRIOL COMBINATION COMPARED WITH METHOTREXATE ALONE IN *PLAQUE PSORIASIS*

Vasanthada Deepthi[1], PM Vasanth Kumar[2], Pasagadagula Krishna Rao[3], Tatapudi Ramesh[4], Malothu Ramesh[4]

[1]*UCEV-JNTUK, Vizianagaram Campus, A.P, India*
[2]*Department of Pharmacy, UCEV-JNTUK, Vizianagaram Campus, A.P, India*
[3]*Department of Dermatology Venerology and Leprosy, Andhra Medical College, Visakhapatnam, A.P, India*
[4]*Department of Biotechnology, UCEV-JNTUK, Vizianagaram campus, A.P, India*

Corresponding author: Dr. PM Vasanth Kumar *vasanthpharma@gmail.com*

Source of Support: Nil
Competing Interests: None

Our Dermatol Online. 2014; 5(2): 118-123 Date of submission: 29.11.2013 / acceptance: 06.02.2014

Abstract
Introduction: Psoriasis is a common chronic, non-contagious, immune mediated disease. Plaque psoriasis is characterized by thick, white, silvery or red patches on the skin. Plaque psoriasis mainly affects scalp, and palms of hands and soles of feet. T-cells are a type of immune system cells which protect the body from foreign substances. But during psoriasis T-cells activated at a great rate than normal, in turn release of cytokines increases as a result skin cells growing too quickly, moving to the surface to the skin and appear on the skin as dead cells.
Materials and Methods: Plaque psoriasis is common form of psoriasis, which mainly affects palms of hands and soles of feet and scalp. Out of 76 patients with plaque psoriasis we selected 50 patients based on PASI scores. Within the 50 patients, 32 patients with Palmoplantar psoriasis and 18 patients with scalp psoriasis. All 50 patients were subjected to randomized control trail, so each type of psoriasis is divided into two groups i.e. A and B. All A group patients were treated with MTX, whereas all B group patients were treated with combination of MTX and Calcipotriol. All necessary investigations like complete blood count, liver enzyme,creatinine, urea, alkaline phosphate, PASI were measured at 0, 2,4 6,8 weeks interval.
Results: We observed that, a significant reduction in PASI is observed with combination of MTX and Calcipotriol as compared to Methotrexate alone.
Conclusion: From the above study we concluded that, combination of MTX and Calcipotriolis more effective than MTX alone in plaque psoriasis.

Key words: Plaque psoriasis; Methotrexate; Calcipotriol; PASI

Cite this article:
Deepthi V, Vasanth Kumar PM, Krishna Rao P, Ramesh T, Ramesh M. Evaluation of therapeutic response of methotrexate and calcipotriol combination compared with methotrexate alone in plaque psoriasis. Our Dermatol Online. 2014; 5(2): 118-123.

Introduction

Psoriasis is a common chronic, non-contagious, immune mediated disease. Psoriasis is mainly five types; they are plaque, guttate, inverse, pustular, erythrodermic. The most common form, plaque psoriasis, is characterized by thick, white, silvery or red patches on the skin. Plaque psoriasis mainly affects the scalp, and the palms of the hands and the soles of the feet. T-cells are a type of immune system cells which protect the body from foreign substances. But during psoriasis T-cells activates at a great rate than normal, in turn releases cytokines, which increases rapidly [1,2]. These cytokines stimulate skin cells to reproduce and mature at a faster rate, as a result skin cells growing too quickly, moving to the surface of the skin and appear on the skin as dead cells.

Methotrexate is an anti folate, anti-metabolite drug, used in the treatment of auto immune diseases Methotrexate inhibits enzyme Dihydrofolatereductaseenzyme that involves in the production of tetrahydrofolate from dihydrofolate. As a result folic acid synthesis is inhibited, it is essential for DNA, RNA, and Thymidine synthesis. DNA, RNA, Thymidine are required for new cell growth and multiplication [3-5]. Methotrexate also inhibits T-cells activation.

Calcipotriol is a vitamin D analogue, upon topical administration which binds with vitamin D receptor (VDR). Vitamin D receptor is found on the cells of many different tissues of thyroid, Bone, kidney and T-cells of immune system. T-cells play a major role in psoriasis; calcipotriol binds with vitamin D receptors of T-cells, and modulate T- cells cell growth and differentiation.
Psoriasis is a complex disease, so combination therapy is beneficial that minimize risks [6-9]. Calcipotriol have anti-inflammatory, anti-proliferative, immunomodulatory properties. By using topical calcipotriol along with methotrexate reduces toxicities that associates with use of methotrexate as monotherapy, as well as calcipotriol also increases safety and efficacy of Methotrexate.

Material and Methods

I. Patient's information

In this study, 76 patients with plaque psoriasis attended to the skin O.P. department K.G.H. Visakhapatnam. We selected 50 patients based on the psoriasis area severity index (PASI) and all necessary laboratory investigations were performed for present study. Out of 50 patients, 33 (66%) were males and 17 (34%) were females, and patients age ranged between 20 to 65 years (Tabl. I).
Among the 50 patients, 32 patients with Palmoplantar psoriasis, 18 patients with scalp psoriasis. The extent of psoriasis was measured by using PASI scores (Tabl. II).

II. Grouping of patients

Grouping of patients is very essential, where each type of psoriasis is divided into two groups, based on Randomized control trail (RCT). By using Randomized control we can achieve equal groups and minimize errors. In this present study we selected Block type of randomized control trail (Tabl. III).

Sex	Male	33 (66%)
	Female	17 (34%)
Age	Minimum	25 years
	Maximum	60 years

Table I. Sex and Age incidence in psoriasis.

Type of psoriasis	No. of patients	Measuring scale
Palmoplantar psoriasis	32	PASI
Scalp psoriasis	18	PASI

Table II. Type of plaque psoriasis.

Palmoplantar psoriasis	Group-A	16
	Group-B	16
Scalp psoriasis	Group-A	9
	Group-B	9

Table III. Grouping of patients.

III. Drug and Dosage information

Methotrexate is administered orally to the patients with plaque psoriasis involving >10 psoriasis area severity index (PASI). Methotrexate has some adverse effects like nausea, abdominal pain, fatigue, fever, and 7.5mg of MTX given once in a week for palmoplantar and scalp psoriasis. Calcipotriol is vitamin-D analogue, applied topically to the affected areas. It is available as ointment form as well as solution form. For treatment of palmoplantar psoriasis, calcipotriol 50 µg/g ointment is applied twice daily topically, whereas for treatment of scalp psoriasis, calcipotriol 50 µg/ml scalp solution is applied twice daily topically. Information about drugs and dosage information was mentioned in the following table (Tabl. IV).

Drug	Dose and Route of administration	Type of dosage form	Nature of application	Plaque psoriasis
Methotrexate	7.5mg Oral	Tablet	Once weekly	Palmoplantar Scalp psoriasis
Calcipotriol	50 µg/g Topical	Ointment	Twice daily	Palmoplantar Psoriasis
	50 µg/ml Topical	Solution	Twice daily	Scalp psoriasis

Table IV. Drug and dosage information.

IV. Experimental Design

In this present study, 50 patients were subjected to all necessary investigations before and during administration of drugs. The investigations include PASI, Complete blood count and liver enzymes, creatinine, urea, alkaline phosphate. They are conducted every two weeks up to eight weeks. Here all group-A patients are treated with methotrexate, whereas all group-B patients were treated with combination of methotrexate and calcipotriol. The Complete information about PASI scores before drug administration are mentioned in the following table (Tabl. V).

			Mean PASI score	Drugs
Palmoplantar Psoriasis	Group-A	16	24.40	MTX
	Group-B	16	23.28	MTX+ Calcipotriol
Scalp psoriasis	Group-A	9	22.42	MTX
	Group-B	9	24.13	MTX+Calcipotriol

Table V. Experimental design.

V. PASI scores

The extent of psoriasis disease is measured by using PASI scales, PASI is used to measure palmoplantar and scalp psoriasis.

PASI scale is considered as gold standards for measurement of psoriasis, here total body is divided into four parts, and these are head, upper extremities, trunk, and lower extremities. The extent of erythema, thickness, and scales is measured for each organ and given scores range from 0-4. Area score is given for each organ based on the percentage of body organ affected with psoriasis and scores ranges from 0-6. The scale mentioned is as below (Tabl. VI).

	Head	Upper Extremities	Trunk	Lower Extremities
Redness				
Thickness				
Scale				
Sum	A1=	A2=	A3=	A4=
Area score	B1=	B2=	B3=	B4=
Multiply	A1×B1×0.1=C1	A2×B2×0.2=C2	A3×B3×0.3=C3	A4×B4×0.4=C4
Total	C1=	C2=	C3=	C4=

Table VI. PASI scores.

Redness, thickness, scale were given score range from 0-4.

Area score:

Score 1:<10%
Score 2: 10-<30%
Score 3: 30-<50%
Score 4: 50-<70%
Score 5: 70-<90%
Score 6: 90-<100%

PASI score: C1+ C2+ C3+ C4=

VI. Inclusion and Exclusion criteria

Inclusion criteria:

1. Patients with plaque psoriasis i.e. >10 PASI score
2. Patients must be suitable for systemic therapy and calcipotriol
3. Age of patients between 20 to 65 years

Exclusion criteria:

1. Patients with hypercalcemia.
2. Patients with previous history of liver diseases.
3. Patients with guttate, erythrodermic, inverse and pustular psoriasis.
4. Pregnancy and lactating women.

Results

Before starting the treatment each patient was evaluated with complete blood count, creatinine, urea, alkaline phosphatase, serum albumin, SGOT, SGPT and PASI score. During the treatment also these parameters were well monitored at 2, 4, 6, 8, week's interval. The entire information was mentioned in the following Table VII.

	Groups	Before drug treatmen, Mean values	Drug treatment	At 2 weeks	At 4 weeks	At 6 weeks	At 8 weeks	% reductionin PASIScores
Palmo plantar psoriasis	G-A	24.40	MTX	23.93	20.54	17.36	13.86	PASI 50
	G-B	23.28	MTX+ Calcipotriol	20.79	15.32	11.58	5.36	PASI 75
Scalp psoriasis	G-A	22.42	MTX	21.32	18.48	16.27	12.58	PASI 50
	G-B	24.13	MTX+Calcipotriol	20.83	16.51	12.86	5.42	PASI 75

Table VII. Reduction in PASI score in palmoplantar and scalp psoriasis.

From the above table, we have observed that 75% reduction in PASI score is achieved with combination of methotrexate and calcipotriol, whereas 50% reduction in PASI score is achieved with methotrexate alone. 75% improvement in PASI score was considered as endpoint for clinical trials.

Methotrexate is considered as well known drug for treating psoriasis. Psoriasis is a complex disease, so combination therapy was preferred to treat psoriasis. Methotrexate may combine with UVB, retinoids, PUVA, Vitamin D analogues for improving its efficiency, limiting side effects, reducing doses.

In this study methotrexate was combined with Vitamin D analogue, Calcipotriol. Methotrexate alone and its combination with calcipotriol were given for 8 weeks for palmoplantar and scalp psoriasis. Calcipotriol 50 µg/g ointment is applied topically twice daily for palmoplantarpsoriasis, whereas 50 µg/ml solution is applied topically twice daily for scalp psoriasis.

7.5mg of Methotrexate is administered once weekly alone to group A patients of palmoplantar, and scalp psoriasis, achieving PASI score between 50-75 % is 8 (32%) patients and < 50% is achieved in 13 (52%) patients, 4 (16%) patients were poor responders to methotrexate. Whereas combination of methotrexate and calcipotriol given for group B patients of palmoplantar and scalp psoriasis, achieving PASI scores, > 75% was achieved in 18 (72%) patients, between 50-75 % was achieved in 7 (28%) patients (Tabl. VIII).

We observed that an increased efficiency in patients who used the combination (MTX+ Calcipotriol) therapy than the methotrexate monotherapy. After treatment with methotrexate, investigations showed that no changes in complete blood count, SGOT, SGPT, alkaline phosphatase, creatinine, and serum albumin. In the present study we used low dose methotrexate, thereby side effects were minor, they were found in four patients, consisting of headache, nausea, skin itching and fever, whereas calcipotriol also produces some adverse effects in two patients, they are erythema, pruritus and burning.

PASI scores	Group-AMTX alone	Group-BMTX+ Calcipotriol
>75	0 (0%)	18 (72%)
50-75	8 (32%)	7 (28%)
<50	13 (52%)	0 (0%)

Table VIII. Number of patients within the PASI score range.

Discussion

Psoriasis is a complex disease; it is very difficult to treat with conventional therapy, in such case combination therapy is preferable to treat the disease (Fig. 1 and 2). During psoriasis skin cells grows too quickly and moves to the surface of the skin appears as dead cells. Psoriasis mainly occur due to cold weather, stress, alcohol drinking, smoking, hormones, cuts, tattoos, allergies, medication for high blood pressure, heart disease and psychiatric disorders.

In summer psoriasis undergoes remission and winter comes then relapse of psoriasis occur. Because sunlight having Ultra violet-A and Ultra violet-B rays. It may act as therapy for psoriasis. Some people suffering from psoriasis in summer more. Because sunlight acts as precipitating agent it may damage the skin.

M. Frincu et al. [10] Explained that, Combination of methotrexate and phototherapy has positive role as methotrexate doses are reduced, the administration time is reduced and the risk of occurrence of severe side effects, both blood and liver is low. A drawback of treatment with phototherapy was that the patient had to come almost every day to perform clinical cure with UV, with duration of at least one hour per day.

Treatment with methotrexate for four weeks cure psoriasis plaques, the same was explained by BL. Masuria et.al, [11] prior to the therapy, average involvement was 47.5% which after four weeks methotrexate therapy reduced to 8.3%. A complete clearing of psoriasis occurred in 40% of patients after methotrexate therapy. The clinical response started as early as 1 sore throat week in most of the patients.

PASI score was considered as more reliable tool for measurement of extent of psoriasis plaques. According to NeerajaPuri et al, [12] PASI score remains the most accepted and widely used measure in clinical trials. Reduction in PASI score indicates decrease in severity of psoriasis. PASI 75 means 75% reduction in symptoms of psoriasis, whereas PASI 50 means 50% reduction in symptoms of psoriasis. PASI 75 considered as meaningful end point for clinical trials.

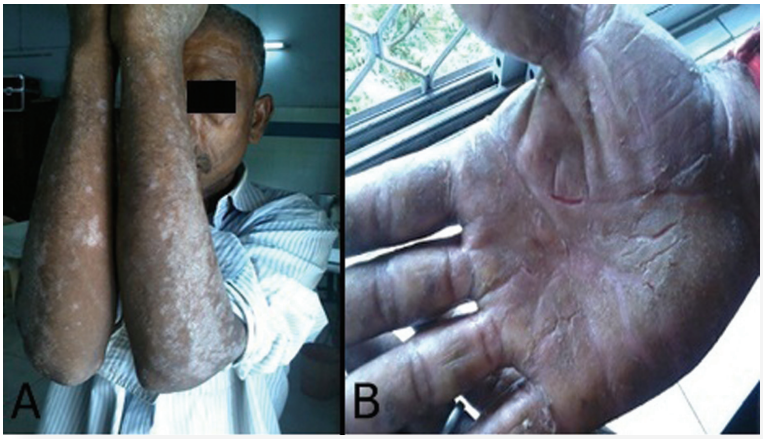

Figure 1A and B. The above picture shows the patient with psoriasis of palms of hands psoriasis.

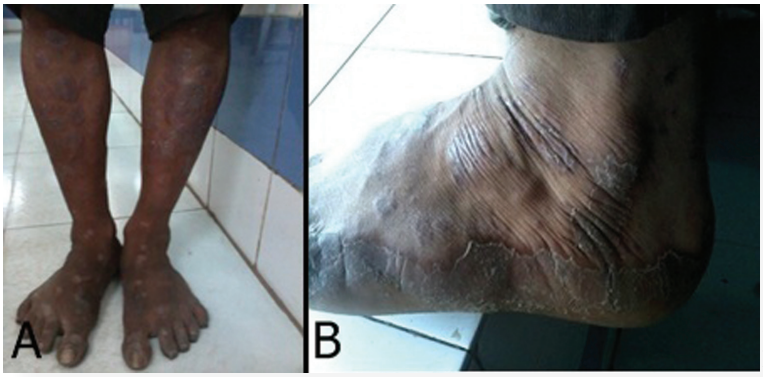

Figure 2A and B. The above picture shows the patients with psoriasis of soles of feet.

Combination therapy is more effective than methotrexate alone; methotrexate was combined with various topical agents, oral agents and phototherapy. According to de Jong et al. [13], Menter MA et al [14]. Combination treatment minimizes the side effects associated with methotrexate and also reduces dose of methotrexate. This combination therapy also minimizes time of exposure of drug.

According to PVS Prasad et al [15] thirty five patients admitted with psoriasis were analyzed. Sixteen patients received 20% crude coal tar and 19 patients received 20% crude coal tar along with Methotrexare in a weekly oral schedule (15mg/wk). After 4 weeks of therapy there was total clearance in 52.6% of the patients with combination therapy, whereas only 12.5% of the patients with conventional therapy achieved this. Chronic plaque psoriasis shows a high clearance rate if coal tar application is combined with oral methotrexate, than with the conventional coal tar alone.

According to Lin YK et al. [16] jerry Bajel et al. [17] topical vitamin D serves as a foundation, it increases safety and efficacy of all medications. There by topical vitamin D used in combination therapy with systemic agents and phototherapy. Vitamin D has immunomodulatory properties that decrease anti-microbial peptides in keratinocytes, which promotes inflammation process. It has anti-inflammatory and anti-proliferative properties. Vitamin D decreases toxicity associated with these drugs used as monotherapy.

Methotrexate is known as gold standard drug for treatment of psoriasis, Leung WY et al. [18] and Talwar S et al. [19] stated that; methotrexate is one of the well-established drugs for the treatment of moderate to severe psoriasis. Careful selection of patients, pretreatment evaluation and post treatment monitoring of methotrexate is essential because of its serious adverse effects of methotrexate. Folate is usually added to reduce the adverse effects of methotrexate. Liver biopsy remains the gold standard to detect the methotrexate related hepatic fibrosis and it is recommended in patients who have received a cumulative dose of 1.0-1.5 g.

Conclusion

From the above study, we concluded that combination therapy is more effective in treating psoriasis compared to methotrexate as monotherapy. Combination therapy increases efficacy, reduce side effects and decreases chances of relapse. PASI 75 is achieved with combination therapy (Methotrexate + Calcipotriol) whereas PASI 50 is achieved with methotrexate monotherapy. PASI 75 was considered as end point for clinical trials. So combination therapy is more effective in treating psoriasis compared to methotrexate as monotherapy. Hence combination (Methotrexate + Calcipotriol) therapy plays a major role in treating palmoplantar and scalp psoriasis.

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EVALUATION OF THERAPEUTIC RESPONSE OF METHOTREXATE AND CALCIPOTRIOL COMBINATION COMPARED WITH METHOTREXATE ALONE IN PLAQUE PSORIASIS

by Vasanthada Deepthi, PM Vasanth Kumar, Pasagadagula Krishna Rao, Tatapudi Ramesh, Malothu Ramesh

comment:

Ass. Prof. Antonio Chuh MD FRCP FRCPCH[1], Prof. Vijay Zawar MD DNB DV&D FAAD[2]
[1]*School of Public Health, The Chinese University of Hong Kong and Prince of Wales Hospital, Shatin, Hong Kong*
[2]*Department of Dermatology, Godavari Foundation Medical College and Research Center, DUPMCJ, India*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 124 Date of submission: 03.04.2014 / acceptance: 07.04.2014

Cite this article:
Antonio Chuh, Vijay Zawar. comment: Evaluation of therapeutic response of methotrexate and calcipotriol combination compared with methotrexate alone in plaque psoriasis. Our Dermatol Online. 2014; 5(2): 124.

We write to express our concerns on the adoption of only physician-rated outcome measurement, namely the Psoriasis Area and Severity Index, in this otherwise exceptionally well conducted randomised controlled trial, without the adoption of any patient-rated outcome variable, such as quality of life (QOL) indexes.

Skin diseases might cast very significant impacts on the quality of life of patients. However, symptoms and impacts on the QOL are known to be not necessarily correlate directly with disease severity as rated by physicians for skin diseases [1, 2], including psoriasis vulgaris [3].

QOL indexes, such as the Dermatology Life Quality Index [4] and the Children Dermatology Life Quality Index [5], have been constructed, validated, and validly translated into a large number of languages [1, 6, 7]. A vast range of skin disease-specific instruments from acne vulgaris [8] to autoimmnune bullous diseases [9] is also available. Treatment options would be tailored-made for individual patients based on such evaluations. For psoriasis specifically, it has been recommended that Psoriasis Area and Severity index and Dermatology Life Quality Index should be measured at the same frequency in daily clinical practice [10].

As for clinical trials, it has been found that the high-quality Cochrane systematic reviews in skin diseases included significantly more QOL as outcome measures than non-Cochrane non-Cochrane systematic reviews [11]. Moreover, Cochrane skin reviews usually adopt QOL indexes as primary outcome measures in randomised controlled studies.

We therefore cast hopes that future clinical trials on psoriasis and other skin diseases would incorporate QOL measurements as outcome measures, so that the symptoms, the impacts on daily activities and self image, and the negative impacts exerted by treatments could be validly and reliably compared for different therapeutic approaches.

Lastly, we congratulate the success of Vasanthada D et al again in reporting this study which will affect treatment decisions for patients with psoriasis vulgaris necessitating systemic immunosuppressive therapies.

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DOI: 10.7241/ourd.20142.30

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HLA-DPDQDR IS EXPRESSED IN ALL LESIONAL SKIN FROM PATIENTS WITH AUTOIMMUNE SKIN DISEASES

Ana Maria Abreu Velez[1,3], Juliana Calle-Isaza[2], Michael S. Howard[1]

[1]*Georgia Dermatopathology Associates, Atlanta, Georgia, USA*
[2]*Clinic El Poblado, Medellin, Colombia, South America*
[3]*Department of Dermatology, School of Medicine, University of Antioquia, Medellin, Colombia, South America*

Corresponding author: Prof. Ana Maria Abreu Velez *abreuvelez@yahoo.com*

Source of Support:
Georgia Dermatopathology Associates, Atlanta, Georgia, USA (MSH, AMAV); Mineros SA, Medellin, Colombia, SA; Embassy of Japan in Colombia, Medellin; University of Antioquia, Medellin
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 125-128 Date of submission: 14.02.2014 / acceptance: 28.03.2014

Abstract
Introduction: Human genes responsible for human antigen presentation and transplant rejection functions are located on the short arm of Chromosome 6 and are called the Major Histocompatibility Complex (MHC). Moreover, the primary physiologic function of MHC molecules is to present peptides to T lymphocytes. MHC molecules are integral components of the ligands that most T cells recognize, since the T cell receptor (TCR) has specificity for complexes of foreign antigenic peptides, as well as self-MHC molecules.
Aim: Our investigation attempts to investigate the presence of HLA-DPDQDR within lesional skin biopsies from patients affected by autoimmune skin blistering diseases (ABDs).
Materials and Methods: We utilized immunohistochemistry (IHC) to evaluate the presence of HLA-DPDQDR in lesional skin biopsies of patients affected by ABDs. We tested 30 patients with endemic pemphigus foliaceus (EPF), 15 controls from the EPF endemic area, and 15 biopsies from healthy controls from the USA. We also tested archival biopsies from patients with selected ABDs, including 30 patients with bullous pemphigoid (BP), 20 with pemphigus vulgaris (PV), 8 with pemphigus foliaceus (PF), 14 with dermatitis herpetiformis (DH) and 2 with epidermolysis bullosa acquisita (EBA).
Results: Most ABD biopsies stained positive for HLA-DPDQDR in the lesional blisters and/or inflamed neurovascular plexus in the superficial dermis, and also at mesenchymal-endothelial like-cell junctions in the dermis. In BP, EBA and EPF, the HLA-DPDQDR staining was also seen in the dermal eccrine sweat gland coils and and ducts.
Conclusion: Here, we document that HLA-DPDQDR is expressed in several anatomic areas of lesional skin in patients with ABDs. Notably, HLA-DPDQDR positivity was also consistently present in areas of the classic immune response in pemphigus epidermal keratinocytic intercellular junctions, and at basement membrane sites in bullous pemphigoid and other subepidermal blistering diseases.

Key words: HLA-DPDQDR; autoimmune skin diseases; endemic pemphigus foliaceus

Abbreviations: Bullous pemphigoid (BP), pemphigus vulgaris (PV), pemphigus foliaceus (PF), dermatitis herpetiformis (DH), epidermolysis bullosa acquisita (EBA), immunohistochemistry (IHC), direct and indirect immunofluorescence (DIF and IIF), hematoxylin and eosin (H&E), basement membrane zone (BMZ), intercellular staining between keratinocytes (ICS), pemphigus vulgaris (PV), autoimmune blistering skin diseases (ABDs), endemic pemphigus foliaceus in El-Bagre, Colombia (El Bagre-EPF), Human Leukocyte Antigen (HLA), Major Histocompatibility Complex (MHC), T cell receptor (TCR).

Cite this article:
Abreu Velez AM, Calle-Isaza J, Howard MS. HLA-DPDQDR is expressed in all lesional skin from patients with autoimmune skin diseases. Our Dermatol Online. 2014; 5(2): 125-128.

Introduction

The Major Histocompatibility Complex (MHC) is central to the adaptive immune response [1]. One of the most polymorphic genetic systems, the Human Leukocyte Antigen (HLA) system is divided into Class I (HLA-A, B and C) and Class II (HLA-DP, DQ and DR) molecules [1-3]. HLA-DP, DQ, and DR represent three differing isotypes, each being highly polymorphic [1-3]. Different HLA-DP variants can be protective, or alternatively, risk factors for infectious diseases, immune dysfunction, and autoimmunity [1-3]. Few studies have investigated the presence of HLA Class II in lesional skin from patients affected by ABDs [4-6].

Our present investigation attempted to study the presence of the HLA-DP, DQ, and DR in multiple ABDs by performing immunohistochemistry (IHC) stains on lesional skin biopsies.

Material and Methods

Subjects of study

We tested 30 biopsies from patients affected by EPF in El Bagre, Colombia, South America (El Bagre-EPF) and 15 normal controls from the endemic area [3-5]. We also utilized 15 control skin biopsies from plastic surgery reduction patients in the USA, taken from the chest and/or abdomen. We also studied 15 biopsies from healthy controls from the USA. We tested archival biopsies from patients with selected ABDs, including 30 patients with bullous pemphigoid (BP), 20 with pemphigus vulgaris (PV), 8 with pemphigus foliaceus (PF), 14 with dermatitis herpetiformis (DH) and 2 with epidermolysis bullosa acquisita (EBA). Biopsies were fixed in 10% buffered formalin, then embedded in paraffin and cut at 4 micron thicknesses. The tissue was then submitted for hematoxylin and eosin (H&E) and IHC staining, performed as previously described [7-11]. In addition, we also tested biopsies from the archival files of two private, board certified dermatopathology laboratories in the USA; these patients underwent primary diagnostic biopsies, and were not taking immunosuppressive therapeutic medications at the time of biopsy. We evaluated 20 biopsies from bullous pemphigoid (BP) patients, 20 from patients with pemphigus vulgaris (PV), 8 patient biopsies with pemphigus foliaceus (PF), 12 from patients with dermatitis herpetiformis (DH) and 3 from epidermolysis bullosa acquisita. For all of the El Bagre area patients and controls, we obtained written consent, as well as Institutional Review Board permission from the local hospital. The archival biopsies were IRB exempt due to the lack of patient identifiers. In both dermatopathology laboratories, each biopsy also was sent for direct immunofluorescence performed as previous described [7-11], for correlation with the H&E diagnoses.

IHC staining

The staining of the antibodies was evaluated utilizing hematoxylin-counterstained histologic sections. IHC staining was performed as previously described [7-11]. For IHC, we utilized a Dako monoclonal mouse anti-human HLA-DP, DQ, and DR Clone CR3/43 antibody.

Statistical analysis

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

Results

Among patients with El Bagre EPF, 23/30 exhibited positive staining in the upper dermal neurovascular vessels and perivascular inflammatory infiltrates with a significance of $p<0.05$. Also, positivity was seen around the neurovascular supply structures of sebaceous glands, and around dermal blood vessels surrounding eccrine ducts (Fig. 1 - 3). Only two controls from the endemic area displayed positive staining, specifically in some upper dermal perivascular infiltrates ($p<0.05$); controls from the USA stained uniformly negative ($p<0.05$). Among BP patients, 18/20 stained positive for HLA-DP, DQ and DR in neurovascular packages around dermal eccrine gland ducts. Positivity was also noted under subepidermal blisters, along the bases of the blisters and within dermal endothelial/mesenchymal cell junction-like structures, especially in the middle dermis ($p<0.05$). In PV patients, 14/20 stained positive within upper dermal perivascular infiltrates, above intraepidermal blisters and around dermal eccrine gland ducts ($p<0.05$) (Fig. 1 - 3). In patient biopsies with PF, 6/8 stained positive within the epidermal stratum granulosum, and around neurovascular packages around eccrine ducts. Among patients with DH, 9/12 exhibited positive staining, primarily under subepidermal blisters, as well as in superficial dermal perivascular infiltrates ($p<0.05$). The 3 cases of EBA stained positive around blood vessels in the middle and upper dermis, with some staining in eccrine sweat glands and in the areas of inflammation below the blisters (Fig. 1 - 3). Figure 1 documents the most common patterns of HLA-DP, DQ, and DR staining positivity found in the patients with ABDs. Please also notice focal cells with positive staining in the epidermis of most of the ABDs.

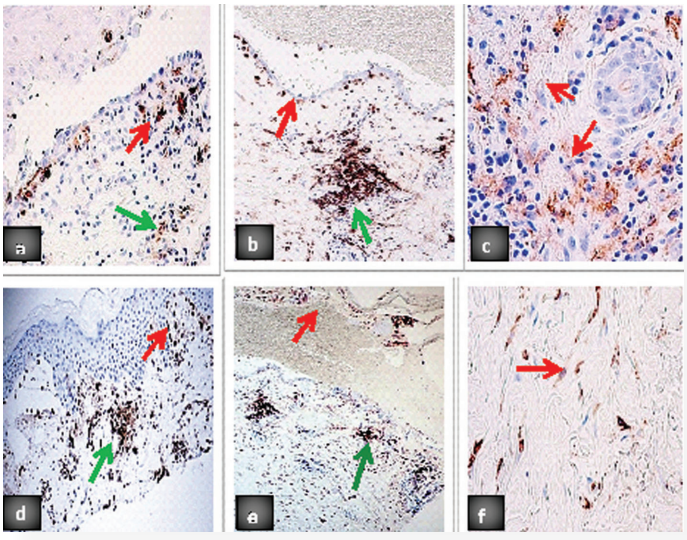

Figure 1. a and **b**. HLA-DP, DQ and DR positive staining, under an intraepidermal blister in a case of PV (brown staining; red arrows), as well as around upper dermal blood vessels (brown staining; green arrows). **c.** HLA-DP, DQ and DR positive staining in a BP case, accentuated around dermal neurovascular bundles around an eccrine gland duct (brown staining; red arrows). **d.** A representative case of DH, demonstrating positive staining to HLA-DP, DQ, and DR in a sub epidermal blisters (brown staining; red arrow) as well as around an upper dermal neurovascular plexus (brown staining; green arrow). **e.** A case of PV, positive for HLA-DPDQDR above an intradermal blister (brown staining; red arrow), as well as around upper dermal blood inflammatory vessels (brown staining; green arrow). **f.** A PV case, with positive HLA-DPDQDR staining on cell junction-like structures between cells of the dermal extracellular matrix (brown staining; red arrow).

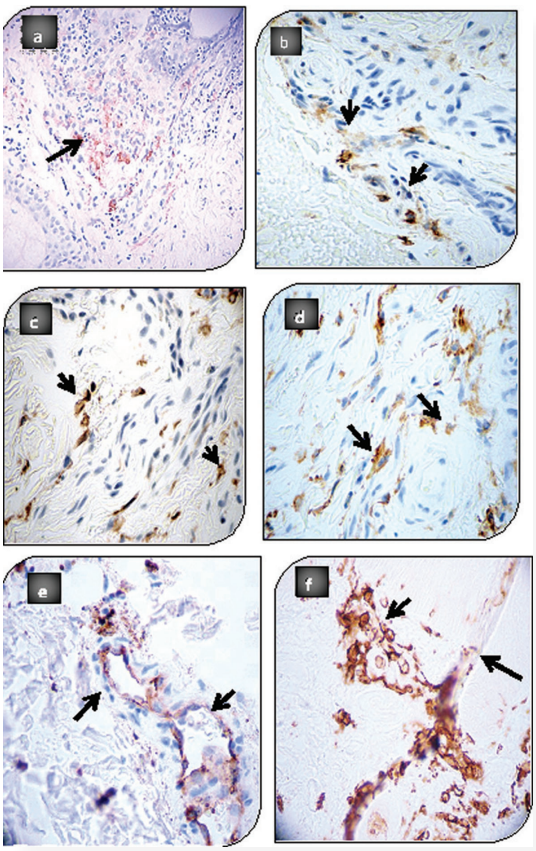

Figure 2. a. A DH case, with positive HLA-DP, DQ, and DR staining around the upper neurovascular plexus subjacent to the blister(brown staining; black arrow). **b** and **c**, A BP case demonstrating positive staining in b at the deep dermal neurovascular plexus, and in c around eccrine ducts (brown staining; black arrows). **d** and **e**, A case of EBA, with positive HLA-DP, DQ, and DR staining in the upper dermal neurovascular plexus of the skin in d, and in e around dermal blood vessels and eccrine glands (brown staining; black arrows). 2. **f** A DH case with positive HLA-DP, DQ, and DR staining in the upper dermal neurovascular plexus and ecrine ductus (brown stain). In this case we didn't use hematoxylin counterstain.

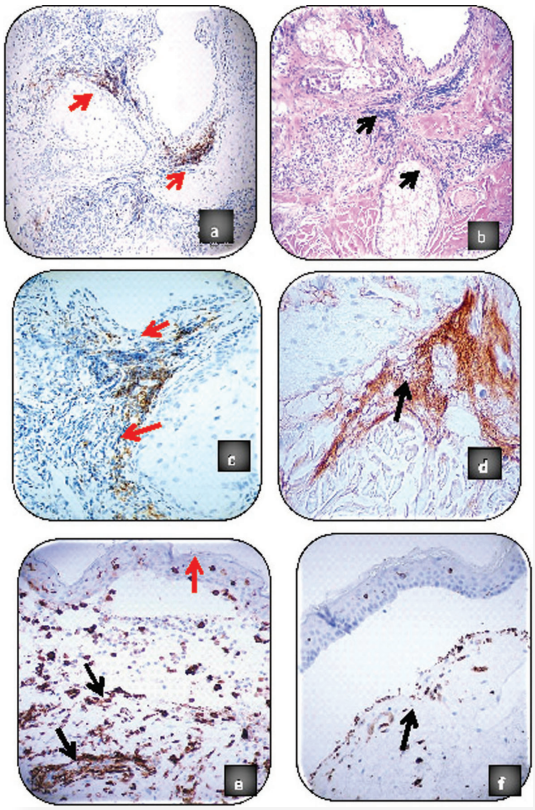

Figure 3. a. A PV case, demonstrating positive staining with HLA-DP, DQ, and DR around dermal neurovascular packages below the blister (brown staining; red arrows) (200X). **b**. Same case as in a; H&E staining of the section confirms a correlating lymphohistiocytic infiltrate, present among neurovascular packages that feed the sebaceous glands (black arrows). **c.** Same case as in a-b, with positive HLA-DP, DQ, and DR staining around dermal neurovascular packages supplying pilosebaceous units (brown staining; red arrows) (100X). **d.** The same case as in a-c, demonstrating positive staining with anti-Complement/C3c against dermal neurovascular packages (brown staining; black arrow) (400X). **e.** An EBA case, with positive staining on epidermal cells above the blister (brown staining; red arrow) and also around dermal blood vessels (brown staining; black arrows). **f.** A BP case, with generally linear staining under the blister along the basement membrane zone (brown staining; brown arrow), and around dermal blood vessels (brown staining; black arrow). Please also note positive staining on some cells in the epidermis.

Discussion

Several previous studies, often utilizing serum, have addressed the HLA haplotype distribution utilizing ABD cases and controls [5,6,12-15]. These studies concluded that some HLA alleles strongly predispose toward and/or protect against ABDs.

Antibodies against HLA-DPDQDR principally label B lymphocytes, lymph node interdigitating reticulum cells, Langerhans cells and non-Langerhans macrophages. The specific antibody we utilized is known to react with the alpha and beta-chains of all products of the DP, DQ and DR subregions.

Our study is one of the few demonstrating the presence of cells carrying appropriate molecules to react in situ with this antibody to multiple HLA Class II antigens. Our study also demonstrates that antigen recognition, and possibly also the active immune response, does not only occur solely in blister areas in pemphigus and/or pemphigoids, as traditionally thought.

These processes also likely occur in other areas where we have previously shown ABD immune reactivity and cell signaling, specifically areas staining positive for ribosomal protein S6-ps240, cyclo-oxygenase 2, proteases and protease inhibitors. These areas specifically include neurovascular supplies to multiple skin appendageal structures, eccrine gland coils and ducts, and mesenchymal/endothelial cell junction-like structures in the dermis [16-21].

Conclusion

The full significance of our findings is unknown. Future research is needed to confirm and expand our research findings, and to address specific reasons for HLA-DP, DQ, and DR positivity in cases of ABDs.

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DOI: 10.7241/ourd.20142.31

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TOLL 7 AND TOLL 9 IN *PSORIASIS VULGARIS* BEFORE AND AFTER PHOTOTHERAPY

Doaa Mahgoub[1], Amira M. El Tawdy[1], Mariam Makari[1], Laila Rashed[2]

[1]*Department of Dermatology, Kasr Aini Hospital, Cairo University, Egypt*
[2]*Department of Biochemistry, Kasr Aini Hospital, Cairo University, Egypt*

Corresponding author: Dr. Amira El Tawdy *amiratawdy@gmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 129-134 Date of submission: 04.02.2014 / acceptance: 28.03.2014

Abstract
Introduction: Psoriasis is a common chronic inflammatory, recurrent, immune mediated disease of the skin and joints. Toll-like receptors are pattern recognition receptors for conserved molecular patterns of pathogenic microorganisms.Under certain circumstances, self nucleic acids can trigger TLR 7 and TLR 9, which can lead to autoimmune diseases such as psoriasis.
Materials and Methods: The study included 15 psoriatic patients (plaque type) and 15 controls, patients received 36 sessions of phototherapy (NB-UVB). Skin biopsies were taken from all the patients (before & after NB-UVB) and controls and were assessed for TLR 7 and TLR 9 by PCR.
Results: Showed significant difference between patients and controls as regards TLR 7 and TLR 9. In addition a significant decrease in thier levels in patients after phototherapy with NB-UVB.
Conclusion: TLR 7 and TLR 9 may play a role in the pathogenesis of poriasis. Decrease in their levels after NB-UVB may be one of the therapeutic mechanisms of NB-UVB in psoriasis.

Key words: Psoriasis; Toll-like receptors 7 and 9; NB-UVB

Cite this article:
Mahgoub D, El Tawdy AM, Makari M, Rashed L. Toll 7 and Toll 9 in psoriasis vulgaris before and after phototherapy. Our Dermatol Online. 2014; 5(2): 129-134.

Introduction

Toll-like receptors are a recently identified group of pattern recognition receptors (PRRs) that recognize distinct conserved microbial components and permit cells to recognize self from non-self in immune activation [1]. By far, ten different receptors have been identified and have unique tissue distribution, ligand binding properties, cellular signaling pathways, and cytokine production profiles. A subgroup of TLRs, namely TLR3, 7, 8, and 9, are located within the cell in endosomal compartments and recognize pathogen derived nucleic acid components [2].
Psoriasis is a chronic inflammatory skin disease mediated by T cells, which trigger keratinocytes to hyperproliferate and perpetuate the disease. Psoriasis has been associated with Th-1 and Th-17 cytokine profiles [3], and angiogenesis. Inappropriate recognition of self-nucleic acids in addition to type I IFNs (IFN-α/β) production by plasmacytoid DCs (PDCs) can lead to psoriasis. PDCs are an important cell population in this condition, because they are 16% of the total dermal infiltrate in psoriatic skin lesions whereas they are nonexistent in normal skin [4]. PDCs and B cells express high levels of TLR 7 and 9 [5,6]. Thus it is possible that abberent expression of both TLR7 and 9 could contribute in the pathogenesis of psoriasis vulgaris. Narrow-band UVB radiation (NB-UVB) therapy offers a well-established treatment modality for psoriasis. However, despite the common use of this form of treatment, the mechanism of action of NB-UVB in psoriasis is not well understood [7]. UVB radiation is a potent immunosuppressive agent that inhibits cell-mediated immune responses. The mechanisms by which UVB radiation influences cell-mediated immune responses have been the subject of extensive investigation. However, the role of innate immunity on photoimmunological processes has received little attention.
The aim of the present study was to find out the effect of NB-UVB on the expression of TLR9 and TLR7 gene expression ` in psoriatic skin, in an attempt to add another possible mechanism of action by which NB-UVB improves psoriatic lesions.

Material and Methods

Patients

The current study was conducted on 15 patients (8 females and 7 males) suffering from psoriasis vulgaris (chronic plaque type). Their age ranged from 14-63 years. They were selected from the outpatient clinic of the Dermatology Department, Faculty of medicine, Cairo University from July 2011 till July 2012, with lesional extent ranging from 20-80%. The duration of the treatment was 3 months (36 sessions) for each patient. An informed consent was signed by each patient and ethical committee approval was fulfilled before the start of the study.
Diagnosis was done on clinical basis and confirmed by skin biopsy.

Inclusion criteria:

· Patients over 12 years.
· Either male or female.
· Psoriasis vulgaris

Exclusion criteria:

· Children less than 12 years old.
· Pregnant and lactating females.
· Patients with systemic diseases e.g. hepatic, renal, and cardiac diseases.
· Erythrodermic and pustular psoriasis (only patients with psoriasis vulgaris).

Before initiation of therapy, each patient was subjected to the following:

I. History taking:

A) Personal history: (name, age, sex, weight, residence (far residence decreases patient's compliance), occupation (sun exposed or not), pregnancy, lactation and any special habits of medical importance).
B) Present history: (onset, course and duration of psoriasis).
C) Precipitating factors:
e.g infection, psychic stress or trauma ,drugs, such as; steroids, β blockers, lithium, antimalarials or nonsteroidal anti-inflammatory drugs. Photosensitizers, such as; tolbutamide, sulfonamides, tetracycline, griseofulvin, phenothiazides or others.
D) Previous treatment and any past history of medical importance
F) Associated disease:
Such as: vitiligo, diabetes mellitus, arthritis or others.
G) Family history:
Psoriasis, vitiligo, arthritis, diabetes mellitus, or others.

II. Examination and investigations:

· Skin examination: to determine the distribution, clinical variant, skin type and extent of psoriasis.
· PASI score was calculated for each patient. The PASI score includes assessment of erythema, infilteration, desquamation and extent of lesions [8].
· Ophthalmologic examination by slit lamp: to exclude lens opacity.

Patients who were treated before by topical treatment (had stopped it 2 weeks) before starting the phototherapy, and those who were treated before by systemic treatment had stopped the last treatment one month before starting the phototherapy.

Control group:

A control group of 15 healthy individuals (age and sex matched with the patient group) with no history of skin or autoimmune diseases, were included in our study.

Methods

Skin Biopsies:

· Two 5mm punch skin biopsies were taken from all the patients, one before treatment and the other after 36 sessions of phototherapy and only one biopsy was taken from each control.
· On taking the biopsy, one half portion of the biopsy specimen was fixed in formalin solution and the other half of the specimen was kept frozen in an empty epindorphe for PCR studies.
The patients received NB-UVB (36 sessions) three times per week (for 3 months).

UVB light:

UVB light was delivered by a UV cabin (waldmann) equipped with an integrated UV photometer equipped with 13 TL-01/100 w fluorescent lamps producing a narrow band UVB peak emission at 311nm.

Dosing schedule:

· The initial UVB dose was 70% of the minimal erythema dose for all skin types.
· The dose of UVB was increased by 20% of the last dose every other session.

Duration of the study:

The study was conducted for 3 months so that the maximum number of sessions was 36 sessions (patients comes 3 times/ week). However, patients showing complete clearance (complete disappearance of all lesions with residual hypo- or hyperpigmentation) before 3 months were biopsied and assessed for TLR 7 and 9 by RT-PCR.

Detection of TLR7 and TLR9 gene expression by Polymerase Chain Reaction (PCR):

Detection of TLR7 and TLR9 by semiquantitative reverse transcriptase- polymerase chain reaction (RT-PCR).
For the detection of TLR7 and TLR9, RNA was extracted, reversely transcribed into cDNA, and amplified by PCR.

Detection of TLR7&TLR9 Gene Expression Level by Real-Time PCR

Total RNA Extraction.

Total RNA was isolated from skin tissue homogenates using RNeasy Purification Reagent (Qiagen, Valencia, CA) according to manufacturers instruction . The RNA sample was dissolved in RNase-free water and. RNA quantity was characterized using a UV spectrophotometer (Beckman, USA), the isolated RNA has an A 260/280 ratio of 1.9–2.1. The integrity of the RNA was studied by gel electrophoresis on a 1% agarose gel, containing ethidium bromide.

cDNA Synthesis

First-strand cDNA was synthesized from 1 μg of total RNA by reverse transcription with a superscript first-strand synthesis system kit (Life Technologies, Breda, the Netherlands) according to according to manufacturers instruction.

Real-time quantitative polymerase chain reaction (PCR)
The sequences of the PCR primers for TLR7&TLR9 and the housekeeping gene glyceraldehydes-3- phosphate dehydrogenase (GAPDH) are listed in Table I. PCR was carried out in a reaction mixture containing iQTM SYBR Green Supermix (Bio Rad Laboratories, CA, USA) and cDNA template. The PCR was performed in an Step one plus Real-Time PCR system (AppliedBiosystems) using the following cycle parameters of 95°C for 10 min (1 cycle), 94°C for 15s, and 60°C for 1min (40 cycles). Data were analyzed with system software and quantified using the v1·7 Sequence Detection Software from PE Biosystems (Foster City, CA). Relative expression of studied genes was calculated using the comparative threshold cycle method. All values were normalized to the GAPDH genes (Tabl. II).

Number of patients	Toll-9		Toll-7	
	Before	After	Before	After
1	1.3	0.9	1.74	1.06
2	1.06	0.92	0.81	0.4
3	1.04	0.68	0.99	0.27
4	2.7	1.04	1.9	0.6
5	1.9	0.73	1.6	0.43
6	2.01	1.2	1.4	0.66
7	1.12	0.96	0.88	0.28
8	1.8	0.42	1.2	0.35
9	2.03	1.5	1.4	0.47
10	1.2	0.46	0.73	0.51
11	2.6	1.02	1.9	1.04
12	2.8	0.8	2.06	1.5
13	1.2	0.4	1.6	0.8
14	2.7	0.6	2.01	1.6
15	2.4	0.49	2.06	0.59

Table I. Levels of both Toll-9 and Toll-7 in patients before and after NB-UVB sessions.

Primer	Sequence
TLR7	Forward primer : 5′- AAACTCCTTGGGGC-TAGATG -3′Reverse primer:5′- AGGGT-GAGGTTCGTGGTGTT -3according to gene bank accession numberNM_016562.3
TLR9	Forward primer : 5'- CGCCCTGCACC-CGCTGTCTCT -3'-Reverse primer:5'-C G G G G T G C T G C C A T G G A G A A G -3'according to gene bank accession num-berNM_017442.3
GAPDH	Forward 5′ GGATTTGGTCGTATTGGG 3′Reverse 5′ GGAAGATGGTGATGGGATT 3' according to gene bank accession number DQ403057.1

Table II. Primer sequences used for RT-PCR.

Statistical Methods
Data were statistically described in terms of range, means ± standard deviation (± SD), median, frequencies (number of cases) and percentages when appropriate. Comparison of TLR 9 and TLR 7 pre and post between cases and controls was done using Mann Whitney U test for independent samples. Comparison between pre and post treatment values was done using Wilcoxon signed rank test for paired (matched) samples. A probability value (p value) less than 0.05 was considered statistically significant.Correlation between various variables was done using Pearson correlation equation for linear relation. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the social science; SPSS; Inc., Chicago, IL, USA) statistical program.

Results
Clinical data
The current study included 15 patients with psoriasis vulgaris and 15 healthy individuals serving as a control group. The patient group included 8 females (53.33%) and 7 males (46.67%). Their ages ranged from 14 to 63 years with a mean of 35.13 ± 16.10 years. The duration of the disease ranged from 1 to 35 years with a mean of 8.3 ± 8.5 years. The mean value of PASI score was15.60 + 7.31 before therapy which was reduced significantly after therapy to be 7.5 + 3.5.

TLRs values before therapy (Fig. 1)
The mean value of Toll-like receptor-9 in patients before treatment with NB-UVB was (1.85 + 0.66 µg/dl) which was higher than that of controls (0.23 + 0.005 µg/dl), with a significant P value (P value 0.001).
On the other hand, the mean value of Toll-like receptor-7 in patients before treatment with NB-UVB was (1.48+0.47 µg/dl) and when compared to that of controls (0.13+ 0.002 µg/dl), it also showed higher levels with a significant P value (P value 0.001).

After NB-UVB sessions
On comparing the mean value of TLR-9 after treatment with NB-UVB (0.80 ± 0.31) and that of controls (0.23 ± 0.005), still higher levels were detected in the patients with a significant P value (0.002).

In addition on comparing the mean value of TLR-7 after treatment with NB-UVB (0.70 ± 0.41) and that of controls (0.13 ± 0.002), still higher levels in the patients were detected with a significant P value (0.001). There was a significant decrease of the mean levels of both TLR-9 and 7 after therapy when compared to their levels before therapy (P value 0.001) (Tabl. I).

No significant correlation was detected between levels of both TLR 7 & TLR9 (before and after therapy) and any of the clinical data of the patients (age, sex, extent, severity and duration).

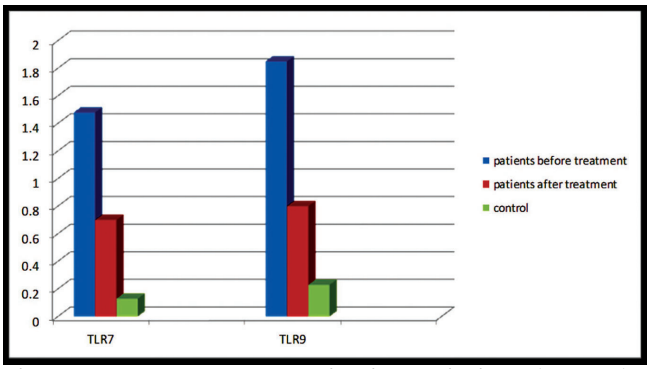

Figure 1. PPARγ gene expression in psoriasis and control.

Discussion

The current study showed significant higher levels of both TLRs 9 and 7 genes in psoriasis vulgaris patients compared to healthy individuals. Besides a significant reduction of their levels was reported after NB-UVB therapy of the same patients. Psoriasis is considered to be a genetically determined disease of dysregulated inflammation, which is driven and maintained by multiple components of the immune system. The pathologic collaboration between innate immunity (mediated by antigen-presenting cells and natural killer T lymphocytes) and acquired immunity (mediated by T lymphocytes) results in the production of cytokines, chemokines, and growth factors that contribute to the inflammatory infiltrate seen in psoriatic plaques [9].

Toll-like receptors are a recently identified group of pattern recognition receptors (PRRs) that recognize distinct conserved microbial components and permit cells to recognize self from non-self in immune activation [1]. There is a growing interest in the role of innate and adaptive immunity in inflammatory diseases such as psoriasis [10]. It is conceivable that certain microorganisms could induce or exacerbate psoriasis through activation of keratinocyte TLRs (innate immunity), leading to the secretion of cytokines which activate the acquired immunity by effects on T cells, antigen presenting cells and endothelial cells [11].

Another study [12], demonstrated that human keratinocytes constitutively express mRNA for TLR1, 2, 3, 4, 5, 6, 9, and 10, but not for TLR7 or 8, confirming previously published studies on the expression of TLR1, 2, 3, 4, 5, and 9 in keratinocytes [13-15]. However, both TLR7 and 8 expression was proved to be achieved by plasmacytoid DCs and monocyte-derived DC in the same study [12].

In addition, others demonstrated that plasmacytoid pre-DCs and B cell express high levels of TLR 7 and 9 [5,6]. PDCs are an important cell population in psoriatic skin lesions, because they constitute 16% of the total dermal infiltrate. Whereas they are nonexistent in the normal skin [4].

The aim of the present study was to find out the effect of NB-UVB on the expression of TLR9 and TLR7 in psoriatic skin, so that we may add another possible mechanism of action by which NB-UVB improves psoriatic lesions.

Our results showed that the mean values of both TLR9 and TLR7 were significantly higher in patients before therapy compared with controls.

Some investigators studied the expression of TLR9 alone in psoriatic patients and found also similar results as Miller et al. [16] who demonstrated an increased expression of TLR9 throughout the epidermis in psoriatic patients. Based on the immunoperoxidase labeling for TLR9, they concluded that the level of expression of TLR9 may depend upon the differentiation stage of the keratinocytes as they mature from the basal layer in the epidermis. They reported that the growth and differentiation factor, TGF-α, which is important during wound healing and is found at increased levels in psoriasis, regulates the expression and function of TLR9 on human keratinocytes.

Moreover, others [3] demonstrated that, keratinocytes from psoriatic plaques express high levels of TLRs 1, 2, 4, 5, and 9, compared with normal skin.

The results of the present study differ from others [17,18] who reported the low expression of TLR9 in psoriatic lesions compared to normal skin.

As far as we know, no previous studies investigated the expression of TLR7 in psoriatic lesions. However some studies [3,4] observed aggravation and spreading of a psoriatic plaque when treated topically with the toll-like receptor (TLR) 7 agonist imiquimod. The exacerbation of psoriasis was accompanied by a massive induction of lesional type I interferon activity.

Furthermore, they found large numbers of PDCs infiltrated psoriatic skin as well, which play as a target for the TLR7 agonist (imiquimod) and hence producing interferon I that augments more the psoriatic lesionss. Those findings support as well the results of the present study verifying the presence of high levels of TLR7 in lesional skin compared to the control.

The use of PCR technique in the current study, did not enable us to detect the exact source of producing such receptors.

It only showed us the upregulation of TLRs 7 and 9 genes in psoriatic skin.However previous studies confirmed the production of both receptors by pDCs and B cells [5,6]. In addition keratinocytes express as well TLR-9 as verified by others [3].

Regarding the possible role played by the abnormal expression of TLRs-7,9 several studies stated that the inappropriate recognition of self-nucleic acids (self-DNA and ssRNA) by both receptors, pushed them to bind to the antimicrobial peptide LL-37 to form aggregated and condensed structures (DNA/LL-37 and RNA/LL-37) which are delivered to and retained within early endocytic compartments in pDCs leading to pDC activation [19,20], and trigger type I IFN production. Type I IFNs produced by pDCs support myeloid dendritic cell maturation and eventual autoreactive T cell activation leading to psoriatic skin lesions [21].

Owing to our findings and previous data results (mentioned above) we suggest that TLRs 7 and 9 have an important impact on the pathogenesis of psoriasis and possibly explaining the role of autoimmunity that is probably involved to induce the psoriatic lesions.

NB-UVB phototherapy is an effective treatment for psoriasis. Owing to its limited penetration, the direct effect of UVB is mostly restricted to cells residing in the epidermis and papillary dermis, and is associated with depletion of epidermal LCs and T cells [22]. To the best of our knowledge no pervious studies investigated the effect of nb-UVB on the expression of TLR7 and TLR9.

In the current study we compared the mean value of both TLR9 and TLR7 in patients before and after phototherapy. Both mean values of TLR9 and TLR7 after therapy were still higher than controls yet they showed significant reduction following thirty six sessions of nb-UVB phototherapy.

One study [23] reported that UVB radiation induces the up-regulation and secretion of endogenous Toll-like receptor ligands such as Heat Shock Proteins (HSPs) from the UV-exposed keratinocytes. These secreted stress signals are transmitted via Toll-like receptors 2 and 4 in an autocrine-paracrine manner, activating the Toll-IL-1 receptor signaling cascade and the subsequent elaboration of IL-10 and TNF-α. Given that regulatory T cells appear to express abundant Toll-like receptors on their surfaces, some of the UV-induced ligands may directly activate these T-cell subtypes to induce IL-10, thereby further augmenting the immunosuppressive cytokine milieu.

Hence we can deduce that the downregulation of both TLRs 7 and 9, following UVB therapy, could be a secondary effect to the this immunosuppressive state induced by the UV-induced ligands possibly by downregulating pDCs, the main producers of both receptors. Such an event leads to suppression of autoreactive T cells and hence the reduction of cytokines needed for psoriatic lesion formation. Keratinocyte proliferation thus, is markedly reduced and hence again more downregulation of all TLRs (especially TLR9) produced by the keratinocytes. Although this current study showed no significant correlation between the levels of both receptors and the clinical severity of the lesions,yet the limited number of the patients may be possibly the cause. Thus further studies with larger scales are highly recommended to elaborate more the exact played role of TLRs 7 and 9 in the aetiopathogenesis of psoriasis.

In conclusion, TLRs 7 and 9 play an important role within the sequence of events taking place in psoriasis vulgaris. Downregulation of those receptors induced by nb-UVB ,may possibly add to the therapeutic mechanisms of nb-UVB in psoriatic patients. TLR 7 and 9 antagonists could be new future therapeutic tools for psoriasis and need further studies to elaborate their possible benefit for treating such a chronic disease.

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DOI: 10.7241/ourd.20142.32

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A STUDY OF CLINICAL AND BIOCHEMICAL CORRELATION IN PATIENTS OF *PSORIASIS* IN ACUTE EXACERBATION

Neerja Puri, B B Mahajan

Department of Dermatology and Venereology, Punjab Health Systems Corporation, Ferozepur, Punjab, India

Source of Support: Nil
Competing Interests: None

Corresponding author: Dr. Neerja Puri *neerjaashu@rediffmail.com*

Our Dermatol Online. 2014; 5(2): 135-139 Date of submission: 20.01.2014 / acceptance: 27.03.2014

Abstract

Introduction: Psoriasis is a genetically determined chronic disease of skin in which a number of biochemical alterations take place during its course. The main objectives of our study were to calculate various biochemical parameters in psoriasis correlate them clinically.

Materials and Methods: An attempt was made to detect the biochemical changes during its exacerbations. Fifty biopsy proved psoriasis patients were selected. Clinical examination and the various biochemical tests were performed at the time of enrollment and at the end of eight weeks of treatment.

Results: Hyperurecemia was seen in 16% patients and hypocalcemia was seen in 10 % patients and hypoalbuminaemia was seen in 56% patients.

Conclusion: With improvement of clinical picture, a shift of biochemical values towards normal was recorded.

Key words: Psoriasis; biochemical; PASI score; hypoalbuminaemia; hyperuricaemia; hypocalcaemia

Cite this article:
Puri N, Mahajan BB. A study of clinical and biochemical correlation in patients of psoriasis in acute exacerbation. Our Dermatol Online. 2014; 5(2): 135-139.

Introduction

Psoriasis is a chronic recurrent papulosquamous disorder characterized by epidermal hyperplasia [1]. There is, increased mitotic activity of the basal cell layer which results in rapid epidermal cell turnover with the 28 day normal epidermal cell cycle reduced to 5 days. The stimulus for the increased rate of keratinization and even the site of the initial pathologic changes remains controversial [2].

Psoriasis even today continues to be a ‚great dermatologic mystery.' Controversy exists regarding the mechanism underlying the rapidly increased epidermal turnover [3]. In any event, the six to nine fold transit time increase does not allow the normal events of cell maturation and keratinization to take place. This is reflected clinically by profuse scaling, histologically by a greatly thickened epidermis with increased mitotic activity and by the presence of immature nucleated cells in the horny layer and under the electron microscope by reduced production of intracellular filaments and granules seen within normal keratinization and biochemically by increased synthesis and degradation of nucleoproteins [4]. Psoriasis is associated with changes in blood biochemistry too.

Aim

1. To classify various types of psoriasis and find out various triggering factors in psoriasis.
2. To calculate various biochemical parameters in psoriasis correlate them clinically

Material and Methods

We selected fifty patients from the dermatology OPD. Prior approval of hospital ethics committee was taken and a written informed consent was taken from all the patients. All the patients were subjected to detailed history and clinical examination. Routine investigations and histopathological examination was performed in all the cases.

The following biochemical investigations were performed in all the patients - serum uric acid, serum calcium, serum albumin, serum globulin, serum bilirubin, serum creatinine, serum alkaline phosphatase, SGOT and SGPT. The biochemical tests were done before the initiation of the therapy and during the remission phase of the disease.

The following patients were excluded from the study:
1. Patients having impaired renal functions or pre-existing renal disease.
2. Patients with acute uncontrolled bacterial, viral or fungal infection.
3. Patients on concomitant use of hepatotoxic or nephrotoxic drugs for any other long standing illness.
The psoriasis area and severity index (PASI) was recorded in all the patients.

Results

The data was compiled and the results were analyzed statistically using chi square test.

Age Distribution

Table I shows that maximum number of cases (22%) were in the age group of 51-60 years, followed by 20% in the age group of 31-40 years, 18% in the age group 21-30 years, 16% in the age group 41-50 years, 16% in the age group 11-20 years, 12% in the age group 0-10 years and 8% of the cases were above 60 years of age. In our study, the mean deviation was 2.694 and the standard deviation was 3.287. The coefficient of variability was 8.54 and the mean age of the patients was 38.46 + 3.287.

Incidence of Different Types of Psoriasis

Table II shows that out of 50 cases of psoriasis, maximum incidence was of psoriasis vulgaris with 16 (32%) cases, followed by 14 (28%) patients of guttate psoriasis. There were 8 (16%) patients of erythrodermic psoriasis, 6 (12%) patients of generalized pustular psoriasis and 6 (12%) patients of palmoplantar psoriasis.

Sr No	Age	Number of patients	Percentage (%)
1	0-10	2	4
2	11-20	6	12
3	21-30	9	18
4	31-40	10	20
5	41-50	8	16
6	51-60	11	22
7	> 60	4	8
	Total	50	100

Table I. Age distribution of psoriasis.

Mean deviation - 2.694

Standard deviation - 3.287

Coefficient of variability - 8.54

Mean age - 38.46 +3.287

Sr No	Types of psoriasis	Number of cases	% age
1	Psoriasis vulgaris	16	32
2	Guttate psoriasis	14	28
3	Erythrodermic psoriasis	8	16
4	Generalized pustular psoriasis	6	12
5	Palmoplantar psoriasis	6	12
	Total	50	100

Table II. Incidence of different types of psoriasis.

Triggering Factors in Psoriasis

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

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

Table III. Triggering factors in psoriasis.

Mean deviation - 5.55

Standard deviation - 7.33

Biochemical Parameters In Psoriasis

Table IV shows that before the start of treatment, hypocalcaemia was seen in 5 (10%) patients and at the end of treatment, serum calcium levels were normal in all the patients, which was found to be statistically significant (p> 0.05). Hyperuricaemia was seen in 8 (16%) patients before treatment and it was normal in all the patients after the treatment, which was found to be statistically significant (p>0.05). Hypoalbuminaemia was seen in 28 (56%) patients before treatment and 2 (4%) patients after treatment which was found to be statistically significant (p>0.05). Hyperglobulinaemia was seen in 22 (44%) patients before treatment and 2 (4%) patients after treatment which was also found to be statistically significant (p>0.05). Liver function tests were deranged in 5 (10%) patients before treatment and 2 (4%) patients after treatment which was found to be statistically significant (p>0.05). Serum creatinine was abnormal in 2 (4%) patients before treatment and it was normal in all the patients after treatment, which was also found to be statistically significant (p > 0.05).

SR No	Biochemical parameters	Time of making biochemical analysis				P value
		At the start of treatment		At the start of treatment		
		Normal	Abnormal	Normal	Abnormal	
1	Serum calcium	45 (90%)	5 (10%)	50 (100%)	0	p> 0.05 (s)
2	Serum uric acid	42 (84%)	8 (16%)	50 (100%)	0	p> 0.05 (s)
3	Serum albumin	22 (44%)	28 (56%)	48 (96%)	2 (4%)	p> 0.05 (s)
4	Serum globulin	28 (56%)	22 (44%)	48 (96%)	2 (4%)	p> 0.05 (s)
5	LFT's	45 (90%)	5 (10%)	48 (96%)	2 (4%)	p> 0.05 (s)
6	Serum Creatinine	48 (96%)	2 (4%)	50 (100%)	0	p> 0.05 (s)

Table IV. Biochemical parameters before and after treatment.

Discussion

There were significant alterations in different biochemical values in patients before and after treatment [5]. With clinical improvement (Fig. 1 - 4), there was shift of biochemical parameters towards normal value. While analyzing the triggering factors, it was seen that mental stress was the most important triggering factor seen in 48% of patients. Psychological factors can trigger the onset or exacerbation of disease [6]. Some say that psoriasis is a psychosomatic disease and profound acute or chronic emotional stresses can induce or aggravate the course of disease. It is still unknown how psychic stress affects the first occurrence or exacerbation of psoriasis. The stress reaction in the patients is mediated by hypothalamic, pituitary adrenal relationship with immunologic effects.

In our study, the most common cause of stress was the death of a family member followed by monetary and matrimonial problems. The commonest factor for the onset of the disease is the environment in which a person has been living and working for a longer period of time and attitude of a person towards such environment.

The other commonest triggering factor was found to be drug intake, which was seen in 36% of patients. In our study, steroid withdrawal was the commonest triggering factor followed by use of beta-blockers. Sore throat was found to be a triggering factor in 36% of cases. ASO titres were positive in 10% of cases and were found to be positive in patients of guttate psoriasis only. Throat swab culture was found to be positive in 20% of cases and in all the cases, streptococcus haemolyticus was found to be the causative organism [7].

Alcoholism was found to be a triggering factor in 32% of cases. Alcohol intake should be discouraged in all the psoriatics. This is because there is a positive correlation between psoriasis and alcohol intake [8]. Moreover, alcohol induced liver problems may preclude the patients from receiving systemic therapy in future.

Trauma as a trigger was found in 22% of cases. Any form of trauma results in psoriasis appearing in the traumatized areas known as koebner's phenomenon [9]. Koebner's phenomenon occurs only at certain times in the lives of-the persons with psoriasis. Koebner effect can be induced by trauma at sites distant from existing lesions [10].

Regarding the seasonal variation, winter aggravation was seen in 52% cases, 6% patients had summer aggravation, 6% patients had spring aggravation and 4% had aggravation in the rainy season [11].

Decreased serum proteins occur in psoriasis. A decrease in albumin occurs when there is either impairment of albumin formation or excessive loss of albumin [12]. There are many causes of hypoalbuminaemia. It is because of loss of albumin through skin in psoriatic patients. lncreased endogenous catabolism of endogenous albumin is the real cause of hypoalbuminaemia. Another cause of hypoalbuminaemia is because of increased albumin clearance from involved psoriatic skin due to an increased lymphatic return, which might serve as a compensatory mechanism.

Hyperuricaemia is seen in psoriasis. In ours study, 16% of patients had increased serum uric acid levels. Increased purine metabolism occurs ill' psoriasis because of increased epidermal cell turnover [13]. Various studies have failed to demonstrate any direct connection between the frequency of hyperuricaemia and the extent of psoriatic skin involvemen [14].

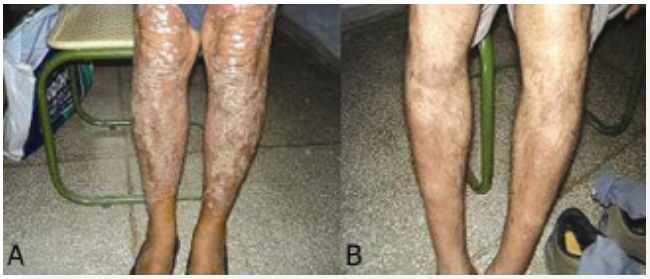

Figure 1A and B. Patient on PUVA therapy before and after treatment.

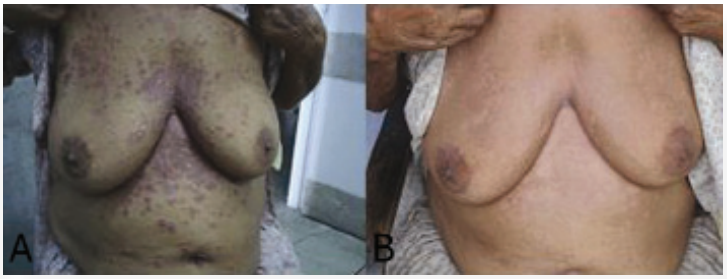

Figure 2A and B. Patient on methotrexate before and after treatment.

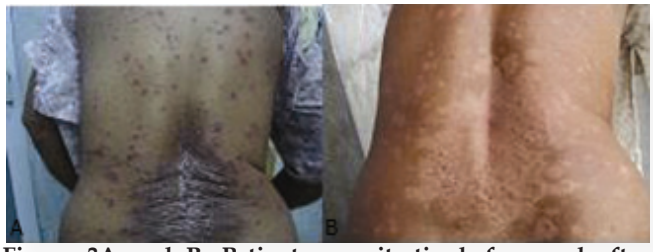

Figure 3A and B. Patient on acitretin before and after treatment.

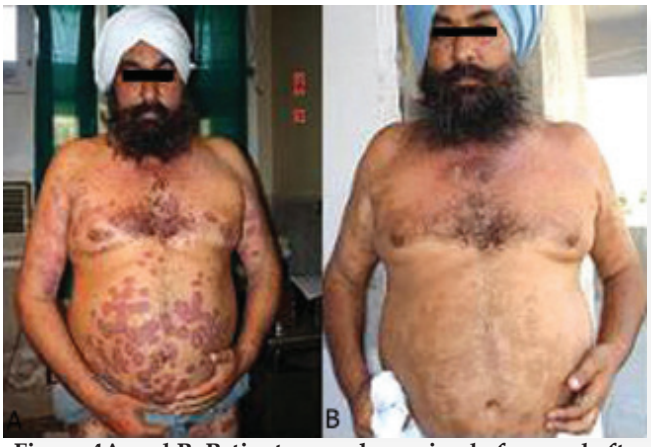

Figure 4A and B. Patient on cyclosporine before and after treatment.

The fact that the incidence of hyperuricaemia in psoriatic subjects is unchanged even after clearing of psoriatic lesions by various medications shows that psoriatic skin changes are not responsible for psoriatic hyperuricaemia. Genetic predisposition could be a reasonable explanation for hyperuricaemia in psoriasis patients.

Thus,the issue is still fraught with speculations. Total serum calcium alterations in psoriasis patients have been varyingly reported, showing thereby a decreased or a normal level [15]. Calcium depletion from horny layer may play a role in the formation of psoriatic skin lesions. In our study, hypocalcaemia was seen in 10% of patients and normal calcium levels in 90% of patients. The significance of total serum calcium in psoriasis is yet to be established. ASO titres were positive in 10% cases in our study. Also, it was seen that ASO titres were positive in patierits of guttate psoriasis only. Throat swab culture was positive in 20% cases arid in all the cases streptococcus haemolyticus was found to be the causative·organism. Significant improvement of PAS I score was seen in all the patients before and after treatment [16]. A 75% reduction in PASI score (PAS 75) used to be the current bench mark of primary end point for most clinical trials of psoriasis. But, many consider this end point to be too stringent as it places potentially useful therapies at risk of failing to demonstrate efficacy. Therefore, a 50% reduction in the PASI score (PASI 50) represents a meaningful change in a persons life and thus is a better primary endpoint [17,18]. In our study, there was 75% reduction in PASI score in 52% cases and 50% reduction in PASI score in 48% cases.

Conclusion

There were significant alterations seen in the biochemistry of the patients before and after treatment. After treatment, clinical improvement along with shift of the deranged parameters towards normal values was seen. Significant improvement in PASI was also seen before and after treatment.

Biochemical changes are important not only in understanding the pathogenesis of psoriasis but also act as a diagnostic and prognostic parameter in psoriasis in acute exacerbation [19]. In addition, the recognition of triggering factors in psoriasis not only helps in the prevention of disease exacerbation but also its better management.

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DOI: 10.7241/ourd.20142.33

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VIMENTIN MAY REFLECT AREAS OF PATHOLOGIC INVOLVEMENT IN BIOPSIES FROM PATIENTS WITH AUTOIMMUNE SKIN DISEASES

Ana Maria Abreu Velez[1,3], Daniel Alberto Vásquez Hincapié[2], Michael S. Howard[1]

[1]*Georgia Dermatopathology Associates, Atlanta, Georgia, USA*
[2]*PECET, University of Antioquia, Medellin, Colombia, South America*
[3]*Department of Dermatology, School of Medicine, University of Antioquia, Medellin, Colombia, South America*

Corresponding author: Ana Maria Abreu Velez, M.D., Ph.D. *abreuvelez@yahoo.com*

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

Our Dermatol Online. 2014; 5(2): 140-143 Date of submission: 02.01.2014 / acceptance: 19.02.2014

Abstract
Introduction: Autoimmune bullous skin diseases (ABDs) represent a group of disorders of the skin and mucosa commonly associated with deposits of immunoglobulins, complement and fibrinogen, and usually directed against distinct adhesion molecules. After studing these diseases for many years, we noted alterations not only between the cells junctions of the epidermis and/or the dermal/epidermal junction, but also in dermal skin appendageal structures and in mesenchymal tissue around the blisters. Based on our findings, we wanted to determine if the observed patterns of autoimmunity correlated with cutaneous vimentin expression.
Materials and Methods: Archival biopsies previously diagnosed with ABDs by clinical, hematoxylin and eosin (H&E) and direct and/or immunofluorescence data were stained with antibodies directed against vimentin via immunohistochemistry (IHC). We tested 30 patients affected by endemic pemphigus, 30 controls from the endemic area, and 15 normal controls. We also tested 30 biopsies from patients with bullous pemphigoid (BP), 20 with pemphigus vulgaris (PV), 8 with pemphigus foliaceus, 14 with dermatitis herpetiformis (DH) and 3 with Senear-Usher syndrome.
Results: The H&E, DIF and vimentin patterns of positivity in the different ABDs confirmed that vimentin was compartmentalized around areas of dermal inflammation, around skin appendages and in epidermal, dermal and mesenchymal cell junction areas.
Conclusion: Vimentin may be a useful tool for highlighting patterns of microenvironmental tissue alteration in multiple ABDs. The vimentin staining pattern observed was analogous to that we have previously described for proteases and protease inhibitors in patients affected by ABDs, expanding the concept that the autoimmune process extends beyond cell junctions.

Key words: Autoimmune blistering skin diseases; vimentin; mesenchymal tissue

Abbreviations: Autoimmune bullous diseases (ABDs), bullous pemphigoid (BP), pemphigus vulgaris (PV), pemphigus foliaceus (PF), dermatitis herpetiformis (DH), endemic pemphigus foliaceus (EPF), linear IgA disease (LAD), immunohistochemistry (IHC), direct and indirect immunofluorescence (DIF, IIF), hematoxylin and eosin (H&E), basement membrane zone (BMZ), intercellular staining between keratinocytes (ICS), intermediate filament (IF), epithelial-to-mesenchymal transition (EMT).

Cite this article:
Abreu Velez AM, Vásquez Hincapié DA, Howard MS. Vimentin may reflect areas of pathologic involvement in biopsies from patients with autoimmune skin diseases. Our Dermatol Online. 2014; 5(2): 140-143.

Introduction

Vimentin is a marker of migrating cells, and is a protein that in humans is encoded by the VIM gene [1-4]. Vimentin is a type III intermediate filament (IF) protein that is expressed in mesenchymal cells [1-4]. Current studies have revealed novel functions for vimentin related to cell migration, such as determination of cellular polarity, regulation of cell contact formation, organization and transport of signal proteins involved in cell motility [1-4]. Pemphigus and bullous pemphigoid are autoimmune bullous diseases of the skin. Pemphigus, an intraepidermal blistering disease, is categorized by autoantibodies reactive to antigens located in epidermal intercellular spaces, or on the surfaces of epidermal cells [5]. These antibodies, which have recently been shown to trigger complement activation, seem to be the source of acantholysis, the basic pathologic process of pemphigus [5-10].

Bullous pemphigoid (BP), an autoimmune subepidermal blistering skin disease, presents with tense blisters with or without concomitant erythema. Bullous pemphigoid blistering occurs along the lamina lucida, due to immunoglobulin G and/or complement deposits at the basement membrane zone (BMZ). Circulating autoantibodies are often also present, directed against hemidesmosomal molecules [5-10].

Material and Methods

In our IHC staining, we utilized monoclonal mouse anti-Vimentin antibody, Dako Clone V9, and stained as previously described [10-13]. Vimentin is a 57 kDa intermediate filament protein which forms part of the cytoskeleton of vertebrate cells, and is characteristically found in cells of mesenchymal origin. Our archival patient tissue selected for this study was prepared as previously described [8-13]. Specifically, we tested 30 patients affected by endemic pemphigus, 30 controls from the endemic area, and 15 normal controls. We also tested 30 biopsies from patients with bullous pemphigoid (BP), 20 with pemphigus vulgaris (PV), 8 with pemphigus foliaceus and 14 with dermatitis herpetiformis (DH).

Results

Vimentin was present in all of the ABDs in areas of inflammation. Specifically, we noted positivity around most skin appendages, around disease blisters, and in dermal areas that demonstrate a high density of epithelial-to-mesenchymal tissue transitions(such as junctions between dermal blood vessels and the extracellular matrix). In these areas, increased cytokine signaling of local inflammation is present. These findings were observed in all the ABDs. In Figures 1 and 2, we demonstrate examples of this immune compartmentalization within dermal, epidermal and blister microenvironments in the ABDs. Moreover, it seems that in addition to the classic immunoglobulin and complement linear deposits at the BMZs, additional, orchestrated immunologic reorganization of the dermis is also present in these areas. Such an immunologic reorganization of the dermis could play a significant role in the pathophysiology of these disorders.

In the majority of the patients with DH, the vimentin positivity was noted in the dermal papillae surrounding and inside the blisters, and in the dermis under the blisters. Positivity was also seen in some dermal fibroblast-like cells, and along neurovascular supplies of skin appendageal structures. In most patients with BP, linear staining was noted under the blisters. Staining was also noted in the upper and intermediate dermis, on several dermal fibroblast-like cells and around eccrine sweat ducts and blood vessels. In most of the El Bagre-EPF and the PF cases, an epidermal ICS-like pattern was seen. In addition, dermal staining was noted in the dermis under the blisters, on eccrine sweat glands, on neurovascular supplies of appendageal structures (including sebaceous glands and hair follicles), and in the subcutaneous adipose tissue. In the bulk of the PV cases, vimentin was positive in the debris within the blisters. However, the majority of the staining was found in a band-like distribution in the upper dermis, including around superficial neurovascular packages and around some skin appendageal structures. In our 3 cases of Senear-Usher syndrome, vimentin staining was primarily positive around hair follicle basal layers and around the neurovascular supplies for hair follicles and sebaceous glands.

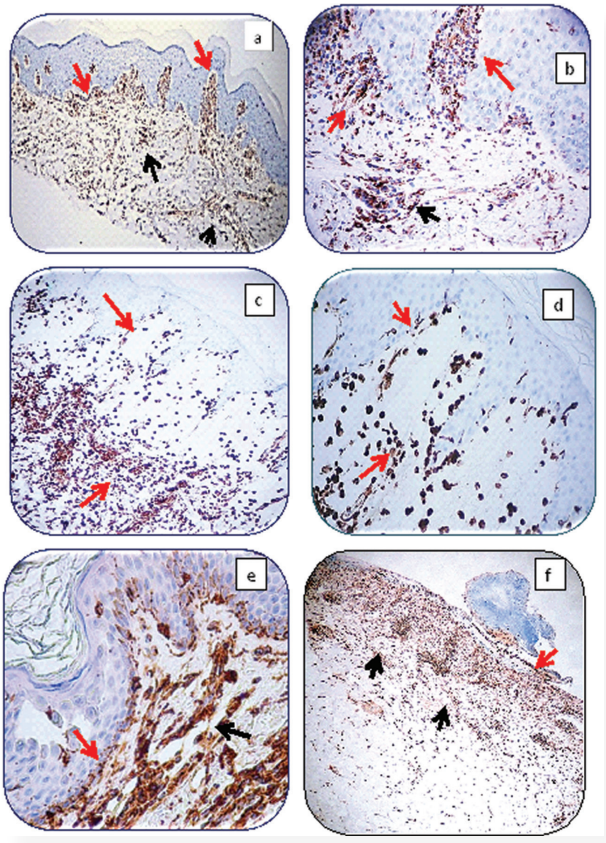

Figure 1. a. IHC staining with vimentin in DH (100x) showing positivity around the blister in the high papillary dermis and BMZ areas (brown staining; red arrows), as well as around upper dermal blood vessels and eccrine ducts (brown staining; black arrows). **b**. A second DH case, demonstrating positive staining with vimentin in the dermal papillae and subepidermal blisters (brown staining; red arrows) and around upper dermal blood vessels (brown staining; black arrow)(200x). **c** and **d**. In **c, a** DH case, showing detailed staining with vimentin around a subepidermal blister (brown staining; red arrows) and in d, around dermal blood vessels (brown staining; red arrows)(100 and 200x, respectively). **e.** Tissue inhibitor of metalloproteinase 1 staining (red staining) in a PV case, showing some positive staining in areas where vimentin staining is also positive (brown staining) (red and black arrows). **f.** IHC staining with vimentin (brown staining) in a PV case. The red arrow designates staining within the blister, and the black arrow highlights staining in the upper dermal tissues including around blood vessels.

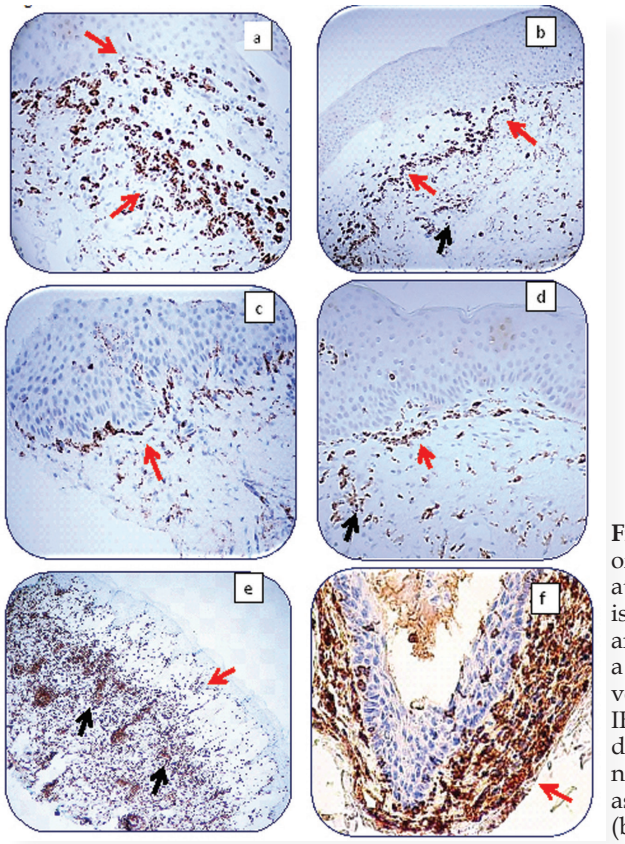

Figure 2. a through d. IHC staining with vimentin in four different cases of BP, showing the stain demarcating the blisters and/or linear staining at the BMZ (brown staining; red arrows). In addition, vimentin staining is noted around upper dermal blood vessels (brown staining; black arrows). **e.** DH case, demonstrating panoramic staining with vimentin in a subepidermal blister (red arrow), and also around dermal blood vessels and other skin appendageal structures (black arrows)(40x). **f.** IHC staining with vimentin in a Senear-Usher syndrome case, demonstrating positive staining within basaloid cells of a hair follicle; note some intercellular staining within spelling, keratynocytes, as well as strong reactivity in dermal blood vessels surrounding the hair follicle (brown staining; red arrow)(400x).

Discussion

Cell migration plays a crucial role in embryonic development, wound healing, regeneration, inflammation and immune responses, as well as in dissemination of malignant neoplasms. Vimentin is often utilized as a marker of mesenchymal-derived cells, or cells undergoing an epithelial-to-mesenchymal transition (EMT) during both normal development and metastatic progression [1-4,14].

Knowing that vimentin is useful for the identification of cells of mesenchymal origin in normal and neoplastic tissues, and based on our observed tissue "compartmentalization", we suggest that rearrangement and/or sequestering of cells of mesenchymal origin occurs in the immune response in ABDs. Further, this process may contribute to the creation of blisters and other pathologic sequelae in these disorders.

In many mouse models described for ABDs, the phenomenon of redistribution of dermal mesenchymal cells has not been documented. Notably, many of these models do not exhibit a chronic ABD state, especially those created via injection of autoantibodies; thus, the redistribution phenomenon may represent a cellular manifestation of a chronic ABD state. Further, our findings with the reorganization of dermal tissue demonstrated by vimentin staining suggests that a complex dermal microenvironment is needed to create the immune responses in ABDs, versus a basic response previously believed to be mediated by autoantibodies and/or complement. Finally, vimentin staining may represent a useful tool to demonstrate patterns of tissue alterations secondary to the inflammatory processes in different ABDs. The pattern of vimentin staining observed is comparable to those patterns we have previously described for proteases and protease inhibitors in lesional skin in ABDs, escalating the concept that the autoimmune process extends into the dermis and below the junctional zone.

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DOI: 10.7241/ourd.20142.34

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SEYLE'S BIOLOGICAL STRESSORS INFLUENCE DRAMATICALLY SKIN PHYSIOLOGY: OUR EXPERIENCES WITH ELECTRICAL ADMITTANCE MAGNITUDE MEASUREMENTS

Lorenzo Martini[1], Roberto Solimé[2]

[1]*University of Siena, Department of Pharmaceutical Biotechnologies, Via A.Moro 2, 53100 Siena, Italy*
[2]*Solimé s.r.l, Via Dalla Chiesa 10, Cavriago, Italy*

Source of Support: Nil
Competing Interests: None

Corresponding author: Lorenzo Martini, M.Sc. *lorenzo.martini@unisi.it*

Our Dermatol Online. 2014; 5(2): 144-147 Date of submission: 15.11.2013 / acceptance: 18.02.2014

Abstract
Introduction: Abrupt changes of environmental temperatures and assault of chemical and physical assaults belong to the series of biological stresses recorded by the austro-canadian endocrinologist Seyle onto skin, phenomena that are progressively overset all natural events and anthropological lifestyles, are too often depreciated and underestimated by dermatologists and cosmetologists at all.
Aims of our study is to evaluate by electrical admittance magnitude measurements the influence these two irrefutable afflictions, designed as stressors, influence negatively human skin and to do this we have selected, to conduct the study, peculiar individuals that, owing to their choice of living, may or not be injured by extreme changes of temperatures and aggressions by chemical and physical pollutants.
Materials and Methods: We have recruited 20 nuns in a cloistered convent in Mid Italy: ten of these have been always accustomed to live inside the cloister and their life-style permits the good conservation of the intact skin physiology (that is living at air temperature and medium-low relative humidity) and the other ten are accustomed to live and work outdoor and to be assaulted by abrupt and extreme changes of environmental temperature and pollutants. Cloistered nuns have the chance to choose where to live, indoor or aoutdoor. We measured the electrical admittance magnitude (in μmho) at the beginning and at the end of the experiment that lasts 29 weeks, using an appropriate instrument based on the system developed by Feldman, working at a single frequency of 30kHz.
Results and Conclusion: It is self evident that after the simulation of phyto-induced cortisol release onto the skins of all the 20 volunteers, the subjects that which live outdoor show an exaggerated value of dehydration with regard to the subjects that live indoor. Changes of environmental temperatures and chemical pollutants, is self evident, jeopardize human skin integrity and safety, but we have disclosed the eventuality that these phenomena may reveal devastative effects onto skin to drive even to a praecox skin senescence and degradation.

Key words: Water loss insensible; Global Warming; Xanthines

Cite this article:
Martini L, Solimé R. Seyle's biological stressors influence dramatically skin physiology: our experiences with electrical admittance magnitude measurements. Our Dermatol Online. 2014; 5(2): 144-147.

Introduction

J.H.B. Selye [1,2] recognized the role glucocorticoids, mineralcorticoids, sexual corticoids and cathecolamines play in the phenomenon of the biological stress and of the adaptation general syndrome, in other words he was aware of the hormonal response to stress in human.
According to the Author, there are four types of stresses: physical (e.g. inadequate sleep or rest, inadequate work/exercise, repetitive or asymmetrical movement at work/play, -physical injuries,-excessive or imbalanced work/exercise) chemical, (e.g. air and/or water pollution, pesticides and herbicides, solvents, industrial chemicals, flavourings, colourings, and preservatives, refined foods like hydrogenated oils, white flour, sugar, antibiotics and manifold medicines, dental amalgam, thermal, (e.g. extreme or prolonged heat or cold, extreme changes in temperature) and emotional (e.g. poor relationships and financial burdens, past emotional trauma, self-judgments like self-expectations of perfection, anticipation of harm, pain, or dreaded events).
Cortisol is the hormone most profoundly influenced by whichever of the aforesaid stresses, and in effect it has been very recently demonstrated that in case of mirthful laughters its level decreases deeply [3].

Actually, under stress, cortisol levels can run very high. Abnormal circadian rhythm normally will not develop until stress is prolonged - usually over years - but it can also occur in just a few months, especially if it is severe and constant.
When the cortisol rhythm stays out of balance [4], more serious problems can appear, such as arthritis, allergies, asthma, colitis, ulcers, recurrent and prolonged infections, auto-immune diseases, degeneration of the nervous system, and, we have supposed and argued, premature skin senescence and degradation, and this shall be the exact prolegomenon of our study.
It is well-known that an 21 old individual, at his acme of maturenesses, presents the following percentages of water in his skin layers [5-7]:

70% in the stratum basale
60% in the stratum granulosum and malpighianum
30-40% in the stratum lucidum
20% in the stratum corneum
10% in the squamous superficial layer.

Physiologically speaking the amount of extracellular water tends to decrease progressively and constantly till the extreme old age and the same percentages of water are then retrieved in cadaver. These values are to be considered legitimate when this individual is supposed to live in a "ideal and theoretical environmental milieu" where temperature is for most of the time at 23°C (air temperature) and relative humidity is 35%, so that TEWL is relatively contained (7.5-10.2 g/m²h) and when every leap of temperature and humidity or excessive sun exposure (for job or mere aesthetical reasons) are classified as accidental exceptions, so that the just time can be accorded to recovery the standard physiological requirements to guarantee safety and integrity to skin.
TEWL seems to follow odd stratagems, actually, when, for instance, at 23°C and at relative humidity of 57% rises to 12.2 g/m²h, but, indeed, at r.h. of 88% decreases to 4.1 g/m²h.
For, high relative humidity appears to represent the touche-sane to yield the decrease of TEWL, and this is undeniable when temperatures are contained and constant.
Environmental pollution, as well extreme changes of temperatures, we have already stated, embody one of the causes of excessive secretion of cortisol, that, dermatologically speaking, it is known to be responsible of the inhibition of the regeneration of the stratum granulosum (which is to be considered the water reservoir par excellence), of the synthesis of melatonin and of the proliferation of collagen and other active mesenchymal elements and of the immune counterattack to external assaults.
Xanthines and cocaine are generally reputed the responsible of cortisol release both endogenously and exogenously.
Conner et. al [8] referred that adhesive patches containing 300mg caffeine dispersed in a 5% agarose and 5% activated carbon hydrophilic gel, applied on the chest of twenty volunteers, permitted the plasmatic collection of caffeine transdermally adsorbed (more than 150ng after 3 hours) and it is not erratic to simulate the neurological stress onto skin employing natural xanthines for external use, in order to evaluate its influence on the cortisol release that can lead to the accelerated skin ageing.
Aims of our research is to evaluate how a simulation of a "phyto-induced" increase of secretion of cortisol may induce praecox human skin senescence.

Material and Methods

We have decided to select to conduct our study particular individuals that may choose to live at physical environmental conditions that can guarantee the conservation of intact skin physiology or may not.
For, we have recruited 20 nuns in a cloistered convent in Mid Italy, located very close to a big polluted town, even if in the countryside: ten of these are accustomed to live and have always lived inside the cloister since the very tenderest age, and their life-style permits the good conservation of the intact skin physiology (that is living at air temperature and medium-low relative humidity so that two of the nuns of this group which are centennial, are characterised by matte, soft and soft skin without any apparent wrinkle) and the other ten are accustomed to live and work outdoor and in contact with the environmental assault of chemical and physical assaults.
Plans of our study were dispatched to the competence of the department of Work, Health and Social Politics at Rome. An informed consent was obtained from each volunteer prior to participate to the experiment.
We have prepared a cosmetic hydrogel made up of 2% hydroxypropylguar, containing a 5% mix of herbal extracts containing 0.5% of titrated pure xanthines (Davilla rugosa folium, Maytenius macrocarpa folium and Sterculia platanifolia folium).The extracts of these three plants are admitted by INCI, COLIPA and CTFA rules.
So we extracted all the collected leaves in ethanol in order to prepare the 5% herbal-hydrogel and to begin the experiments at half March and conclude these at half October (29 weeks of treatment or simulation of the aggression by effects of global warming).
All the 20 volunteers were gently requested to spread every morning and every afternoon, at the same time, the gel onto the left ventral forearm for all the 29 weeks, to simulate the phyto-induced cortisol release.
At the beginning of the experiment we had previously measured the electrical admittance magnitude (in μmho) using an appropriate instrument based on the system developed by Feldman [9] working at a single frequency of 30kHz.This special excitation frequency was generated using a 4Khz crystal with digital counter chip. The counter output was converted into a sinusoidal current signal which was applied to two outer electrodes, meanwhile the instantaneous voltage signal between the inner signal was amplified by appropriate amplifier [9-12]. All the aforesaid tools and the amplifier were furnished by Bio-Logic Science Instruments, France.
We distinguished with precise accuracy the two groups of indoor (1001-1010) and the outdoor nuns (2001-2010) and we have been able to fill out Table I, as far as the values measured at the very beginning of the warm season, and afterwards, Table II, as far as the final values measured after 29 weeks of treatment with the xanthines-hydrogel, that is the simulation of the phyto-induces praecox senescence of skin.

Results and Discussion

After 29 weeks, simple observational analysis and analysis by magnifying glass of the treated skin (with the xanthines-hydrogel) of the 20 volunteers revealed that skin rubor was evident only in all the volunteers of the second group, except for 2003 and 2008 that are dark and olive skinned (Malagasy and Nigerian).

Here follow the Tables I and II, that should exhaustively, through their comparison, disclose the complete comprehension of the phenomenon we decided to study and clarify that the hypothesis mentioned in the introduction of our study is true and therefore conclusions can be derived.
Suggestive are the values of the electrical admittance magnitude with regard to the age of the volunteers, and this demonstrates the irreducible fact that the higher is the hydration (regarded as water content and water permeability through the layers of derma), the lower is the value of the electrical admittance magnitude, and vice versa, the lower is the hydration, the higher will be the electrical admittance magnitude.
The Hydration degree (and par consequence the coefficient of Skin Moisture) is irrefutably due to age and distantness from excessive changes of temperature and pollutants aggression.

Volunteer and her age	µMho at the beginning of the experiment (at 30kHz). March, 14th
1001 44	2710
1002 27	1790
1003 31	1980
1004 59	2650
1005 55	2590
1006 47	2610
1007 19	990
1008 22	1880
1009 68	2840
1010 51	2600
2001 31	1140
2002 24	1250
2003 27	1460
2004 32	1440
2005 30	1030
2006 28	1250
2007 36	1610
2008 21	1220
2009 30	1470
2010 24	1350

Table I. Values of the electric admittance amplitude at the beginning of the experiment.

Volunteer and her age	µMho at the end of the experiment (at 30kHz). October, 16th
1001 44	3330
1002 27	2020
1003 31	2070
1004 59	3040
1005 55	3060
1006 47	3170
1007 19	1890
1008 22	2470
1009 68	3110
1010 51	3440
2001 31	2600
2002 24	2470
2003 27	1860
2004 32	2910
2005 30	2740
2006 28	1980
2007 36	3000
2008 21	1560
2009 30	1990
2010 24	2210

Table II. Values of the electric admittance amplitude at the end of the experiment.

In the case of the volunteers of the first group (the indoor nuns), the influence of the sole simulation of the phyto-induced cortisol release appears to be lower than in the case of the volunteers of the second group (the outdoor nuns) where the influence of the xanthine-hydrogel that induced cortisol release is macroscopic.
Values of the volunteers of the first group are evident in Table III, while values of the volunteers of the second group are plotted in Table IV.
All values are recorded as percentage of absolute dehydration.

Conclusion

It is undeniable that biological stress (by mean of exposition to changes of environmental temperature and pollutants, by mean of a simulation evoked by the use of a xanthine-hydrogel) does represent a very liaison dangereuse for the integrity and wellness of human skin.

It is suggestive the fact that we have expressly selected these peculiar types of subjects (the cloistered nuns) because they are able to show the devastative degradation evoked by climate changes and pollutants onto skin in dependence of their own choice they can do to live outdoor or indoor.
The must impressive results come out from the values of the electrical admittance magnitude recorded in all the volunteers of the second group, where the simulated phyto-induced stress reveals an huge increase of the absolute dehydration after 29 weeks.
It is noticeable that even in the volunteers of the first group (the indoor nuns), the values of the electrical admittance magnitude are relatively higher, notwithstanding the volunteers have the chance not to be assaulted by abrupt changes of climate and temperature and pollutants, as well.

Volunteer and her age	Absolute dehydration after 29 weeks
1001	18.62%
1002	11.39%
1003	4.40%
1004	12.90%
1005	15.40%
1006	17.70%
1007	47.62%
1008	23.89%
1009	8.62%
1010	24.42%

Table III. Values of skin dehydration recorded after 29 weeks in the indoor volunteers.

Volunteer and her age	Absolute dehydration after 29 weeks
2001	56.20 %
2002	49.40%
2003	21-51%
2004	50.52%
2005	62.50%
2006	36.87%
2007	46.40%
2008	21.80%
2009	26.14%
2010	39.00%

Table IV. Values of skin dehydration recorded after 29 weeks in the outdoor volunteers.

Acknowledgement

We really can boast not to have received absolutely any funding or reimbursement by any authority or governmental corporation to conduct this study.

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DOI: 10.7241/ourd.20142.35

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AMOXICILLIN AND CLAVULANATE POTASSIUM RELATED *LEUCOCYTOCLASTIC VASCULITIS*

Snehal Balvant Lunge, Vijaya V. Sajjan, Ashok M. Pandit, B.S. Manjunathswamy, Shivakumar Patil, Anshul Agrawal

Department of Dermatology, Jawaharlal Nehru Medical College, Belgaum, India

Corresponding author: Ass. Prof. Snehal Balvant Lunge drsnehallunge@gmail.com

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 148-150 Date of submission: 16.02.2014 / acceptance: 27.03.2014

Abstract
Leukocytoclastic vasculitis (LCV) is a small-vessel vasculitis with a reported incidence rate of 30 cases per million persons per year. It usually presents as a palpable purpuric skin rash on legs, though any part of the body can be affected. LCV rash may have an associated burning sensation or pain and in some cases may involve internal organs. In some cases, LCV rash may present as nodules, recurrent ulcerations or asymptomatic lesions. The diagnosis of LCV is usually made on skin biopsy. Etiological triggers may not be identified in as many as half of the cases. Treatment is usually conservative and includes identification and removal or treatment of the etiological trigger except in cases with internal organ involvement where systemic steroids and immunosuppressant may be necessary. In this article we present a case of Amoxicillin and Clavulanate potassium associated LCV that improved with discontinuation of the offending agent and treatment with systemic corticosteroids.

Key words: Amoxicillin and Clavulanate potassium; Leukocytoclastic vasculitis, perivascular and vascular leucocytic infiltrates

Cite this article:
Lunge SB, Sajjan VV, Pandit AM, Manjunathswamy BS, Patil S, Agrawal A. Amoxicillin and clavulanate potassium related Leucocytoclastic vasculitis. Our Dermatol Online. 2014; 5(2): 148-150.

Introduction

Leukocytoclastic vasculitis (LCV) (hypersensitivity vasculitis) is a term commonly used to denote a small-vessel vasculitis. Many possible causes or associations have been proposed for LCV, but a cause or an associated disorder may not be found in as many as half of the cases.

LCV presents clinically as a cutaneous disease with or without internal body organ involvement. The prognosis of LCV is usually good if internal organs are not affected. The internal organs most commonly involved in LCV are the joints, gastrointestinal tract, and the kidneys. Clinical presentation of LCV varies from an acute self-limiting episode to recurrent or chronic forms.

In this article we report a case of a patient who developed painful skin lesions identified to be LCV almost one week after the use of Amoxicillin and Clavulanate potassium.

Case Report

A 22 year male presented to us with complain of fluid filled lesions over bilateral lower limbs since 9 days. The patient initially had red raised skin lesions which eventually became fluid filled, and these lesions initially localized to the dorsal aspect of right leg and over a period of 3 to 4 days spread to bilaterally extending upto the thigh, also involving the both forearms and hands. These lesions was associated with itching, burning sensation. There was H/o pain in large joints and pedal odema. There was no H/o upper respiratory tract infection, pain in abdomen, Hematemesis and hemoptosis. Patient gave H/o taking Amoxicillin and Clavulanate potassium and paracetamol for 3 day for fever following which the skin lesions occurred 7 days later. On General examination patient was afebrile, pulse 78/min, BP -110/ 70 mmHg, no signs of pallor, icterus, clubbing, cyanosis, lymphadenopathy. Patient had pedal odema and arthralgia. Systemic examination was within normal limits. On cutaneous examination there was multiple palpable purpura of varying sizes mainly distributed on both upper and lower limb. Few of them had vesiculo-bullous eruption predominantly present on both lower legs (Fig. 1). Few bulle were ruptured with serosanguinous discharge were present over bilateral lower limbs sparing the trunk and face. Oral, genital and anal mucosae were normal. Then we investigated the patient for complete blood count (CBC) revealed eosinophilia. Liver function test, Renal function test, Urine analysis and USG abdomen were normal. HbsAg, ANA, ASO titre and HIV test were negative.

Clinically we thought the differential diagnosis for the patient was of Henoch Schonlein purpura because of the patient age, Leucocytoclastic vascultits secondary to drugs, Allergic contact dermatitis and Erythema Multiforme.

Then we did skin biopsy with 4mm punch from ant. compartment of thigh showed palpable purpura clinically. Histopathology report revelaed that inflammatory pathology was predominantly confined to superficial dermis consisting of perivascualar infiltrate consisting of mainly neutrophils and few lymphocytes. Neuclear fragmentation and vascular wall damage was also seen suggestive of leucocytoclastic vasculitis (Fig. 2). The patient had taken paracetamol for his fever in the past with no adverse reactions. So paracetamol being the causation of his lcv was ruled out. On the basis of clinical & histopathological findings confirm the diagnosis of Leucocytoclastic vasculitis secondary to Amoxicillin and Clavulanate potassium was made. The patient was treated with primarily removal of the offending drug, and elevation of the leg because LCV rash involves dependent areas. On systemically we treat him with I.V Dexamethasone, for ten days followed by oral prednisolone in tapering doses. Oral antibiotic (Azithromycin), topical corticosteroids were also given and patient was advised to follow up after one week. Patient showed signs of improvement as only mild erythema was seen after a week and post-inflammatory hyperpigmentation after a month.

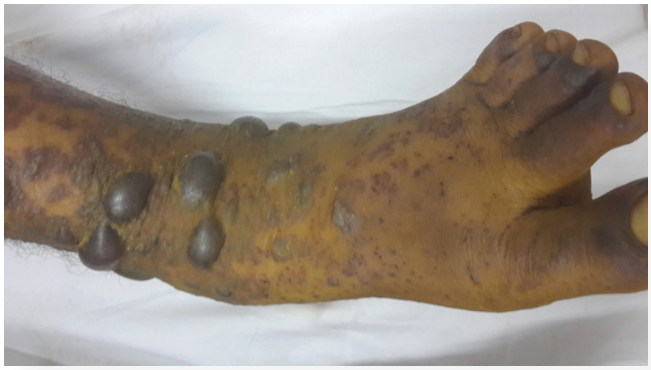

Figure 1. Multiple palpable purpura with vesiculobullous eruptions over the left lower leg.

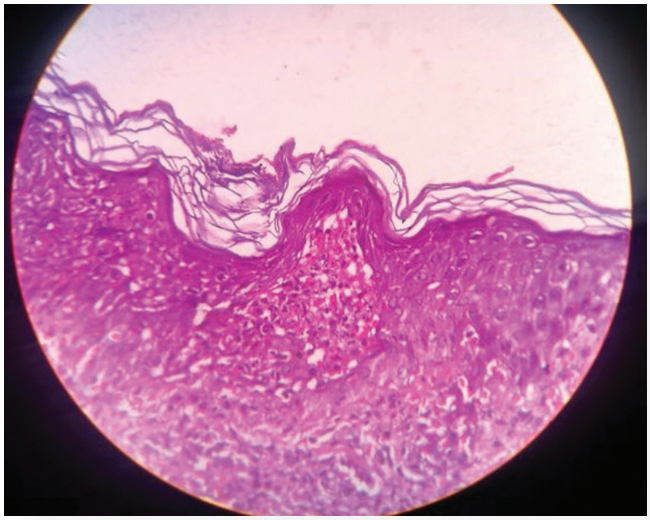

Figure 2. Histopathology showing epidermis and dermis with characterstic neuclear dust in dermis. (H&E stain 40X)

Discussion

LCV is a small-vessel hypersensitivity vasculitis with a reported incidence rate of about 30 cases per million people per year [1]. LCV can occur at any age group and is thought to effect men and women in equal numbers but few studies suggest male predominance [2]. Multiple etiologic factors including drugs, infections, foods, autoimmune diseases, collagen vascular diseases and malignancies have been suggested to associate with LCV [3-6]. Though exact pathogenic mechanism of LCV remains to be elucidated, circulating immune complexes are believed to be involved in the pathogenesis of LCV [7].

LCV usually presents as a palpable purpuric rash associated with burning sensation or pain and is most commonly observed on the legs, but any surface may be involved. Rarely the presentation may include completely asymptomatic lesions, nodular lesions or ulcerations. Thorough history of recent infections, change in medications or food etc. along with a detailed physical examination to find etiologic trigger or an associated disorder should be performed. Identification and avoidance or treatment of the etiologic trigger may prevent recurrent episodes of LCV.

Diagnosis of LCV is confirmed on histological examination of the sample obtained on biopsy of the affected area. Histologically, LCV demonstrates perivascular and vascular leucocytic infiltrates along with fibrinoid necrosis. Etiological triggers are usually identified with the temporal association.

In our patient, palpable purpura start after Amoxicillin and Clavulanate potassium tablet intake of duration 3 to 4 days and its stop spreading after removal of drug. Considering patient had history of migraine and he had took paracetamol multiple times, chances paracetamol was involved in the pathogenesis of LCV were less likely. Furthermore Azithromycin and I.V. Dexamethasone was continued throughout the course of the treatment and rash resolved for 10 days. Then patint shifted to oral prednisolone in tapering doses with topical corticosteroids & antibactrials. Since Amoxicillin and Clavulanate potassium was the only new medicine to which the patient was recently exposed to, it was thought to be the etiologic trigger for LCV in this case. Further, the LCV rash improved after the discontinuation of the Amoxicillin and Clavulanate potassium confirming our hypothesis.

Treatment of LCV is identification and removal or treatment of the offending etiologic factor, and elevation of the leg and use of compression stocking if LCV rash involves dependent areas. Colchicine [8] and dapsone [9] have been shown to be useful in cases of LCV. Urticarial lesions can be managed with the antihistaminic medicines.

Systemic steroids and other immunosuppressive agents [10] may be used in cases of deep organ involvement.

In conclusion, Clinicians need to be suspect of drug-induced vasculitis to enable prompt diagnosis and treatment. Identification of potential etiological triggers in cases of LCV can prevent significant morbidity related with recurrences. Multiple antibiotics including Amoxicillin and Clavulanate potassium can act as a potential trigger for LCV which was very commonly used in daily practice.

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DOI: 10.7241/ourd.20142.36

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KERATOSIS FOLLICULARIS SPINULOSA DECALVANS ASSOCIATED WITH ACNE KELOIDALIS NUCHAE

Ilteris Oguz Topal[1], Ilknur Mansuroglu Sahin[2], Betül Berberoglu[3], Mehmet Ozer[2]

[1]*Department of Dermatology, Okmeydani Research and Training Hospital, Istanbul, Turkey*
[2]*Department of Pathology, Okmeydani Research and Training Hospital, Istanbul, Turkey*
[3]*Department of Pathology, Batman State Hospital, Istanbul, Turkey*

Corresponding author: Dr Ilteris Oguz Topal *drilteris@yahoo.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 151-154 Date of submission: 02.01.2014 / acceptance: 11.02.2014

Abstract
Keratosis follicularis spinulosa decalvans (KFSD) is a keratinization disorder characterized by diffuse follicular hyperkeratosis, progressive cicatricial alopecia, corneal dystrophy, and photophobia. Acne keloidalis nuchae (AKN) is a syndrome of chronic folliculitis that manifests as follicular-based pustules and papules on the occipital region of the scalp, which may eventually lead to cicatricial alopecia.
Various diseases such as cutis laksa, deafness, aminoaciduria, mental retardation, and atopy have been reported to be associated with KFSD, but AKN is a rare cutaneous manifestation. Herein, we report the case of a patient with KFSD associated with AKN. He was presented to our clinic with follicular-based pustules and papules that had been progressively advancing for five years that were now manifesting as cicatricial alopecia.

Key words: Keratosis follicularis; cicatricial alopecia; acne keloidalis nuchae

Cite this article:
Topal IO, Sahin IM, Berberoglu B, Ozer M. Keratosis follicularis spinulosa decalvans associated with acne keloidalis nuchae. Our Dermatol Online. 2014; 5(2): 151-154.

Introduction

In 1905, Lamaris first described keratosis follicularis spinulosa decalvans (KFSD) as ichthyosis follicularis [1]. Later, Siemens provided more detailed phenotypic characteristics of the disease and first used the term KFSD in 1926 [2]. This condition is characterized by diffuse keratosis pilaris, cicatricial alopecia, and photophobia and is associated with cutis laksa, deafness, aminoaciduria, mental retardation, and atopy [3]. However, only very rarely has acne keloidalis nuchae (AKN) been associated with KFSD in the literature. Herein, we report a case of KFSD with acne keloidalis lesions.

Case Report

A 22-year-old male patient was admitted to our outpatient clinic because of hair loss that had begun five years earlier. He had consulted with several doctors and had used various antibiotics for what was considered to be acne vulgaris. The patient, who had also been treated with oral doxycycline for a period of time, said that he had received some benefits from this treatment but that the hair loss was nevertheless gradually increasing.

A dermatological examination revealed a cicatricial plaque with a diameter of 7x8 cm, follicular tufting, especially on the periphery of the plaque, erythematous papules and pustules, and partial follicular crusts on the vertex of the scalp (Fig. 1A). There was also a wide range of keloidal hard papules and pustules measuring a few millimeters in diameter on the patient's neck (Fig. 1B). In addition, persistent erythema was detected on the cheeks, and millimetric follicular papules were present on his face, including the eyebrows (Fig. 2A). The thinning of his lateral eyebrows was also remarkable. Furthermore, diffuse millimetric follicular papules, suggestive of keratosis pilaris, were present on the trunk and extremities (Fig. 2B). However, the patient's oral mucosa and nails were normal. In the biopsy specimen taken from the pustular lesion on the vertex region, the epidermis was normal, but prominent lymphocytic inflammation was present which was destroying the follicle epithelium. In addition, neutrophils and plasma cells were seen in the dermis (Fig. 3A, B).
The biopsy taken from the neck showed epidermal acanthosis and perivascular mixed- type infiltrates along with neutrophils and fibrosis in the dermis (Fig. 4).

The stains were negative for bacteria and fungi, but the clinical and histopathological features of the nuchal lesions were consistent with AKN.

Moreover, an ophthalmological examination showed mild blepharitis, and a topical antibiotic was prescribed for treatment. We also established that there were no similar clinical features in the family of the patient, and the findings of a psychiatric evaluation were normal. The patient said that the lesions, which were consistent with keratosis pilaris, had been present since his childhood. Taking into account all of the clinical and laboratory results, we then diagnosed the patient with sporadic KFSD and initiated isotretinoin treatment.

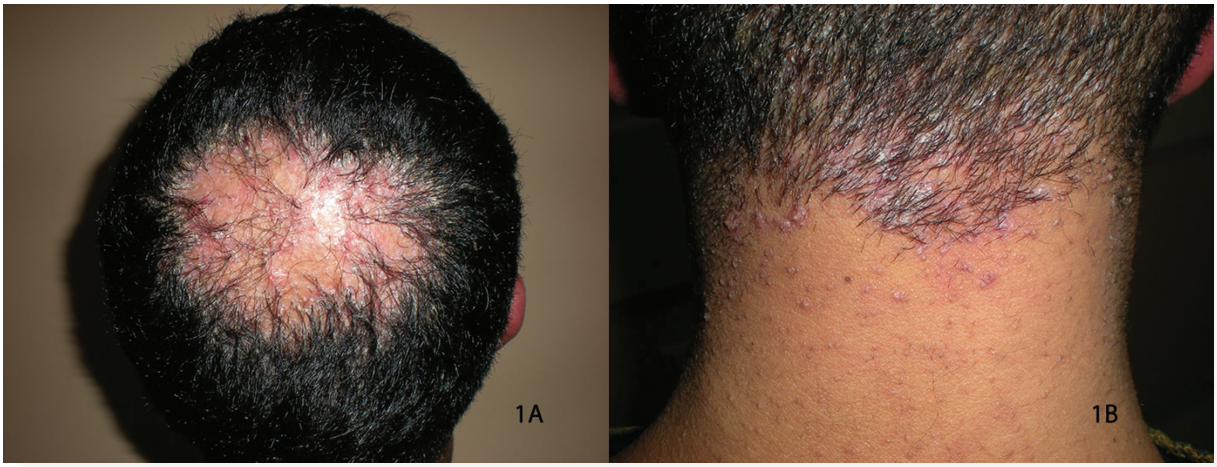

Figure 1A. Vertex of the scalp with scarring alopecia and tufted folliculitis. **B.** Acne keloidalis affecting the nuchal region.

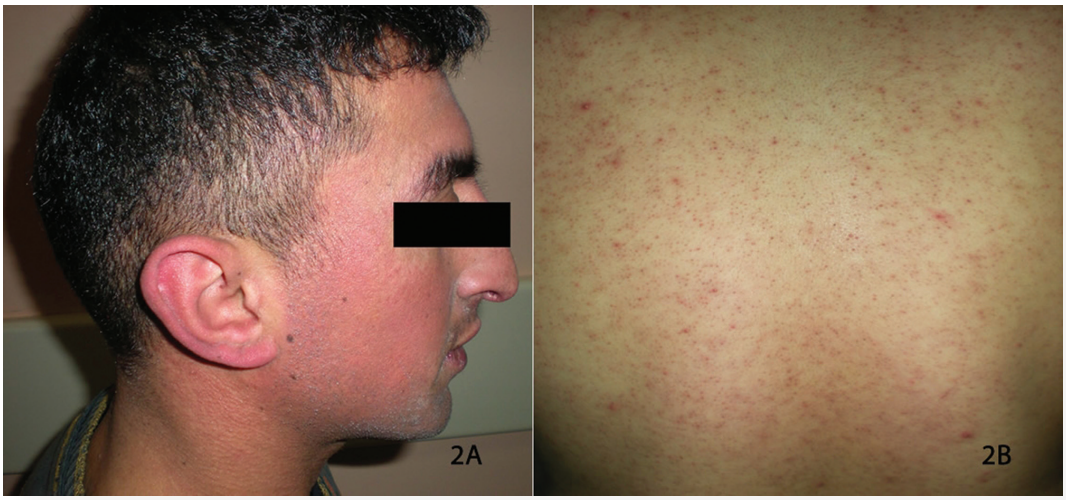

Figure 2A. Millimetric follicular papules affecting the lateral eyebrows and face. **B.** Keratosis pilaris on the trunk.

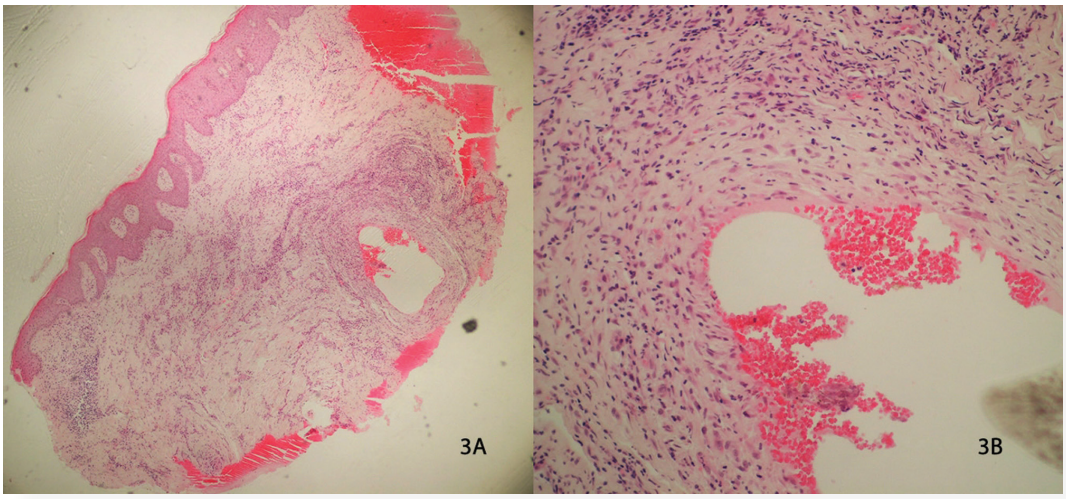

Figure 3A and B. Scalp histology showing the prominent, inflammatory perifollicular lymphocytic infiltrate in the dermis (H&Ex40 and H&Ex200).

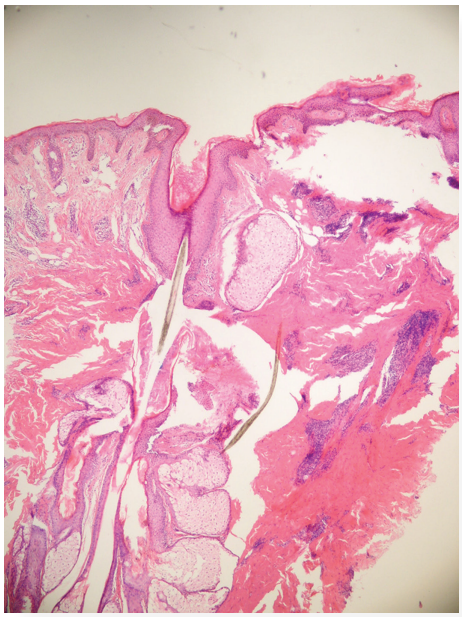

Figure 4. Histopathology of a nuchal papule showing the epidermal acanthosis and the perivascular mixed-type infiltrate along with the neutrophils and fibrosis in the dermis (H&E x40).

Discussion

Keratosis follicularis spinulosa decalvans is considered to be a keratinization disorder, and follicular hyperkeratosis, variable degrees of inflammation, and atrophic scars are characteristic features of this skin condition [4,5]. Follicular hyperkeratosis first appears on the cheeks and face in childhood, and keratosis pilaris lesions occur due to excessive accumulation of keratin in the hair follicles. In addition, progressive cicatricial alopecia may occur on the scalp, eyebrows, and eyelashes [6].

The mechanism of alopecia is not known. At first, it was suggested that the potential mechanism could be keratinization and follicular destruction associated with inflammation in the hair follicles that was caused by hyperkeratosis and hypergranulosis in the infundibulum and isthmus [6,7]. Follicular destruction is caused by hyperkeratosis as well as abnormal cytokine formation stemming from inflammatory reactions. Ophthalmologic findings of the disease include photophobia and corneal dystrophy. The photophobia is thought to be caused by conjunctivitis and hyperkeratotic lesions on the eyelids that occur because of corneal trauma [8]; however, this symptom usually regresses after puberty [7]. However, not all of the published cases include reports of photophobia in connection with alopecia. Palmoplantar hyperkeratosis, clinodactyly, and arachnodactyly should also be considered when examining the hands and feet in KFSD cases. In addition, nail examinations have revealed subungual hyperkeratosis, onycholysis, and cuticular hypertrophy, and gingival hypertrophy and dental agenesis may be seen in the oral mucosa [2,7,9,10]. Other clinical associations may include deafness, wooly hair, aminoaciduria, cutis hyperelastica, and mental retardation [8,9,11].

Acne keloidalis nuchae is a chronic disorder associated with folliculitis that is often seen in the neck area of young adult males. Grouped papules and pustules occur in the first stages of the disease, and in the later stages, keloidal papules, nuchal hypertrophic scars, chronic abscesses, and hair loss can be seen [12,13].

The exact cause of AKN is not yet known, but frequently suggested etiological possibilities are short haircuts along the posterior hairline and penetration of the cut hair into the skin, as in patients with pseudofolliculitis. In addition, constant irritation by shirt collars, a chronic low-grade bacterial infection, seborrhea, and increased testosterone levels are other possible causes [14,15].

In histopathological examinations of KFSD lesions, superficial intra- and perifollicular fluid along with neutrophil infiltration are present during the acute phase. In advanced stages, lymphocytic infiltration is accompanied by follicular destruction as well as concentric perifollicular fibrosis. Some factors should be considered when trying to distinguish between KFSD and AKN lesions histopathologically. For example, KFSD is classified under the lymphocytic group of primary cicatricial alopecias by the North American Hair Research Society, whereas AKN is classified under the group of alopecias in which mixed infiltration takes place. Furthermore, the presence of especially advanced-stage follicular plugs that can cause perforations in the follicular infundibulum, the formation of an abscess in the follicular environment, and hypertrophic scars in the dermis are all important indications of AKN [16].

It is extremely rare to find KFSD associated with AKN, and to date, only two cases have been reported in the literature. One of these cases, reported by Goh et al.,[5] had suffered from cicatricial alopecia and nuchal papular eruptions for ten years. Additionally, acute suppurative folliculitis was identified via a biopsy of the patient's scalp and neck. As in our case, cicatricial alopecia and concurrent nuchal follicular papules had been present for five years. Furthermore, the thinning of the lateral eyebrows in their patient was also accompained by, diffuse follicular papules on the face and body. Other cases pointed to acne keloidalis as well as tufted folliculitis [17]. In our case, follicular tufting was also found in the areas where cicatricial alopecia had developed, and this type of tufting can occur as the result of diseases associated with superficial purulent inflammation that cause cicatricial alopecia of the scalp. We believe this is what took place in our patient since we found fibrous scars caused by cicatricial alopecia and inflammation of the hair follicles.

In conclusion, our case featured a unique association between AKN and KFSD. Lesions related to AKN are an immune response to the presence of a stimulating factor, and we believe that KFSD was the stimulating factor in our patient. In other words, the KFSD increased the predisposition of the AKN. However, it is not known how AKN lesions develop nor is it clear how KFSD caused cicatricial alopecia of the scalp. Therefore, further investigations are needed to explore these topics.

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DOI: 10.7241/ourd.20142.37

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HERPES ZOSTER ON SEGMENTAL VITILIGO: ISOTOPIC RESPONSE?

Mankesh Lal Gambhir, Kritika Pandey, Tejinder Kaur

Department of Dermatology, Venereology & Leprosy, Government Medical College, Amritsar, Punjab, India

Source of Support:
Nil
Competing Interests:
None

Corresponding author: Ass. Prof. Mankesh Lal Gambhir *drmlgambhir@gmail.com*

Our Dermatol Online. 2014; 5(2): 155-156 Date of submission: 31.01.2014 / acceptance: 15.03.2014

Abstract
"Wolf's isotopic response" describes the occurrence of a new skin disorder at the site of another, unrelated and already healed skin disease. In most cases of isotopic response, the initial dermatosis is herpes zoster, herpes simplex, varicella, thrombophlebitis, scrofuloderma and striae distense. The most frequent second dermatoses are granulomatous reactions, particularly granuloma annulare, and lichenoid diseases. Various etiological reasons including viral, immunologic, neural and vascular have been put forth. We report here a case in which the second disease was herpes zoster that appeared over the same dermatomes of pre-existing segmental vitiligo. The occurrence of vitiligo as first and herpes zoster as second disease in the "Wolf's isotopic response" has not, to the best of our knowledge, been reported previously.

Key words: vitiligo; herpes zoster; isotopic response

Cite this article:
Gambhir ML, Pandey K, Kaur T. Herpes zoster on segmental vitiligo: Wolf's isotopic response? Our Dermatol Online. 2014; 5(2): 155-156.

Introduction

"Wolf's isotopic response" describes the occurrence of a new skin disorder at the site of another, unrelated and already healed skin disease. In most cases of isotopic response, the initial dermatosis is herpes zoster, herpes simplex, varicella, thrombophlebitis, scrofuloderma and striae distense. The most frequent second dermatoses are granulomatous reactions, particularly granuloma annulare, and lichenoid diseases. Various etiological reasons including viral, immunologic, neural and vascular have been put forth.

We report here a case in which the second disease was herpes zoster that appeared over the same dermatomes of pre-existing segmental vitiligo. The occurrence of vitiligo as first and herpes zoster as second disease in the "wolf's isotopic response" has not, to the best of our knowledge, been reported previously.

Case Report

A 56 year old female presented with a two day history of multiple vesicular lesions with burning pain at the site of depigmented patches of vitiligo of 8 years duration of the same region. On examination there were grouped vesicles distributed in a dermatomal fashion over the right mid thoracic region (T5-T6). On the background were the depigmented patches of segmental vitiligo involving T2-T6 thoracic dermatome (Fig 1). A clinical diagnosis of herpes zoster with segmental vitiligo of the same dermatome was made. Tzanck smear showed multinucleated giant cells. Routine investigations were normal. Oral acyclovir tablets 800mg five times daily were given for 7 days. The lesions healed completely within two weeks, with minimal scarring.

Discussion

The term, "Wolf's isotopic response", describes the occurrence of a new skin disorder at the site of another, unrelated and already healed skin disease [1]. It is important that the primary disease should have healed before the onset of the subsequent disease for it to be labeled as an isotopic response, to avoid mistaking it for reactivation of the primary disease, especially if the subsequent disease arise immediately [2].

In most cases of isotopic response, the initial dermatosis is herpes zoster [1], herpes simplex [3], varicella [3], thrombophlebitis [3], scrofuloderma [4] and striae distense [5].

The most frequent second dermatoses are granulomatous reactions, particularly granuloma annulare, and lichenoid diseases. Others are comedones and acneiform eruptions, tinea, furunculosis, contact dermatitis, nodular solar degeneration, morphea, graft-versus-host disease, eosinophilic dermatosis, reactive perforating collagenosis, lymphomas and leukemias, Kaposi sarcoma, angiosarcoma, vitiligo, basal cell carcinomas, squamous cell carcinomas and viral infections such as molluscum contagiosum or common warts.

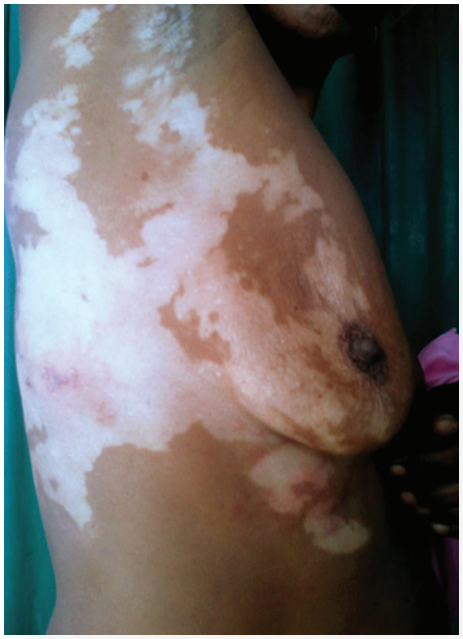

Figure 1. Herpes Zoster over segmental vitiligo: isotopic phenomenon.

A case of herpes simplex on scrofuloderma has been described [4,6].

Viral, immunologic, neural and vascular etiologic reasons have been put forth. Immunologic changes like an increased sensitivity to tissue antigens in the primary viral infection, scarring, altered microcirculation, collagen rearrangement, and an imperfect skin barrier have been described. The main possibilities were that: the first disease causes skin changes that lead to the occurrence of a second disease at the same site; each event is being caused by a different stimulus; a coincidence factor; and a "locus minoris resistentiae" which means "an area, site, structure or organ of lessened resistance, genetically inherited or acquired, offering little resistance to invasion by micro-organisms and/or their toxins" [2-4,7,8].

Alternatively, some authors proposed that altered tissue antigens might be playing a role in the pathomechanism of this phenomenon. The skin's memory may last a lifetime and this is particularly true concerning the immunologic memory [4].

Researchers have recently proposed the role of tumor necrosis factor (TNFα) in the immune response to herpes zoster and in a wide variety of inflammatory skin diseases, which may explain the occurrence of different diseases at same site [6].

Another interesting postulation puts forth is of bi-directional neuroimmunologic interaction. The secretion of neuropeptides from sensory nerve fibers in the skin has a variety of effects on mast cells, T-lymphocytes, monocytes and endothelial cells [4].

In many of the already reported cases a viral disease (herpes zoster or herpes simplex) was the first disease. It was assumed that the viral particles remaining in the tissue were responsible for the occurrence of a second disease [2,3,7,9,10].

We report here a case of "Wolf's isotopic phenomenon" in which the second disease was herpes zoster that appeared over the same dermatomes of pre-existing segmental vitiligo. The occurrence of vitiligo as first and herpes zoster as second disease in the "wolf's isotopic response" has not, to the best of our knowledge, been reported previously.

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DOI: 10.7241/ourd.20142.38

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PEMPHIGUS VULGARIS MASQUERADING AS *SUBCORNEAL PUSTULAR DERMATOSES* – A CASE REPORT

Vandini Kabra[1], Kanthilatha Pai[2], Sathish B. Pai[1], Shrutakirthi Shenoi[1], Raghavendra Rao[1]

[1]*Department of Dermatology, Kasturba Medical College, Manipal, Manipal University, Karnataka- India*
[2]*Department of Pathology, Kasturba Medical College, Manipal, Manipal University, Karnataka- India*

Source of Support: Nil
Competing Interests: None

Corresponding author: Dr Sathish B. Pai drsbpai@yahoo.co.in

Our Dermatol Online. 2014; 5(2): 157-159 Date of submission: 05.02.2014 / acceptance: 23.03.2014

Abstract
Both pemphigus vulgaris and subcorneal pustular dermatoses are intraepidermal blistering disorders though the treatment for the two varies. We present a 26 years old male patient with multiple vesicles and bullae filled with clear fluid as well as pus, hypopyon sign present, predominantly over the trunk and crusted lesions over the scalp. The patient did not have mucosal involvement at presentation and Nikolsky's and bulla spread sign were negative. A clinical diagnosis of subcornealpustulardermatosis and IgA pempgigus was made; however, direct immunofluorescence was suggestive of pemphigus vulgaris as was histopathology examination. The patient responded to treatment with oral corticosteroids. A previous case report of pemphigus foliaceous presenting as IgA pemphigus and responding to dapsone has been reported and so has a report of pemphigus vulgaris presenting with multiple pustules.

Key words: Pemphigus vulgaris; IgA pemphigus; Subcorneal pustular dermatosis

Cite this article:
Kabra V, Pai K, Pai B S, Shenoi S, Rao R. Pemphigus vulgaris masquerading as subcorneal pustular dermatoses – a case report. Our Dermatol Online. 2014; 5(2): 157-159.

Introduction

Pemphigus is a group of chronic autoimmune bullous diseases of the skin and/or mucosae characterized by the presence of desmoglein 3 and/or 1 antibody. There are mainly two types of pemphigus, pemphigus vulgaris (and its variant pemphigus vegetans), and pemphigus foliaceus (and its variant pemphigus erythematosus) [1]. In pemphigus vulgaris flaccid blisters filled with clear fluid arise either on normal skin or an erythematous base. Mucosal erosions may precede cutaneous lesions by many days or months. Direct immunofluorescence shows deposition of IgG and C3 in the intercellular spaces in a 'fishnet' pattern.

Subcorneal pustular dermatosis presents with flaccid pustules in which the pus characteristically accumulates in the lower half. Both direct and indirect immunofluorescence is negative.

IgA pemphigus presents as flaccid vesicles or pustules usually associated with pruritus. The lesions have a predilection for the axillae and groins. Intercellular IgA deposition is seen in the epidermis either at different levels or throughout.

This case is unique as the patient presented with lesions which were clinically suggestive of subcorneal pustular dermatosis but DIF proved otherewise.

Case Report

26 years old married male, fisherman, presented to us with painful lesions over the scalp since two months and fluid and pus filled vesicles and bullae over the trunk and upper limbs since 5-6 days associated with itching. Few lesions had ruptured after scratching to give rise to erosions. No history of spontaneous rupture of lesions, peripheral extension or history suggestive of healing with milia formation. There was no history of mucosal lesions at presentation. No history of prior drug intake, or any constitutional symptoms. No history suggestive of wheal formation or severe itching prior to development of lesions. There was no history suggestive of systemic involvement.

On examination he had crusting, erosions and matting of hair over the scalp. Multiple tense vesicles and bullae filled with both clear fluid and pus predominantly over the trunk (Fig. 1) and few over the arms, neck and medial aspect of thigh. Hypopyon sign was positive (Fig. 2).

Few erosions over trunk were seen. Oral cavity examination revealed single erosion over the left buccal mucosa. Genitals were normal. Both marginal and direct Nikolsky's and bulla spread sign were negative. A clinical diagnosis of subcorneal pustular dermatoses and IgA pemphigus was made and he was investigated.

Tzanck smear showed only pus cells and gram staining from pustule revealed gram positive cocci and pus cells. A perilesional skin biopsy for direct immunofluorescence showed intercellular staining with Ig G and C3 and skin biopsy from a vesicle showed suprabasal acantholysis with cleft formation and detached roof of the bullae. (Fig. 3) Basal cells with increased melanin pigmentation arranged in a row of tomb stone fashion in the base of the bulla were also seen. Indirect immunofluorescence showed intercellular staining with Ig G at 1:100 dilutions. ELISA for desmoglein 1 and 3 was positive with >200 RU/ml. Complete blood count, fasting, post prandial blood sugars, renal function, liver function tests and urine examination were within normal limits. Chest x-ray was normal. Serum protein electrophoresis showed normal pattern. On the basis of DIF, IIF, ELISA and histopathology findings a diagnosis of pemphigus vulgaris was made and patient as treated with oral prednisolone 1mg per kg body weight, to which he had a dramatic response.

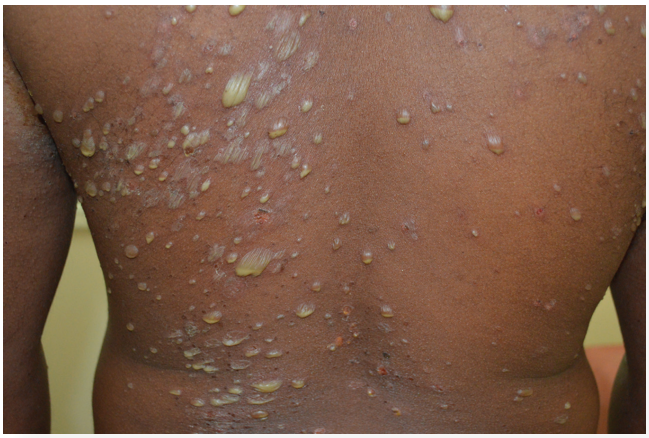

Figure 1. Multiple tense vesicles and bullae filled with both clear fluid and pus predominantly over the trunk.

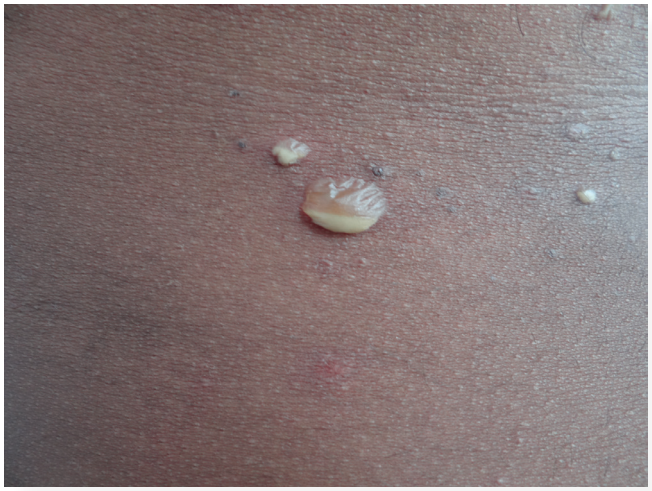

Figure 2. Hypopyon sign positive.

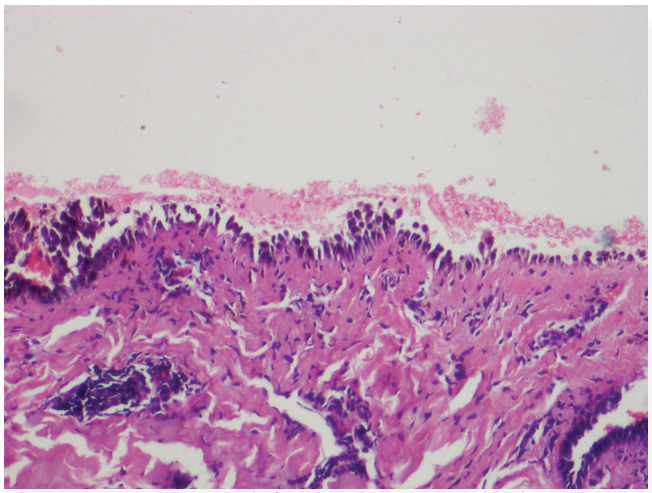

Figure 2. suprabasal cleft with few acantholytic cells and tombstoning of basal cells (the roof of bulla has denuded). (H&E 200X)

Discussion

The typical presentation of pemphigus vulgaris is as flaccid blisters which may occur anywhere on the skin surface. The blisters burst to give rise to erosions which have a tendency to spread at their periphery. 50-70 % of the patients may present with oral erosions which are irregularly shaped over the palate or buccal mucosa [2].

Many atypical presentations of pemphigus vulgaris have been reported. A 60 years old patient presented with ulceration over bilateral dorsa of feet which persisted for four months before the characteristic lesions of pemphigus vulgaris appeared. A 30 year old female patient presented with a single erythematous crusted plaque in the right nasal wing. On histologic examination and immunofluorescence it was found to be pemphigus vulgaris [3]. A 50 years old male patient presented with erythematous scaly plaques and was diagnosed as psoriasis which however did not respond to treatment for the same.

Direct immunofluorescence revealed pemphigus foliaceous [4]. Pemphigus foliaceous masquerading as IgA pemphigus and responding to dapsone has been reported [5]. There has also been a case report of pemphigus foliaceus presenting with prominent neutrophilic pustules where the lesions mimicked subcorneal pustularder matosis clinically [6]. In both cases a correct diagnosis was made based on the findings of direct immunofluorescence. No case reports have yet been reported where pemphigus vulgaris presented with subcorneal pustular dermatoses like lesions.

In our case a diagnosis of subcorneal pustular dermatosis and IgA pemphigus (subcorneal pustular dermatoses type) was made clinically but direct and indirect immunofluorescence showed features of pemphigus vulgaris. The treatment for pemphigus vulgaris and IgA pemphigus/subcorneal pustular dermatosis varies and thus a correct diagnosis is a must for proper treatment.

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DOI: 10.7241/ourd.20142.39

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TUBEROUS SCLEROSIS IN PREGNANCY

Sanjay N. Agrawal, Yoganand A. Kulkarni,
Yogeshree R. Deshmukh, Subodh D. Jane

Department of Dermatology, Dr. Panjabrao Deshmukh Memorial Medical College, Amravati-444603, Maharashtra, India

Source of Support:
Nil
Competing Interests:
None

Corresponding author: Dr Yogeshree R. Deshmukh dr.yogeshree@gmail.com

Our Dermatol Online. 2014; 5(2): 160-162 Date of submission: 04.02.2014 / acceptance: 22.03.2014

Abstract
Tuberous sclerosis is an autosomal dominant neurocutaenous disorder or neuroectodermatosis affecting multiple organ systems with variable clinical manifestations. We are reporting a case of a 26 years old female with history of epilepsy with mental retardation presented with fever and convulsions following an episode of stillbirth on first time with normal fetal outcome on second time. She had facial angiofibromas, shagreen patch, ash-leaf macules, periungual and subungual fibromas. She also had bilateral renal angiomyolipomas with haemorrhages and sub ependymal cortical tubers in brain. We report such a unique case having all clinically diagnostic physical sings of tuberous sclerosis with complicated obstetric history.

Key words: tuberous sclerosis; multisystem involvement; stillbirth; renal angiomyolipomas; cortical tubers

Cite this article:
Agrawal SN, Kulkarni YA, Deshmukh YR, Jane SD. Tuberous Sclerosis in Pregnancy. Our Dermatol Online. 2014; 5(2): 160-162.

Introduction

Tuberous sclerosis or Bourneville's disease is an autosomal dominant neurocutaneous disorder affecting multiple organ systems with various skin manifestations. It is characterised by presence of potato like tumours (Tuberous) in multiple organs. 30 percent of cases have Vogt's triad comprising of epilepsy, mental retardation and adenoma sebaceum. Many cases have been reported, but our case is unique in presence of nearly all major signs in a single patient, with association of a stillbirth [1].

We report such a unique case having all clinically diagnostic physical sings of tuberous sclerosis with complicated obstetric history.

Case Report

A 26 years old female presented with history of epilepsy since the age of 2 years with mental retardation. The patient had multiple asymptomatic skin lesions over face and back since the age of 7 years (Fig. 1A - C). No other family member had similar complaints or lesions. Patient presented with fever and generalised tonic clonic convulsions following an episode of stillbirth. The baby was stillborn with a large head and distended abdomen at 27 weeks of gestation. After two years she had normal healthy male child without any maternal complications. On examination, patient had angiofibromas (adenoma sebaceum) on face, shagreen patch over lumbosacral area, subungual and periungual fibromas on right forefinger and middle finger. She had ash leaf macules on the back.

Patient's encephalogram was normal. Patients Intelligent Quotient was 60, suggestive of mild mental retardation. Chest radiograph and radiograph of skull were normal. Ultrasonography of abdomen and pelvis showed large angiomyolipoma (with hemorrhages within) in upper pole of right kidney with multiple small sizes angiomyolipoma in rest of both kidney with mild splenomegally. Computed tomogram (CT) of brain showed calcified and enhancing sub ependymal cortical tubers along both lateral ventricles and Enhancing cortical tubers noted in left frontal lobe with gyriform enhancement of left frontal lobe suggestive of hamartoma (Fig. 2).

Discussion

Tuberous sclerosis is an autosomal dominant disorder. Two genetic loci have been identified in Tuberous Sclerosis Complex. The first gene, tuberous sclerosis complex-1 (TSC-1), maps to chromosome 9, specifically 9q34, and encodes the protein hamartin, which is a tumour suppressor gene. The second gene (TSC -2) maps to chromosome 16, specifically 16p13, and codes for tuberin. Hamartin and tuberin act synergistically to regulate cellular growth and differentiation. The desregulation in organogenesis results in hamartomas, which may affect any organ in the body [2].

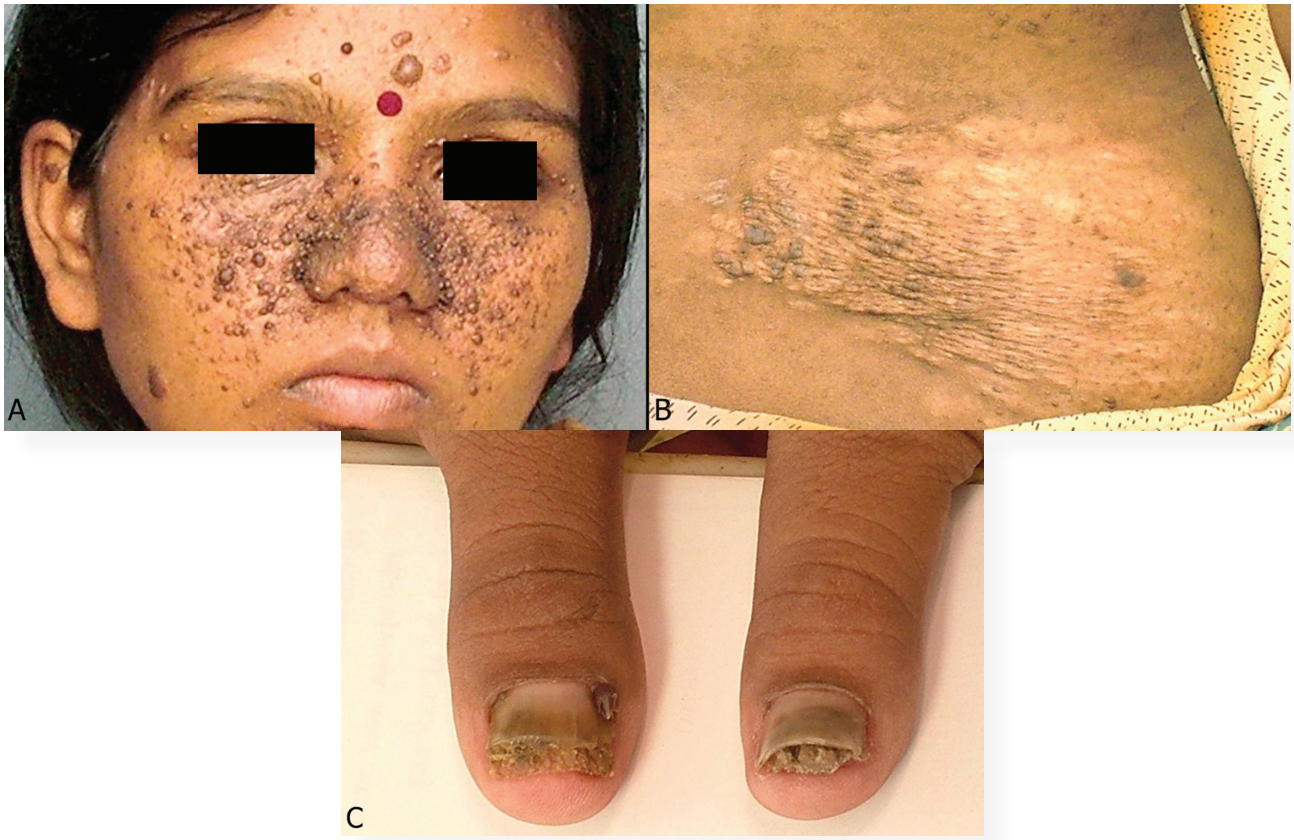

Figure 1A - C. A. Facial angiofibroma, previously termed adenoma sebaceum, in a patient with tuberous sclerosis complex (TSC); **B.** A shagreen patch is a connective tissue hamartoma with a leathery texture and is found most commonly in the lower back region; **C.** Periungual fibroma on the thumb of a patient with tuberous sclerosis complex (TSC).

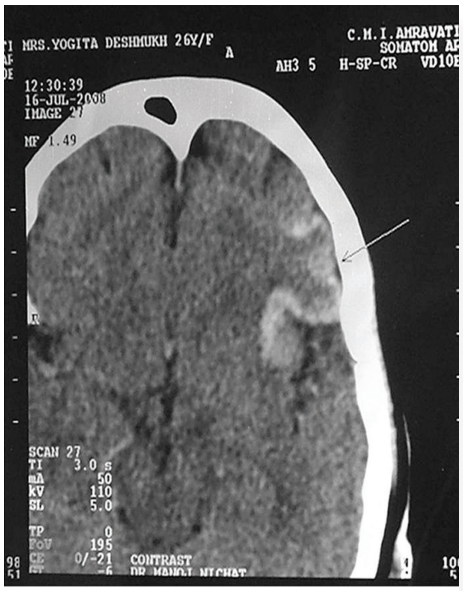

Figure 2. Frontal lobe hamartoma.

The characteristic Vogt's triad comprising of Epilepsy, Mental retardation and Adenoma sebaceum is present in 30% of patients. Gomez, in 1979 gave criteria for diagnosis of tuberous sclerosis. Gomez criteria include [3]:

Primary Criteria: (one of the following)

Adenoma sebaceum, Periungual fibroma, Cortical tubers, Retinal hamartomas.

Secondary Criteria: (two of the following)

Infantile spasms, Ash leaf macules, Shagreen patch, Bilateral renal AML, Cardiac Rhabdomyomas, single retinal hamartaomas.

The Vogt's triad is present in our patient and Gomez criteria are also fulfilled confirming the diagnosis of tuberous sclerosis. Our case had all the major criteria of Gomez (Fig. 1A - C).

Our patient had a stillbirth at 27 weeks of gestation with large head and distended abdomen, most probably due to nonimmune hydrops fetalis or renal involvement Tuberous sclerosis can lead to intrauterine fetal death. So it is important that the patient's genetic counseling has to be done and regular antenatal follow up is required if the patient conceives.

The renal angiomyolipomas may enlarge, rupture and bleed which can cause retroperitoneal haemorrhage and death. Renal angiomyolipomas, though major criteria, is uncommonly looked for. Ultrasonography should be done in all patients of tuberous sclerosis, to rule out renal angiomyolipomas (Fig. 3, 4).

There is no specific treatment for this disease. The seizures can be treated with carbamazepine, lamotrigene and vigabatrin. Surgical decompression can be tried for renal angiomyolipomas and ungual fibromas can be excised Laser, cautery, diathermy and dermabrasion can be used for adenoma sebaceum and shagreen patch.

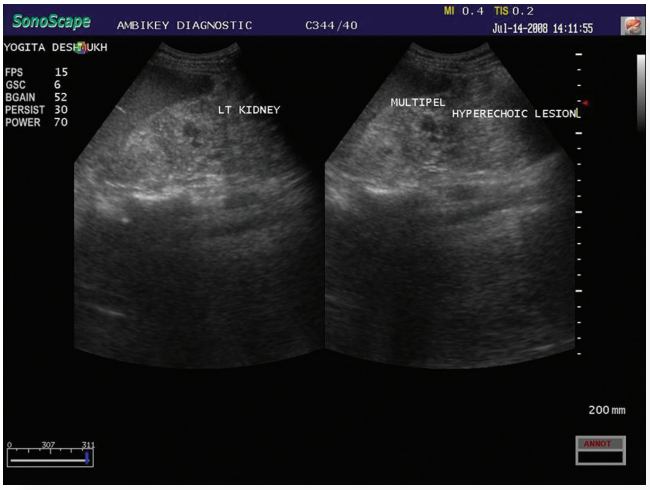

Figure 3. Renal angiomyo lipoma.

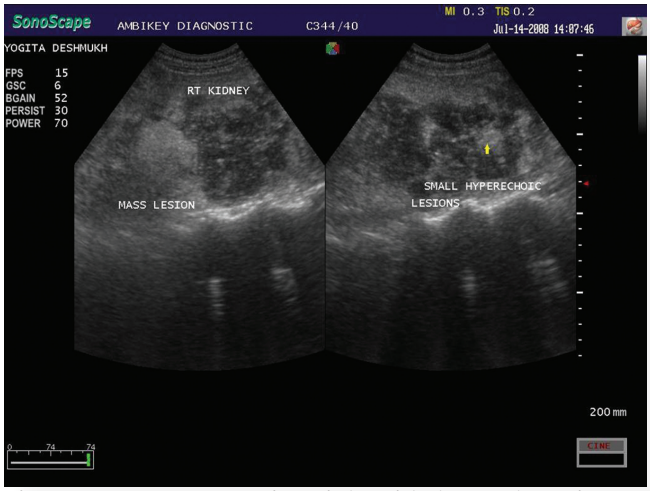

Figure 4. Haemorrage in Right sided Renal angiomyo lipoma.

There are only four cases of tuberous sclerosis in pregnancy in the literature. Two of these had favourable maternal and fetal outcomes and the remaining two presented with serious maternal and fetal complications. These included acute intra-abdominal bleeding due to a ruptured renal tumour, which led to renal failure requiring haemodialysis, and severe preeclampsia with pathologically enlarged kidneys noted at the time of caesarean section.

We present a case of tuberous sclerosis in pregnancy with renal involvement with bleeding into a renal cyst, renal failure, preeclampsia, and severe intrauterine growth retardation during first conception. Similar case on second time delivered healthy male child with no maternal complication. Renal involvement appears to be the single most important prognostic factor in pregnancies with tuberous sclerosis. Renal evaluation should be performed in any patient who presents for pre-conceptional counselling [4].

We report this case due to its rare association between pregnancy and tuberous sclerosis.

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DOI: 10.7241/ourd.20142.40

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POROQUERATOSIS. REPORTE DE TRES CASOS.
POROKERATOSIS. REPORT OF THREE CASES

Celeste Valiente Rebull, Lourdes Rodríguez, Gabriela Martinez Braga, Beatriz Di Martino Ortiz, Mirtha Rodriguez Masi, Oilda Knopfelmacher, Lourdes Bolla de Lezcano

Cátedra de Dermatología. Hospital de Clínicas. Facultad de Ciencias Médicas. Universidad Nacional de Asunción. Paraguay

Corresponding author: Prof. Beatriz Di Martino Ortiz *beatrizdimartino@gmail.com*

Source of Support: Nil
Competing Interests: None

Our Dermatol Online. 2014; 5(2): 163-168 Date of submission: 19.02.2014 / acceptance: 30.03.2014

Resumen
Las poroqueratosis (PQ) son un grupo de trastornos de la queratinización cutánea, de carácter adquirido o hereditario. Su expresión clínica consiste en una mácula o placa anular de centro atrófico y bordes bien definidos e hiperqueratósicos, cuya imagen histológica es una columna paraqueratósica compacta, denominada laminilla cornoide. El número y la distribución de las lesiones definen las diferentes formas clínicas: poroqueratosis de Mibelli, poroqueratosis actínica superficial diseminada (PASD), poroqueratosis lineal, poroqueratosis palmo-plantar y poroqueratosis punctata.
Presentamos 3 casos clínicos y hacemos una breve revisión de la literatura.

Abstract
The porokeratosis are a group of disorders of the skin keratinization of acquired or hereditary character. Its clinical expression is a macular or annular plaque, atrophic in the center and with well-defined hyperkeratotic edges and the histological picture is a compact parakeratotic column, called cornoid lamella. The number and distribution of lesions define the different clinical forms of porokeratosis: Mibelli, disseminated superficial actinic porokeratosis (DSAP), linear porokeratosis, palmoplantar porokeratosis and punctate porokeratosis.
We report 3 cases and make a brief review of the literature.

Palabras clave: poroqueratosis; laminilla cornoide; Poroqueratosis de Mibelli
Key words: porokeratosis; cornoid lamella; Porokeratosis of Mibelli

Cite this article:
Valiente Rebull C, Rodríguez L, Martinez Braga G, Di Martino Ortiz B, Rodriguez Masi M, Knopfelmacher O, Bolla de Lezcano L. Poroqueratosis. Reporte de tres casos. [Porokeratosis. Report of three cases]. Our Dermatol Online. 2014; 5(2): 163-168.

Introducción

Las poroqueratosisis, son trastornos de la queratinización, que se caracterizan por lesiones hiperqueratósicas con un anillo periférico prominente, cuyo sustrato histopatológico es una columna paraqueratósica compacta, denominada laminilla cornoide. Se observa con más frecuencia en áreas geográficas con alta exposición solar. Se transmite con un patrón de herencia autosómico dominante y penetrancia reducida, y la enfermedad se desarrolla habitualmente a partir de los 35-40 años de edad [1-3].

La etiopatogenia de las PQ todavía no ha sido totalmente aclarada, pero parece ser compleja y multifactorial. Una hipótesis clásica, aunque no demostrada formalmente, establece que las lesiones de PQ se deben a la extensión centrífuga de un clon de queratinocitos epidérmicos anómalos mutantes, situados en la base de la laminilla cornoide [2-3].

Los factores de riesgo para DSAP, la forma más común y estudiada de poroqueratosis incluye factores genéticos, exposición ultravioleta, e inmunosupresión. Existe un incremento del 7.5% al 10% en poroqueratosis-principalmente poroqueratosis de Mibelli y poroqueratosis superficial diseminada, una variante similar a DSAP que ocurre en piel no expuesta al sol- en individuos inmunosuprimidos por la reducida inmunidad.

Estos factores de riesgo incluyen transplantes de órganos, linfomas, infección por HIV, y enfermedades inflamatorias o autoinmunes tratadas con inmunosupresores, con incidencia más alta en trasplantados de órganos sólidos, principalmente de riñones [4].

Casos clínicos

Caso 1

Varón, 42 años, procedente de Asunción, pintor de obra. Presenta cuadro de 20 años de evolución de lesiones tipo quemadura de cigarrillo, primero en piel de abdomen, luego en brazos y piernas y un año antes de la consulta máculas hipocrómicas que se tornan eritematosas con la exposición solar.

Al examen físico se observan múltiples placas hiperpigmentadas entre 0,5 a 3 cm de diámetro, de bordes sobreelevados irregulares, límites netos, con centro deprimido, que asientan en abdomen y tronco (Fig. 1).

Al examen histopatológico se observa una invaginación de la epidermis de cuyo centro emerge una columna paraqueratósica o laminilla cornoide que atraviesa la capa córnea. En la base de la laminilla se observa la ausencia de la capa granulosa y células vacuoladas (Fig. 2).

Diagnóstico final: de Poroqueratosis de Mibelli. Se iniciaron retinoides y queratolíticos tópicos con parcial mejoría.

Caso 2

Mujer, 55 años, ama de casa, procedente de área urbana del Paraguay, hipotiroidea en tratamiento con T4. Cuadro de dos meses de evolución de prurito en brazos, piernas y rostro, que se exacerba con el sol, tratada previamente con trivalentes y antialérgicos sin mejoría.

Al examen físico se aprecian múltiples pápulas hiperpigmentadas hiperqueratósicas entre 0,5 a 1,5 cm de diámetro, con centro levemente deprimido, distribuidas en brazos y piernas (Fig. 3).

El examen anatomopatológico revela laminilla cornoide y cambios actínicos del colágeno dérmico (Fig. 4).

Diagnóstico: Poroqueratosis Actínica Superficial Diseminada.

Se inició protección solar, retinoides y queratolíticos tópicos, con parcial mejoría.

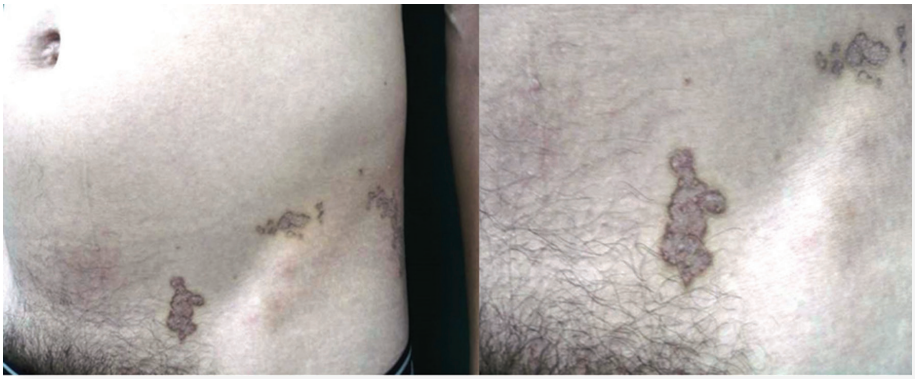

Figura 1. Caso 1. Clínica. Placas hiperpigmentadas entre 0,5 a 3 cm de diámetro, de bordes sobreelevados irregulares, límites netos, con centro deprimido, que asientan en región inguinal izquierda.

Figure 1. Case 1. Clinic. Hyperpigmented plaques between 0.5 to 3 cm in diameter, with irregular raised edges, net limits, depressed center, located in the left inguinal region.

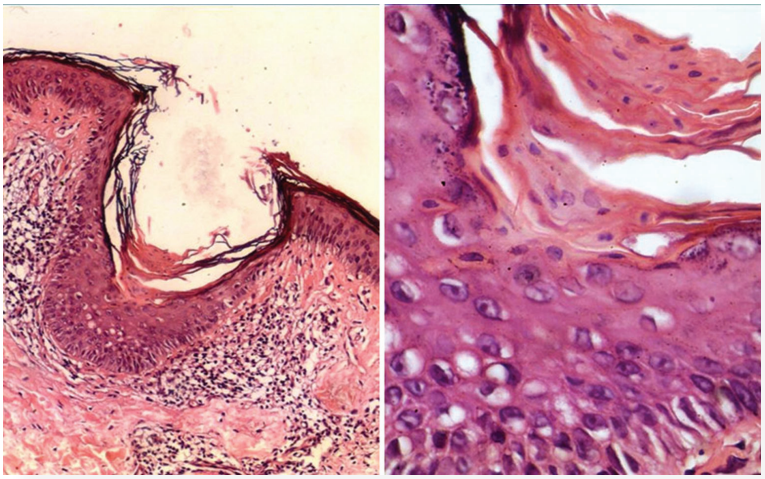

Figura 2. Caso 1. Histopatología. Invaginación epidérmica de cuyo centro emerge una columna paraqueratósica o laminilla cornoide que atraviesa la capa córnea (izquierda). En la base de la laminilla se observa la ausencia de la capa granulosa y células disqueratósicas (derecha).

Figure 2. Case 1. Histopathology. Epidermal invagination, of the center emerges a parakeratotic column traversing the stratum corneum (left). At the base of the lamella the absence of the granular layer and dyskeratotic cells is observed (right).

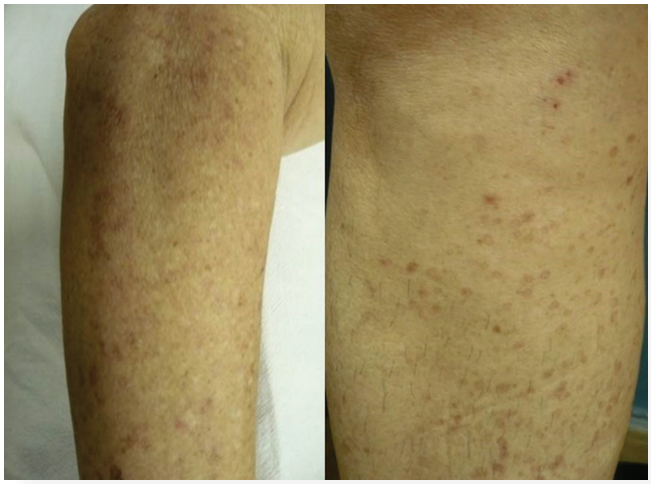

Figura 3. Caso 2. Clínica. Múltiples pápulas hiperpigmentadas hiperqueratósicas entre 0,5 a 1,5 cm de diámetro, con centro levemente deprimido, distribuidas en brazos (izquierda) y piernas (derecha).
Figure 3. Clinic. Multiple hyperpigmented hyperkeratotic papules between 0.5 to 1.5 cm in diameter, with slightly depressed center, distributed arms (left) and legs (right).

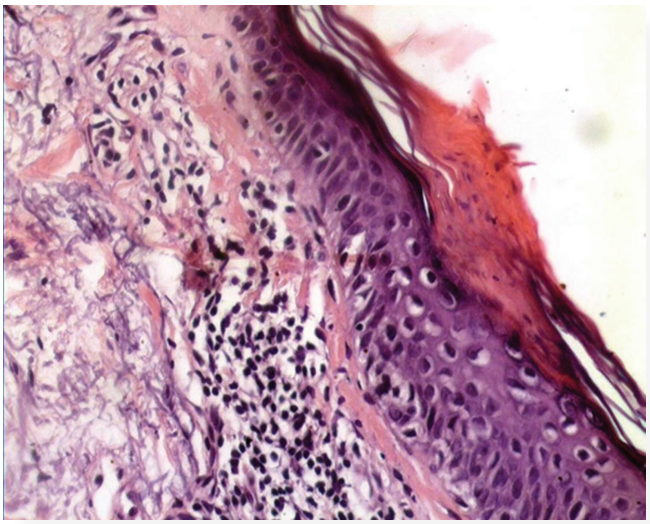

Figura 4. Caso 2. Histopatología. Laminilla cornoide y cambios actínicos del colágeno dérmico.
Figure 4. Case 2. Histopathology. Cornoid lamella and actinic changes of dermal collagen.

Caso 3

Mujer, 45 años, soltera, vendedora ambulante, con historia de un año de evolución, de máculas en piel de ambos brazos, acompañadas de prurito, con extensión posterior de las lesiones al rostro y cuello.

Al examen físico se observan múltiples placas anulares de bordes hiperqueratósicos, hiperpigmentadas, con centro atrófico de 0,5 a 0,8 cm de diámetro, bordes regulares, límites netos, que asientan en piel de rostro, escote, brazos (Fig. 5).

En la histopatología se aprecia laminilla cornoide oblicua a la superficie cutánea, ligera degeneración granulosa en su inserción epidérmica y epidermis de los márgenes con pérdida de redes de crestas, hiperpigmentación basal y ortoqueratosis. Dermis con telangiectasias, cambios degenerativos de fibras elásticas y colágenas y numerosos melanófagos (Fig. 6).

Diagnóstico: Poroqueratosis Actínica Superficial Diseminada.

Se inician fotoprotección e isotretinoína oral, con mejoría de lesiones.

Comentarios

Las poroqueratosis (PQ) constituyen un grupo de genodermatosis poco frecuentes. Se caracterizan por un trastorno de la queratinización de origen desconocido [2].

Las poroqueratosis se manifiestan por el desarrollo de lesiones queratósicas en la piel con una imagen histológica característica, la laminilla cornoide [2,3].

La genética de la poroqueratosis no se ha resuelto completamente, pero se han propuesto varias explicaciones para las manifestaciones clínicas.

La poroqueratosis actínica superficial diseminada (DSAP) se hereda de manera autosómica dominante con disminución de la penetrancia del 22%.

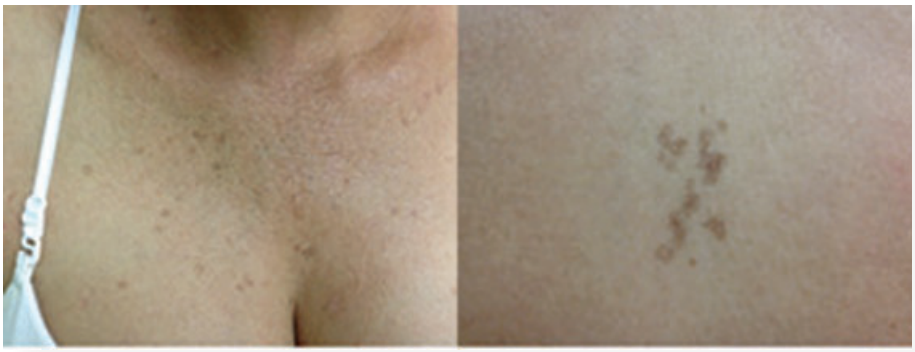

Figura 5. Caso 3. Múltiples placas anulares de bordes hiperqueratósicos, hiperpigmentadas, con centro atrófico de 0,5 a 0,8 cm de diámetro, bordes regulares, límites netos, que asientan en escote.
Figure 5. Case 3. Clinic. Multiple hyperkeratotic annular plaques, hyperpigmented, with atrophic center 0.5 to 0.8 cm in diameter, regular margins, net limits, located in the neckline.

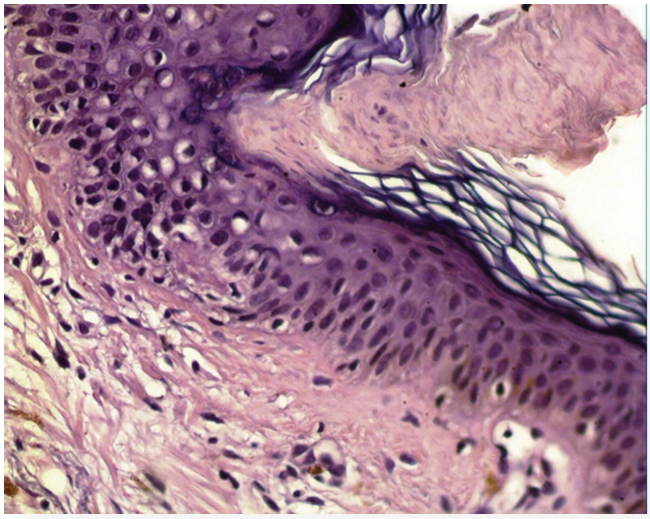

Figura 6. Caso 3. Histopatología. Laminilla cornoide oblicua a la superficie cutánea.
Figure 6. Case 3. Histopathology. Cornoid lamella obliquely to the skin surface.

Un alelo defectuoso en el genoma de un individuo heterocigocico es suficiente para expresar la enfermedad. La expresión cutánea es difusa, porque todas las células del cuerpo tienen la mutación. La expresión retardada de DSAP en el adulto es probablemente por eventos de mutación gatillados por la exposición a largo plazo. Las formas que se presentan en la infancia y niñez (poroqueratosis de Mibelli y poroqueratosis linear) probablemente tengan genéticas diferentes [4].

A las poroqueratosis las podemos clasificar en:

· Formas localizadas: poroqueratosis de Mibelli clásica o localizada, poroqueratosis lineal, poroqueratosis punctata [2,3].

· Formas diseminadas: poroqueratosis superficial diseminada, poroqueratosis actínica superficial diseminada, poroqueratosis palmo-plantar diseminada [2,3].

En otra revisión, existen 6 variantes clínicas, incluyendo el tipo de Mibelli o en placas, superficial diseminada, actínica superficial diseminada, linear, punctata, y diseminada palmar y plantar [5].

La poroqueratosis de Mibelli es una variedad poco frecuente, puede aparecer en cualquier edad, generalmente después de la niñez, pero en los casos sin antecedentes familiares el inicio es tardío. Las lesiones predominan en los miembros y pueden localizarse también en la cara, los labios, las regiones palmo-plantares, áreas genitales, las nalgas y la mucosa bucal. Existe un predominio masculino (2:1). Se caracteriza por una a varias placas anulares o policíclicas de gran tamaño asintomática (de 2 hasta 20 cm), generalmente unilaterales y con menos frecuencia bilaterales y simétricas, inician como pápulas hiperqueratósicas pequeñas y asintomáticas que aumentan paulatinamente de tamaño, de manera centrífuga, para formar una placa oval de borde bien definido, con un reborde hiperqueratósico elevado y un surco a lo largo del mismo. El diagnóstico diferencial liquen plano, verrugas, queratosis actínicas, epitelioma basocelular, y carcinoma de células escamosas [2,6].

La poroqueratosis lineal, es sumamente rara y no ha podido establecerse relación, a diferencia del caso presentado por De Kok E y cols, con rasgos hereditarios. Puede presentarse desde el nacimiento hasta la edad adulta y el número de las lesiones es variable. Las lesiones presentan una distribución lineal, zosteriforme, que involucra principalmente las extremidades, su disposición lineal y unilateral constituye el rasgo característico para el diagnóstico, puede afectar las palmas y plantas [7-9]. Puede presentarse también como fenómeno de Koebner. Es muy parecido a un hamartoma epidérmico, una psoriasis lineal o un liquen estriado o un nevus verrugoso lineal [2,6]. En esta variedad se han descrito degeneración maligna y metástasis [6].

La poroqueratosis punctata es una variante también poco frecuente, presencia de numerosos tapones queratósicos pequeños con borde elevado, que no presentan tendencia a aumentar de tamaño y se localizan en palmas y plantas. Patrón de herencia y edad de inicio de difícil determinación [6]. El diagnóstico diferencial incluye síndrome de nevo carcinoma celular, queratosis arsenicales, enfermedad de Darier, liquen nítido palmoplantar y de la queratodermia punctata. En ocasiones las lesiones son sensibles a la presión. Esta forma puede estar asociada a la PQ de Mibelli o a la PQ Lineal [2].

Las lesiones exclusivamente faciales son raras, aunque el 15% de los pacientes que tiene el tipo generalizado, presenta lesiones faciales, ya que generalmente, la poroqueratosis se presenta en el tronco y las extremidades [9,10]. Las formas localizadas en cara se producen, usualmente, en mujeres en la edad media, con un promedio de duración de la enfermedad de uno a diez años, caracterizada por pápulas y placas entre 0,1 cm y 1 cm, en la nariz y la región perinasal [10,14].

La poroqueratosis actínica superficial diseminada (PASD) es una dermatosis crónica, más generalizada que la poroqueratosis de Mibelli y limitada a las áreas del cuerpo expuestas a la luz solar. Los pacientes refieren exacerbaciones asociadas con prurito y ardor en la piel durante los meses de verano [14]. En el caso de la PASD, el gen identificado como responsable de esta dermatosis es el SSH1, localizado en 12q23.2-24.1 y en el cromosoma 15q25.1-26.1 [3] En el diagnóstico diferencial de la PASD deben considerarse la acroqueratosis de Hopf, el liquen plano atrófico, la estucoqueratosis, la queratosis actínica, la enfermedad de Bowen, las verrugas planas, la epidermodisplasia verruciforme y la elastosis perforante serpiginosa [2,15,16].

El diagnóstico clínico de la PASD es sencillo en los casos en los que la laminilla cornoide es evidente. Sin embargo, el borde hiperqueratósico de las lesiones de PASD es a menudo sutil, por lo que el diagnóstico clínico puede facilitarse mediante la aplicación de violeta de genciana o povidona yodada sobre las mismas [15,17,18].

Actualmente no existe un tratamiento ideal para la PASD que sea seguro, eficaz y sin efectos indeseables derivados de su aplicación (p. ej., cicatrices no estéticas y dolor) [3].

La Poroqueratosis superficial diseminada es una forma de PQ de predominio femenino, que clínicamente se asemeja a la PASD pero que puede ocurrir en zonas tanto expuestas como no expuestas a la luz [2].

En la variedad palmo plantar, las lesiones inician principalmente durante la segunda década de la vida y generalmente existe historia familiar, afectan mayormente a varones. Las lesiones numerosas son maculopapulares de borde elevado e hiperqueratósico no mayor de 1mm de altura, con un surco longitudinal a lo largo del mismo, inicialmente en palmas y plantas y se extienden a las extremidades y tronco. Puede presentarse prurito y lesiones en mucosas, en la bucal pueden ser anulares opalescentes. No existe relación con la exposición solar y puede afectar áreas no expuestas a la luz [2,6].

Además se cita un raro síndrome, asociado a este trastorno, conocido como el síndrome CAP consistente en craneosinostosis familiar, hipoplasia de clavícula, anomalías anales y poroqueratosis [10]. Tiene una prevalencia de menos de 1 habitante en 1.000.000, herencia autosómica recesiva, con edad de inicio neonatal/infancia. Se ha descrito en siete pacientes de cuatro familias no relacionadas. Las anomalías craneales incluyen sinostosis coronal con fontanelas (anterior y posterior) ampliamente abiertas y foramenes parietales grandes, además malformaciones genitourinarias, en algunos pacientes la erupción cutánea ha sido clasificada como poroqueratosis (trastorno de la queratinización). Son comunes la pérdida de audición neurosensorial y un retraso en el desarrollo de leve a grave [11].

Recientemente se ha aplicado la dermatoscopia al diagnóstico clínico de la poroqueratosis; es una técnica no invasiva que permite observar una estructura anular blanquecina o amarillenta que se corresponde con la laminilla cornoide, junto a un área central atrófica de aspecto cicatricial [15,19].

Es fundamental la biopsia cutánea, debido a que el diagnóstico se basa en el hallazgo de la laminilla cornoide. La laminilla es un defecto localizado de la queratinización caracterizada por una fina columna de células paraqueratósicas con una ausencia o disminución del espesor de la capa de células granulosas y células vacuoladas o disqueratósicas en el estrato espinoso. Aunque es un hallazgo característico de la poroqueratosis y sus variantes clínicas puede ser encontrada como un fenómeno incidental en un gran rango de enfermedades inflamatorias, hiperplásicas y condiciones neoplásicas de la piel [1-4,15].

Se describe a la poroqueratosis asociada a estados de inmunosupresión, casos relacionados con enfermedades hematológicas, enfermedades hepáticas, terapia inmune debido a trasplante de órganos, infección por HIV y enfermedades autoinmunes. De todos, el tipo más común de inmunosupresión asociado a poroqueratosis es el trasplante de órganos. La incidencia de poroqueratosis luego de trasplante varía entre 0,34% y 3,4% en las diferentes series, según una revisión realizada por Kanitakis et al [20,21].

Es importante considerar el potencial maligno de esta dermatosis, puesto que se ha descrito transformación maligna en todos los tipos de poroqueratosis [15].

Se especula con que la inmunosupresión pueda activar clones anormales de queratinocitos en sujetos predispuestos; sin embargo, algunos autores resaltan la importancia de factores como la alteración de la inmunidad humoral o agentes transmisibles como el virus de la hepatitis C (VHC) [22,23].

Se ha estimado el riesgo global en un 7-10 % de todos los tipos de poroqueratosis, la enfermedad de Bowen es la lesión maligna más encontrada, seguida del carcinoma espinocelular y con menor frecuencia el carcinoma basocelular [15,24].

Considerando el potencial maligno de la dermatosis, las recomendaciones generales deben orientarse hacia las medidas destructivas como: crioterapia, láser ablativo como el de CO2 o la extirpación quirúrgica en los casos con lesiones escasas [3].

Son esenciales, en cualquier caso, las medidas preventivas orientadas a evitar factores desencadenantes, especialmente la fotoprotección [3].

Las terapéuticas como crioterapia con nitrógeno líquido o aplicación tópica de 5-fluoruracilo (5-FU) en crema son generalmente impracticables o no satisfactorias [2,15].

El imiquimod tópico al 5% en crema puede ser un tratamiento útil. La limitada experiencia de los autores sugiere que el tratamiento se debería introducir cuidadosamente y debería usarse inicialmente 3 veces por semana para evitar la inflamación excesiva [25].

Los queratolíticos tópicos como diclofenaco al 3% en gel provee alguna protección contra la progresión de la enfermedad, láser Q-switched, terapia fotodinámica, acitretin y extirpación han sido parcial o completamente satisfactorias en casos individuales [25].

En conclusión presentamos estos tres casos debido a la escasa frecuencia de esta enfermedad, sobre todo porque somos un país mediterráneo, con una gran cantidad de radiación solar recibida diariamente. Cabe destacar la importancia de la fotoprotección y más aún la fotoeducación desde temprana edad, no solo en la población de riesgo, sino en la población en general. Se cita en la literatura múltiples tratamientos, que no proporcionan una cura definitiva, por lo que ninguna terapéutica es altamente efectiva ni estandarizada. Lo fundamental es proporcionar al paciente la mejor calidad de vida posible, vigilándolo muy de cerca por el riesgo de malignidad potencial existente con estas patologías.

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DOI: 10.7241/ourd.20142.41

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TUBERCULAR ABSCESS OF THE LOWER LIP: A RARE CASE OF MISTAKEN IDENTITY

Safia Rana[1], Seema Monga[2], Sabina Khan[1], Shaan Khetrapal[1], Sujata Jetley[1]

[1]*Department of Pathology, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, Hamdard Nagar, New Delhi 110062, India*
[2]*Deparment of ENT, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, Hamdard Nagar, New Delhi 110062, India*

Corresponding author: Prof. Sujata Jetley sujatajetley@gmail.com

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2011; 5(2): 169-171 Date of submission: 01.03.2014 / acceptance: 04.04.2014

Abstract
Tuberculosis of the oral cavity accounts for less than one percent of all cases of tuberculosis, seen in both the primary and secondary stages of the disease. It presents usually as a single, painful, ulcer however, multiple painless ulcers may also be seen. The most common location in the oral cavity is tongue. The palate, buccal mucosa, floor of the mouth, gingiva, and lip are other possible sites of involvement. In secondary tuberculosis, oral lesions are accompanied by lesions in the lungs, lymph nodes, or in any other part of the body. We hereby report a case of tuberculosis of lip in a 24 year old female, secondary to pulmonary tuberculosis.

Key words: Tuberculosis; lip; secondary

Cite this article:
Rana S, Monga S, Khan S, Khetrapal S, Jetley S. Tubercular abscess of the lower lip: a rare case of mistaken identity. Our Dermatol Online. 2014; 5(2): 169-171.

Introduction

Oral lesions of tuberculosis can be seen either as primary lesion or may manifest as secondary stage of the disease. The commonest site of tubercular involvement in the oral cavity is the tongue and involvement of lip, as was seen in this case is exceptionally rare. Primary oral tuberculosis may present as a diagnostic challenge for the clinician especially when it is the the sole manifestation of the disease [1]. Secondary oral tuberculosis usually results from inoculation by the infected sputum or hematogenous spread by Mycobacteria [2].

Case Report

A 24 year old female patient presented in the ENT Outpatient Department with lower lip swelling for past 25 days. There was no history of fever, cough or hemoptysis. The patient complained of loss of appetite and weight since the last few months. On enquiring, a history of contact was elicited, as her husband was a known case of tuberculosis who was diagnosed 3 years back. A history of irregular intake of anti-tubercular drugs was also obtained from him. The patient was a non-smoker and there was no history of alcohol intake or tobacco chewing. Her general condition was stable, she was afebrile and no pallor, icterus or cervical lymphadenopathy was noted. Local examination showed a swelling on the mucosal aspect of the lower lip which had a soft cystic consistency, measuring 1x1 cm in size and reddish blue in colour (Fig. 1). A provisional diagnosis of retention cyst was made in the ENT OPD and patient was referred for fine needle aspiration cytology of the lip swelling. Aspiration yielded a blood mixed fluid aspirate which was stained with Giemsa stain and examined microscopically. The FNAC smears showed moderate cellularity comprising of sheets of histiocytes along with neutrophils in a highly necrotic background. Many epithelioid cell granulomas and multinucleated giant cells were also evident (Fig. 2). Ziel Neilson stain for acid fast bacilli was found to be positive (Fig. 3). A cytological impression of tubercular abscess, lower lip was made.

Routine haematological and biochemical investigations were all within normal limits however Erythrocyte Sedimentation Rate was raised with a 40 mm fall in 1st hour. Routine urine and microscopy was within normal limits. Serological tests for Hepatitis B Surface Antigen, HIV-1 and HIV-2 were non–reactive.

Chest X ray PA view showed a lobulated soft tissue opacity in the right hilum suggestive of lymphadenopathy and also small opacities in right upper lobe. CECT chest was advised for further evaluation. CECT thorax showed multiple enlarged, conglomerate, necrotic peripherally enhancing lymph nodes in right paratracheal, pretracheal, subcarinal and prevascular, right hilar locations. Few small discrete nodular opacities with surrounding ground glass haze were seen in the posterior segment of right upper lobe, subpleural in right base, apical segment of left lower lobe and in left basal region. The radiological impression of an infective pathology, likely Koch's etiology was made A. standard combination treatment of four drug regimen (anti-tuberculous treatment) was started, which resulted in symptomatic improvement in the patient and healing of the lesion.

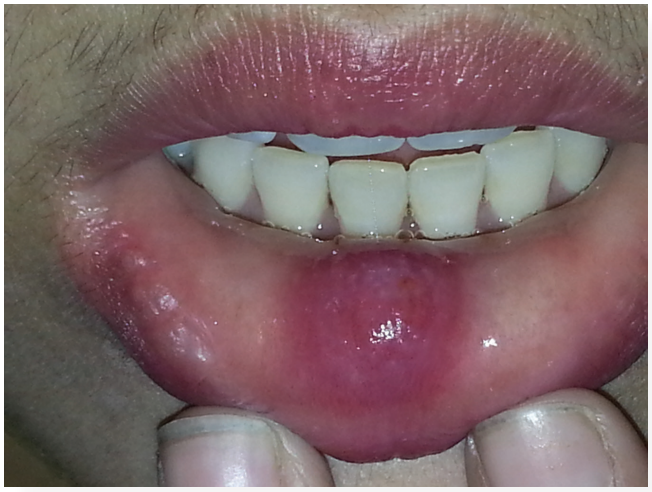

Figure 1. A swelling on the mucosal aspect of lower lip.

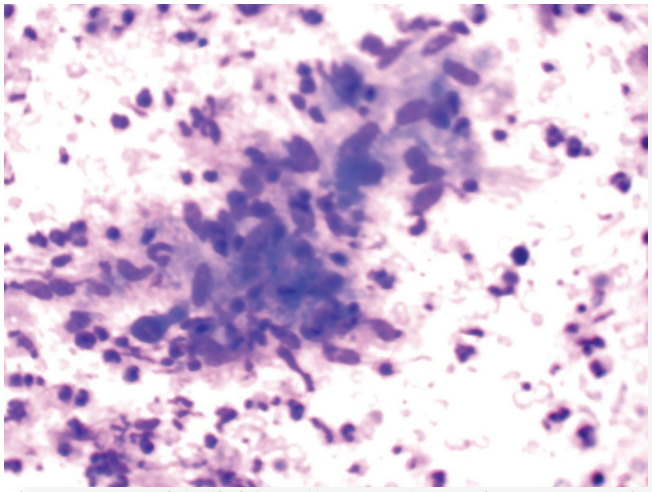

Figure 2. Epithelioid cell granuloma in a necrotic background. (Giemsa, 40X)

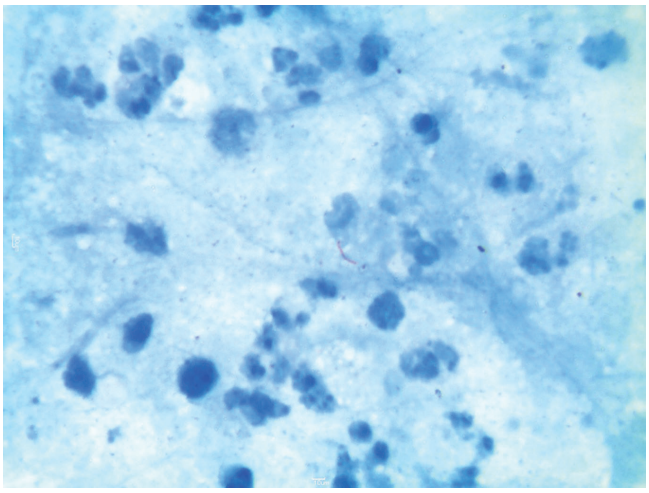

Figure 3. Presence of acid fast bacilli. (Z.N stain, 100X)

Discussion

The oral cavity is an uncommon site of involvement by tuberculosis. Oral TB is rare and accounts for less than 1% of all cases of TB. However with increase in number of TB cases, these unusual forms of oral cavity are more likely to occur and may be misdiagnosed [3]. Oral tuberculosis is seldom primary, but more commonly secondary to pulmonary disease. A study has reported four cases of tuberculosis of oral cavity one of which was primary and three were secondary. [4] It was found as a secondary infection in 58% and as primary infection in 42% patients [5]. Oral lesions of tuberculosis are non-specific in their clinical presentation and are often overlooked by the clinician. Tuberculous lesion occasionally precedes the detection of pulmonary tuberculosis as seen in the present case. Mostly lesion presents as a non healing painful ulcer [5] in which a differential diagnosis of simple traumatic ulcer and carcinoma can also be considered. In the present case the clinical presentation was unusual, a cystic lesion was seen in the lower lip and the first impression was a retention cyst. There were no enlarged cervical lymphnodes which also was an unusual feature.

M. tuberculosis infects all parts of the oral cavity, more often in males [5]. The tongue, gingiva and palate are the most frequent sites of involvement by oral tuberculosis. In the tongue the common sites of ulcer formation are the lateral border and the tip of the tongue, whereas the hard palate is more frequently involved than the soft palate [1]. Tubercular involvement of the lip, as seen in our case is even rarer.

Although the exact pathogenesis, is still unknown, the organism enters through breach in the mucosal surface. Abbot et al were able to isolate the tubercle bacilli from mouth washings of 44.9% of the patients with active pulmonary tuberculosis [6]. It is usually acquired through infected sputum coughed out by a patient with open pulmonary tuberculosis or by hematogenous spread [7]. The tubercle bacilli are transferred from a primary focus in some part of the body and localized in oral cavity, after trauma. The systemic factors include impaired host resistance and increased virulence of the organisms [8].

The involvement of maxilla and the mandible may occur secondary to the extension of gingival lesion or by hematogenous route leading to tuberculous osteomyelitis. FNAC suggested the diagnosis of a granulomatous lesion and the diagnosis of tuberculosis was considered. It was further confirmed by AFB staining. FNAC may show similar findings in atypical mycobacterial infections, sarcoidosis and lymphomas [9].
In oral cavity TB, standard treatment regimen is successful, so a planned standard combination treatment of four drug regimen was started, resulting in gradual relief of symptoms and healing of the lesion [10,11].

Conclusion

Tubercular involvement of the lip is a rare presentation of a common disease. This case highlights the importance of a high index of suspicion among clinicians for this manifestation of tuberculosis which will lead to timely diagnosis and institution of specific anti-tubercular treatment. Evidence of systemic or lung involvement may not be present in all cases and laboratory and radiological findings serve as a good marker, especially when there is high index of suspicion. Definitive tissue diagnosis along with demonstration of AFB, as in the present case remains the gold standard.

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DOI: 10.7241/ourd.20142.42

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PLASMOACANTHOMA OF ORAL CAVITY AND PLASMA CELL CHEILITIS: TWO SIDES OF SAME DISORDER "ORAL PLASMA CELL MUCOSITIS"?

Gayatri Khatri[1], Vikram K Mahajan[1], Pushpinder S. Chauhan[1], Karaninder S. Mehta[1], Bal Chander[2], Mrinal Gupta[1]

[1]*Department of Dermatology, Venereology & Leprosy, Dr. R. P. Govt. Medical College, Kangra (Tanda) -176001 (Himachal Pradesh), India*
[2]*Department of Pathology, Dr. R. P. Govt. Medical College, Kangra (Tanda) -176001 (Himachal Pradesh), India*

Corresponding author: Dr. Vikram K. Mahajan *vkm1@rediffmail.com*

Source of Support: Nil
Competing Interests: None

Our Dermatol Online. 2011; 5(2): 172-175 Date of submission: 22.11.2013 / acceptance: 20.01.2014

Abstract
Plasmoacanthoma and plasma cell cheilitis are rare disorders of obscure etiology characterized by a plasma cell infiltrate. An 80-year-old woman presented with a verrucous, fleshy, skin colored plaque over lips, gingiva, and the palate and painful swallowing for over a period of 6 months. Histopathology of the lesion showed dense infiltrate of plasma cells. The lesions resolved completely after intralesional triamcinolone acetonide. Another 52-year-old male had progressively enlarging, erosive lesion over vermilion border of lower lip for 6months resembling actinic cheilitis. Histology was diagnostic of plasma cell cheilitis. Treatment with topical clobetasol propionate was effective. Plasma cell cheilitis and plasmoacanthoma perhaps represent a spectrum of oral "plasma cell mucositis" with plasmoacanthoma being an advanced version of the former.

Key words: Atypical gingivostomatitis; Paraneoplastic acanthosis nigricans; Plasmoacanthoma; Plasma cell cheilitis; Plasma cell mucositis

Cite this article:
Khatri G, Mahajan VK, Chauhan PS, Mehta KS, Chander B, Gupta M. Plasmoacanthoma of oral cavity and plasma cell cheilitis: two sides of same disorder "oral plasma cell mucositis"? Our Dermatol Online. 2014; 5(2): 172-175

Introduction

Reactive plasma cell proliferation represents a heterogeneous spectrum of mucocutaneous disorders manifesting clinically with intensive hyperemia, erosions or lobulated warty lesions affecting mostly mucosal/orificial areas [1]. These have been considered to be benign immunologic inflammatory reaction to known (subclinical infection, friction, poor hygiene, trauma, etc.) or unknown stimuli. However, its etiology largely remains speculative. Plasmoacanthoma is a rare benign tumor with plasma cell infiltrate involving the oral mucosa, particularly oral commissures, and perianal areas. Plasma cell cheilitis and plasma cell balanitis of Zoon too have similar dense plasma cell infiltrate. Zoon's balanitis occurs almost exclusively in uncircumcised men and is speculated to be due to poor hygiene, heat, chronic irritation or *Mycobacterium smegmatis* infection [2]. Although White et al [3] tried to clarify some of the confusion by grouping together these similar disorders involving different body sites (vulva, buccal mucosa, tongue, palate, epiglottis, and larynx) under the nomenclature of "plasma cell mucositis", its exact clinical status remained under studied. Recent reports on co-occurrence of plasma cell mucositis and plasmoacnathoma or intertriginous plasmacytosis of skin, plasma cell orificial mucosistis together with plasmoacanthoma of oral commissures and peri-anum [4,5] has evoked considerable interest for pathogenesis of this rare entity. Cases of plasma cell infiltrate of gums, tongue, oral and labial mucosa have been described mostly under atypical gingivostomatitis, plasma cell gingivostomatitis, plasma cell gingivitis or plasmacytosis mucosae in dental literature but this unusual entity remains under reported in dermatology literature. We feel that both are two sides of one disorder, oral plasma cell mucositis' and should be evaluated as such.

Case Report

Case 1

This 80-year-old woman presented with fleshy, verrucous, skin colored plaque involving the lips and oral cavity. She had feeling of sore mouth and chewing was associated with pain. She was not known to have allergy to any food, beverages, toothpaste, or dentifrices. She was non-smoker, had never consumed alcohol or used nasal snuff/mouth wash, and received no treatment.

It had started with a painful ulcer and papules on the lower lip that over a period of 6months had increased in size and number and coalesced to form a verrucous plaque involving the lips, gingiva, palate and buccal mucosa (Fig. 1 A, B). A small ulcer was visible on the right buccal mucosa with shaggy necrotic base, undermined edges and yellowish necrotic slough. She also had swelling, fissuring and crusting of the lips, more so of the lower lip. Cervical and right submandibular lymph nodes were enlarged, firm and mobile. Systemic examination including for ear, nose and throat (ENT) was normal. She was investigated with the provisional diagnosis of paraneoplastic (malignant) acanthosis nigricans. Laboratory work up including complete hemogram, peripheral blood film for abnormal cells, erythrocyte sedimentation rate, serum biochemistry, thyroid and hepato-renal function tests, VDRL, urinalysis were normal. Fine needle aspiration cytology from an enlarged cervical lymph node showed reactive hyperplasia. Chest and skull x-rays, barium meal and follow-through, ultrasonography for abdomen and pelvic organs, and computed tomography scan for thorax showed no abnormality. No organisms were identified in KOH mounts, Giemsa or Gram's stained tissue smears or on culture of biopsy specimen. Histologic features of ulcerated epidermis with focal neutrophilic exocytosis and dense plasma cell infiltrate in the dermis were suggestive of plasma cell cytoma or multiple myeloma (Fig. 2 A - D). Serum electrophoresis for ‚M' proteins spike and urine for Bence-Jones proteins were negative. With the final diagnosis of plasmoacanthoma the whole lesion (labial, buccal, palatal) was infiltrated with triamcinolone acetonide (40mg/ml). On follow up after 3weeks there was marked improvement in the lesions (Fig. 1 C, D) and a second dose of intralesional triamcinolone acetonide 40 mg was infiltrated as earlier. No recurrence has occurred during 2-year follow up.

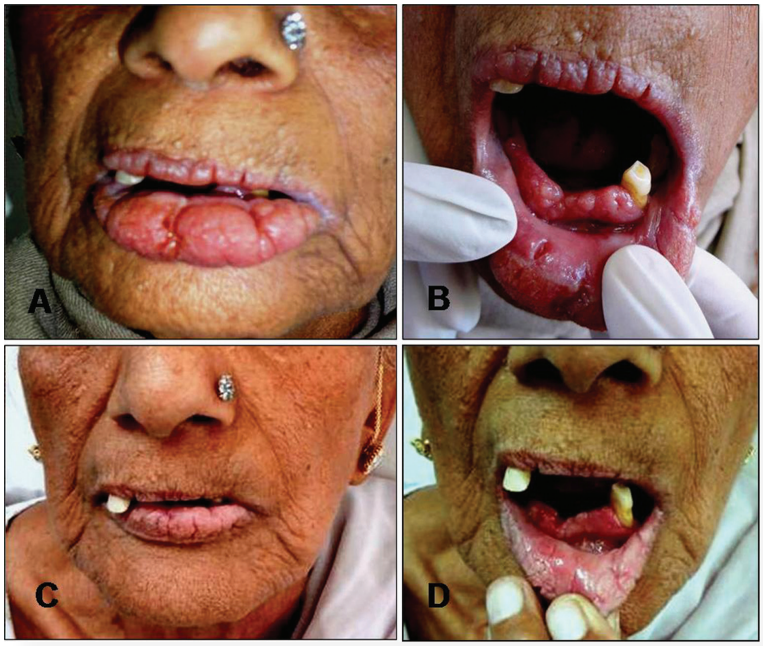

Figure 1A and B. Fleshy, verrucous plaque over lips and angle of mouth, gingiva, and oral mucosa. Both lips show fissuring and cracking, lower lip is more involved. Note edentulous lower jaw and cobblestone like verrucous surface of gingiva. Upper gingiva and palate had similar lesions. **C and D.** Three weeks after the first intralesional triamcinolone acetonide injection).

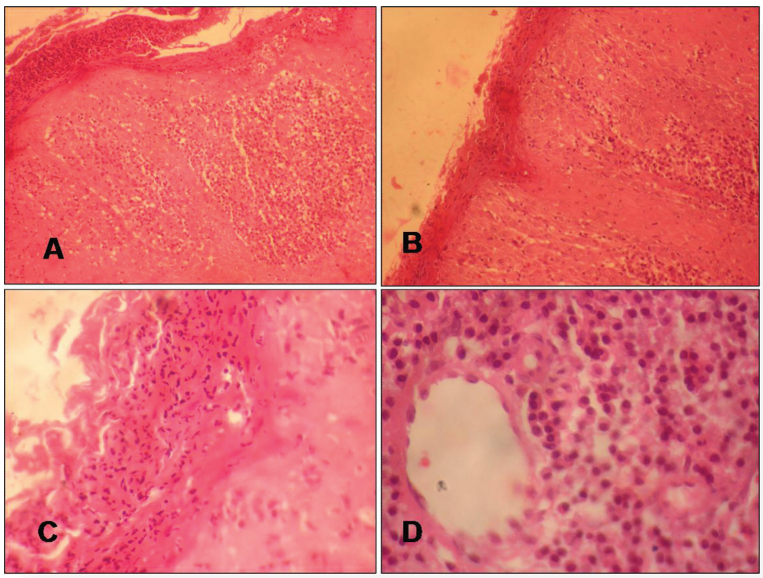

Figure 2A and B. Histology of skin lesion shows focally ulcerated epidermis, prominent rete rigdes, neutrophilic infiltrate in the epidermis and dense plasma cell infiltrate in the dermis (H&E, x10). **C and D.** Focally ulcerated epidermis with focal neutrophilic exocytosis, dense plasma cell infiltrate in dermis (H&E, x40).

Case 2

This 52-year-old male developed a small erosive lesion over lower lip which had progressed to involve the whole lip in 6months. Irritation, burning and occasional bleeding following minor trauma were common symptoms. The erosion was mainly confined to vermilion border of lower lip, showed ill defined to well demarcated and irregular borders, and bright erythematous floor having white slough, crusting and small bleeding at places (Fig. 3A). Regional lymph nodes were not enlarged. He was a smoker for many years but did not consume alcohol or used nasal snuff. He had no allergy to any food, beverages, toothpaste, or dentifrices. He had poor orodental hygiene, gingivitis and few missing teeth. Systemic examination, complete blood counts, serum biochemistry, VDRL, urinalysis and x-ray chest were normal. Lesional biopsy with a clinical diagnosis of actinic cheilitis showed ulcerated epithelial lining, dermal inflammatory infiltrate comprising dense aggregates of plasma cells, few lymphocytes, occasional neutrophils and few macrophages especially in the peri-appendagial and peri-vascular areas suggestive of benign plasma cell cheilitis (Fig. 3B, C). The smooth muscle cells in deeper tissue showed no inflammation. He did not follow up after initial improvement with topical clobetasol propionate 0.05% ointment applied twice daily.

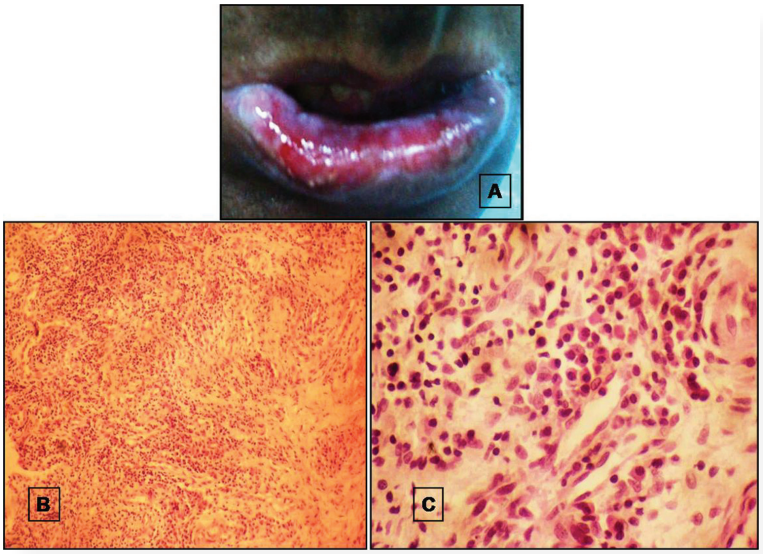

Figure 3A. Superficial, brightly erythematous, poorly demarcated, irregular shaped erosion over vermilion lower lip having white slough at places. **B.** Histology of skin lesion shows dense inflammation in the dermis (H&E, x4). **C.** Chronic inflammatory infiltrate comprises mainly plasma cells along with few lymphocytes (H&E, x40).

Discussion

Plasmoacanthoma is a verrucous tumour with plasma cell infiltrate involving the oral mucosa, particularly oral commissures. Perianal, periumbilical, or inguinal areas and toe web involvement has been reported [4]. Plasma cell cheilitis is another idiopathic benign inflammatory condition of lips having similar dense plasma cell infiltrate histologically. The usual presenting feature is an asymptomatic patch or plaque of erythema and induration of the lower lip in an elderly person akin to Zoon's plasma cell balanitis. The significance of trauma/chronic irritation in the pathogenesis of plasma cell cheilitis too has been emphasized from its enhanced incidence in persons habitually chewing tobacco and certain gums, using dentifrices, mint and artificial dentures or snuff intranasally [6]. Similarly, plasmoacanthoma too has been reported following trauma from beak of a bird or insect bites [6]. *Candida albicans* has been implicated in some cases [4]. However, its association with low levels of serum and secretary IgA remains unsubstantiated [4]. Poor orodental hygiene and associated inflammation seems likely cause in our patients as we could not elicit history of any other preceding trauma/irritation, allergies, tobacco/gum chewing, or use of other dentifrices and causal relationship with smoking will be speculative in case-2. Both plasmoacanthoma and plasma cell cheiltis are entirely benign conditions. Resolution after treatment with intralesional/topical and systemic steroids, griseofulvin, anti-candidial drugs, surgical excision or destructive procedures (Co2 laser ablation, electro-coagulation, cryotherapy) has been observed [1]. Response to intralesional triamcinolone acetonide or topical clobetasol propionate in our patients was notable. Papillomatous plaques of plasmoacanthoma in the oral cavity clinically mimic paraneoplastic acanthosis nigricans (P-AN) on mucous membranes. P-AN is a cutaneous manifestation of underlying malignancy especially adenocarcinoma of the gastrointestinal tract (gastric, gall bladder, pancreas, liver or colorectal adenocarcinoma), lungs, breast, prostate and ovaries [1,6]. P-AN often involves nasolarynx and esophageal mucosa, eyelids and conjunctiva accompanying with extensive cutaneous involvement. Similarly, lower lip plasma cell cheilitis needs be differentiated from actinic cheilitis that may have similar clinical presentation but contrarily therapeutic response to oral antimalarial is usually dramatic.

The benign nature of the lesions in our cases was apparent from clinicopathologic features and therapeutic response to intralesional/topical corticosteroids. Moreover, we did not find any laboratory evidence (serum electrophoresis, Bence-Jones proteins in urine) of plasma cell cytoma or multiple myeloma in case-1. Similarly, the histopathology showed no features of erosive lichen planus in case-2. Although seems speculative, we opine that plasma cell cheilitis and plasmoacanthoma perhaps represent a spectrum of the same disease "the oral plasma cell mucositis".

This appears plausible in view of the reports of co-occurrence of plasma cell mucositis and plasmoacnathoma or intertriginous plasmacytosis of skin, plasma cell orificial mucosistis together with plasmoacanthoma of oral commissures and peri-anum [4,5]; plasmoacanthoma perhaps representing its papillomatous version. However, due to lack of significant number of cases there is paucity of literature on the subject.

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DOI: 10.7241/ourd.20142.43

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A CASE OF *PYOGENIC GRANULOMA* AT AN UNUSUAL LOCATION

Yugandar Inakanti, Akshaya Nagaraja, Srilakshmi Peddireddy, Vijayshankar Metikurke

Department of Dermatology, Venerology and Leprosy, P.E.S. Institute of Medical Sciences and Research, Kuppam, AP, India

Source of Support: Nil
Competing Interests: None

Corresponding author: Dr. Yugandar Inakanti dryugandar@gmail.com

Our Dermatol Online. 2014; 5(2): 176-178 Date of submission: 16.12.2013 / acceptance: 27.01.2014

Abstract
Pyogenic granulomas are common, acquired, benign vascular lesions of the skin and mucousmembranes that can develop both spontaneously and traumatically. Pyogenic Granuloma more commonly involves Gingiva (75% of all the cases). An extragingival occurrence of pyogenic granuloma is rare. We present an unique case of a male patient aged 24 years affected by Pyogenic Granuloma of urethral meatus. Although penile pyogenic granulomas have previously been observed over glans penis, prepuce and shaft of penis,there are no reports affecting meatus.

Key words: Benign lesions; Botromycosis; Pyogenic Granuloma; Urethral Meatus

Cite this article:
Inakanti Y, Nagaraja A , Peddireddy S, Metikurke V. A case of Pyogenic Granuloma at an Unusual Location. Our Dermatol Online. 2014; 5(2): 176-178.

Introduction

Pyogenic Granuloma described first byHullihen,is a benign, non-neoplastic, mucocutaneous lesion. The name, "pyogenic granuloma" is a misnomer,since this condition is not associated with pus and as it does not represent a Granuloma histologically. PG is thought to represent an exuberant tissue response to a local irritation or trauma [1].

Case Report

A 24 years old male patient reported to our department with the complaints of a growth over the glans penis near meatus of six months duration, sudden in onset, had gradually increased to the present size and was associated with spotting.

The unmarried patient denied genital trauma and history of sexual intercourse during the preceding 6 months. The physical examinations were with in normal limits. No lymphadenopathy observed. On systemic examination no abnormality was revealed. Clinically there was no evidence of sexually transmitted diseases. Following investigations of complete blood counts, ESR, chest radiography, HIV, VDRL and mantoux test were within normal limits.

The clinical examination revealed a small, erythematous papuleover the glans penis at the meatus, measuring about 0.5cm in diameter (Fig. 1, 2). The lesion was soft in consistency and non tender, with minimal bleeding.

A differential diagnosis of Pyogenic Granuloma, Cherry angioma, Urethral caruncle Angiokeratoma, genital wart and Pyoderma gangrenosum [6] was considered.

Because of its small size, an excisional biopsy was done and submitted for histological examination.

The histopathologic examination showed an intact epidemis. The sub epithelial region showed many thin walled varying sized capillaries, few dilated and filled with RBC's. The intervening stroma showed infiltrate predominately of neutrophils, occasional areas showing hemosiderin deposits (Fig. 3 A, B).

Histology confirmed the diagnosis of Pyogenic Granuloma.

Discussion

Pyogenic Granuloma is a vascular nodule that develops rapidly, often at the site of a recent injury, and is composed of a lobular proliferation of capillaries in a loose stroma [2].

In 1844, Hullihen described the first case of pyogenic granuloma. In 1897 Pyogenic granuloma in man was described as "botryomycosis hominis." Hartzell in 1904 is credited with giving the current term of "pyogenic granuloma" or "granuloma pyogenicum." It was also called as Crocker and Hartzell's disease. Angelopoulos histologically described it as "hemangiomatous granuloma" due to the presence of numerous blood vessels and the inflammatory nature of the lesion [1].

Gingiva is the predominant site followed by lips and hard plate. Oral pyogenic granuloma is more common in females, in second and fifth decades due to the vascular effects of the female hormones [1].

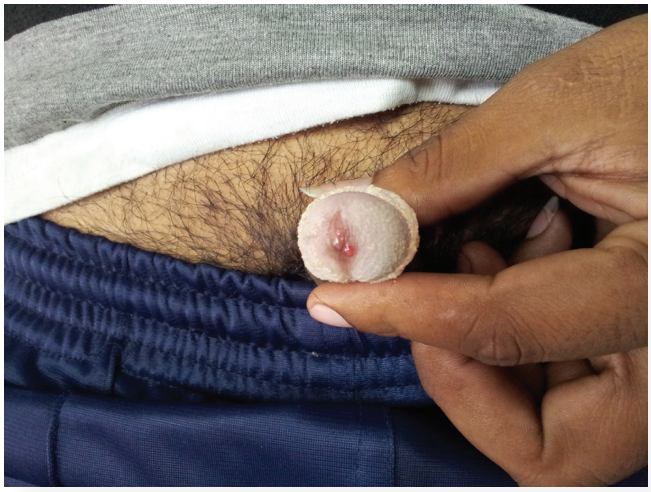

Figure 1. Glistening, red papule over urethral meatus with poor hygienic glans penis.

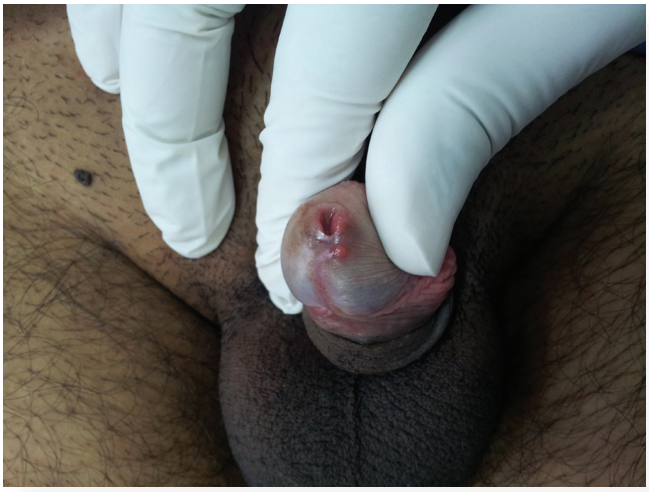

Figure 2. Small Erythematous papule, 5mm in size over urethral meatus.

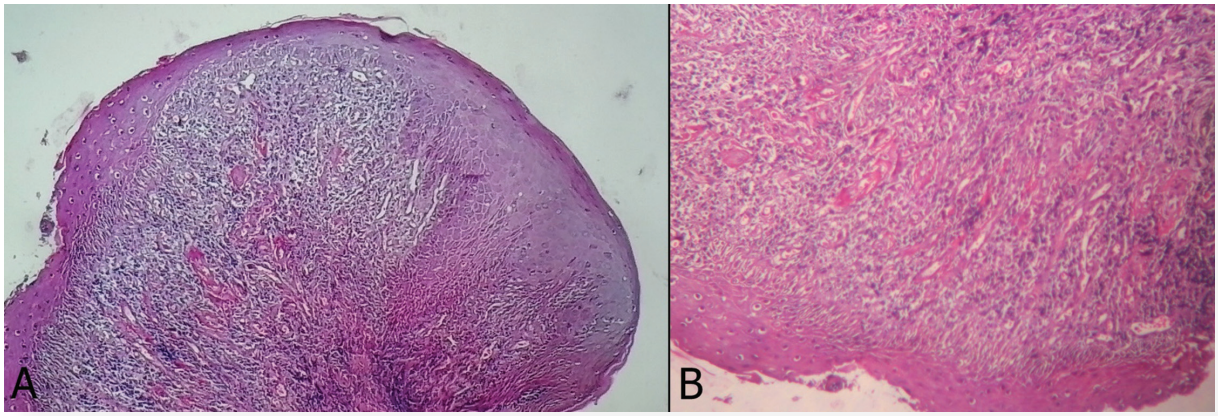

Figure 3 A and B. Scanner view Shows nodular configuration underneath epidermis. On High power magnified view shows mild hyperkeratotic, Parakeratotic, irregular acanthotic epidermis. Sub epidermal zone shows different sizes of dilated blood vessels filled with RBC's and endothelial cell lining walls. The stroma shows neutrophils infiltrate predominantly. Foci of Haemosiderin deposits shown.

Clinically, pyogenic granulomas begin as small red papules that rapidly increase in size ranging from a few millimeters to several centimeters. Pyogenic granulomas may have an initial period of rapid growth, followed by stabilization and occasionally regression [3].

We present here an unmarried male patient aged 24yrs, presented with a small erythematous papule with sessile base over meatus of glans penis with occasionalspotting. He denied history of genital trauma.

Clinically we considered adifferential diagnosis of Pyogenic Granuloma, urethral prolapse, cherry angioma, urethral caruncle, angiokeratoma,genital warts and pyoderma gangranosum of penis [4].

The histological examination showed an intact epidemis. The sub epithelial region showed many thin walled varying sized capillaries, few dilated and filled with RBC's. The intervening stroma is showing infiltrate predominately by neutrophils, occasional areas showing hemosiderin deposits.

The Histopathology of Pyogenic Granuloma shows a angiomatous tissue with endothelial cell proliferation, inflammatory cell infiltrate is seen in the form of few neutrophils, lymphocytes and plasma cells covered by parakeratinized epithelium [5].

A literature scan revealed a few cases of Pyogenic granuloma involving the shaft of penis [6] andprepuce of glans penis [7-9]. Literature search (using Medline) has revealed no previous reports of Pyogenic granuloma involving the meatus of glans penis. This is the first case report of Pyogenic Granuloma involving the urethral meatus.

Conclusion

Pyogenic granuloma is a common lesion of the skin and oral cavity, especially the gingiva. This case report emphasizes that the diagnosis of a penile pyogenic granuloma is complex and leads the dermatologist to consider distinct lesions with its myriad etiologies, clinical features, histological presentations and treatment modalities. We call attention to the uncommon location of Pyogenic Granuloma over meatus. Surgical excision is a safe method for diagnosis and treatment of Pyogenic Granuloma over meatus of glans penis.

Acknowledgement

We gratefully acknowledge the help of,

1. Principal, Pesimsr, Kuppam.
2. Professor and Hod, Department of DVL, Pesimsr, Kuppam.
3. Professor, Department of Pathology, Pesimsr, Kuppam.

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DOI: 10.7241/ourd.20142.44

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CONCURRENT OCCURRENCE OF *SEBORRHEIC KERATOSIS* AND *MELANOCYTIC NEVUS* IN THE SAME LESION

Yosep Chong[1], Dae-Hyun Song[2], Kee-Taek Jang[2], Kwang Hwa Park[3], Eun Jung Lee[1]

[1]*Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[2]*Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[3]*Department of Pathology, Yonsei University Wonju College of Medicine, Wonju, Korea*

Source of Support: Nil
Competing Interests: None

Corresponding author: Prof. Eun Jung Lee, MD PhD *ejlpath@catholic.ac.kr*

Our Dermatol Online. 2014; 5(2): 179-182 Date of submission: 23.12.2013 / acceptance: 28.01.2014

Abstract
Seborrheic keratosis (SK) is common benign epithelial tumor of the skin that can be associated with other cutaneous tumors such as basal cell carcinoma, squamous cell carcinoma and melanoma. On the other hand, melanocytic nevus (MN) is another very common disease, showing anecdotal association with other cutaneous tumors such as trichoepithelioma, syringoma, basal cell carcinoma, trichilemmal cyst and epidermoid cyst. Although it has recently been reported that somatic mutation of BRAF gene is implicated in MN quite frequently, their pathogenic mechanisms, especially the association with other cutaneous tumors, are still elusive. Despite the high frequency of both tumors, however, collision tumors of SK and MN are extremely rare that only a few case reports have been documented so far.
Hereby, we report five cases of simultaneous occurrence of SK and MN in 14-year-old female, 36-year-old female, 39-year-old female, 58-year-old male, and 62-year-old male patients. Additional molecular tests for BRAF mutation (V600E) on micro-dissected tissue of the 58-year-old man revealed positivity on the MN and negativity on the SK. Although these results cannot give direct evidence that both tumors have different pathogenic mechanisms, it seems to be more relevant that these collision tumors may occur by chance.

Key words: seborrheic keratosis; intradermal nevus; skin neoplasms

Cite this article:
Chong Y, Song D-H, Jang K-T, Park KH, Lee EJ. Concurrent Occurrence of Seborrheic Keratosis and Melanocytic Nevus in the Same Lesion. Our Dermatol Online. 2014; 5(2): 179-182.

Introduction

Seborrheic keratosis (SK) is one of the most common benign epithelial tumors of the skin. Despite its frequency, many aspects of SK, especially its pathogenetic mechanism, remain elusive. Not a small number of cutaneous malignant tumors such as basal cell carcinoma, squamous cell carcinoma and melanoma have been documented to be found with SK [1]. Benign tumors that have very occasionally been documented include cutaneous ganglioneuroma, sebaceoma, eccrine poroma and trichilemmoma [1]. However, whether these combined tumors and SK share the same pathogenic mechanism is unclear. Likewise, melanocytic nevus (MN) is another very common disease, showing anecdotal association with other cutaneous tumors such as trichoepithelioma, syringoma, basal cell carcinoma, trichilemmal cyst and epidermoid cyst [1]. Although it has recently been reported that somatic mutation of *BRAF* gene is implicated in MN quite frequently, their pathogenic mechanisms, especially the association with other cutaneous tumors, are still elusive [2].

Considering the frequency of these two tumors, there have been surprisingly few additional reports of the cases in the literature that SK and MN are combined in the same lesion [3-9]. Some of the cases even showed additional concurrent occurrence of other tumors such as basal cell carcinoma, which suggests the hypothesis that multipotential differentiation capacity of the follicular germ may explain the coexistence of these tumors [6,8].

Here we report additional four cases of simultaneously occurring SK and MN in the same lesion. Moreover, the mutation analyses of *BRAF* gene were performed on the separately micro-dissected tissue from MN and SK in one of the cases.

Case Report

A 58-year-old Korean man presented with a dark pigmented lesion on his posterior neck that has been slowly growing for last few years. On physical examination, the size and shape was recorded as 0.6 - 0.5 cm-sized, ovoid brown pigmented papule with focal area of dense pigmentation (Fig. 1A). Two additional pigmented papules were found on the lower part of the neck and inguinal area.

On microscopic finding, epidermal layer of the lesion showed monotonous proliferation of basaloid cells with a variable degree of squamoid differentiation. Hyperkeratosis, acanthosis, focal parakeratosis and multiple pseudohorn cysts were characteristically noted, which made the lesion easily identified as SK (Fig. 2A). Underneath the epidermal lesion, relatively well-circumscribed small nests of bland pigmented melanocytes were found (Fig. 2B). The cytologic atypia of the melanocytes was minimal, consistent with intradermal MN. Additionally excised lesions on the cheek and inguinal area were diagnosed as SK after histologic evaluation.

A second case was a 39-year-old Caucasian woman with a similar pigmented tumor on her right forearm. On physical examination, it measured 1.0 - 0.9 cm and showed a brown-black warty plaque with a rather greasy texture. The microscopic findings revealed SK overlapping MN of intradermal type (Fig. 2B).

A third case was a 62-year-old Korean man with a pigmented lesion on his face. It measured 1.2 - 1.0 cm and showed a brown warty plaque with greasy surface and focal area of black pigmentation. Microscopically, it was diagnosed as MN of intradermal type juxtaposed with SK (Fig. 2C).

A fourth case was a 36-year-old Korean woman with a 1.0 - 0.7 cm-sized, mulberry-shaped, pigmented lesion on her abdomen. It reveals a brown warty appearance with greasy surface (Fig. 1B). Microscopically, it was SK overlapping MN of intradermal type (Fig. 2D).

Finally, a 14-year-old Korean woman presented with a 0.9 - 0.8 cm sized, pigmented lesion on her back. It was SK overlapping MN of compound type.

As an ancillary test, peptide nucleic acid clamp real-time polymerase chain reaction (RT-PCR) for *BRAF* mutation (V600E) were performed on DNAs separately collected from MN and SK in the first case by micro-dissection (PNA Clamp BRAF mutation detection kit, Panagene Ltd., Daejeon, Korea), according to the manufacturer's instruction. Genomic DNAs were extracted from the micro-dissected, formalin-fixed, paraffin-embedded tissue of MN and SK using Maxwell® 16 FFPE Plus LEV DNA purification kit (Promega Co., WI, USA) with Maxwell® 16 Research System (Promega Co., WI, USA). Extracted DNAs were quantified by NanoDrop LITE spectrophotometer (Thermo Fisher Scientific Inc., MA, USA) and diluted properly. About 10 ng/ul of DNA was used as a template DNA in each PCR. RT-PCR was performed with CFX 96™ Real time system (Bio-Rad, CA, USA) and analyzed with PNA Clamp™ analyzer Kor v.4.0.6 for Bio-Rad (Bio-Rad, CA, USA). Tests with threshold cycle (Ct) of 22 to 30 were considered to be appropriate to use. The cut-off value of delta-Ct values, referred to as the difference between Cts of control and samples, were 2.0 to determine the presence of mutant DNA.

Interestingly, $BRAF^{V600E}$ mutation was found only in MN in the first case while the mutation was not detected in SK.

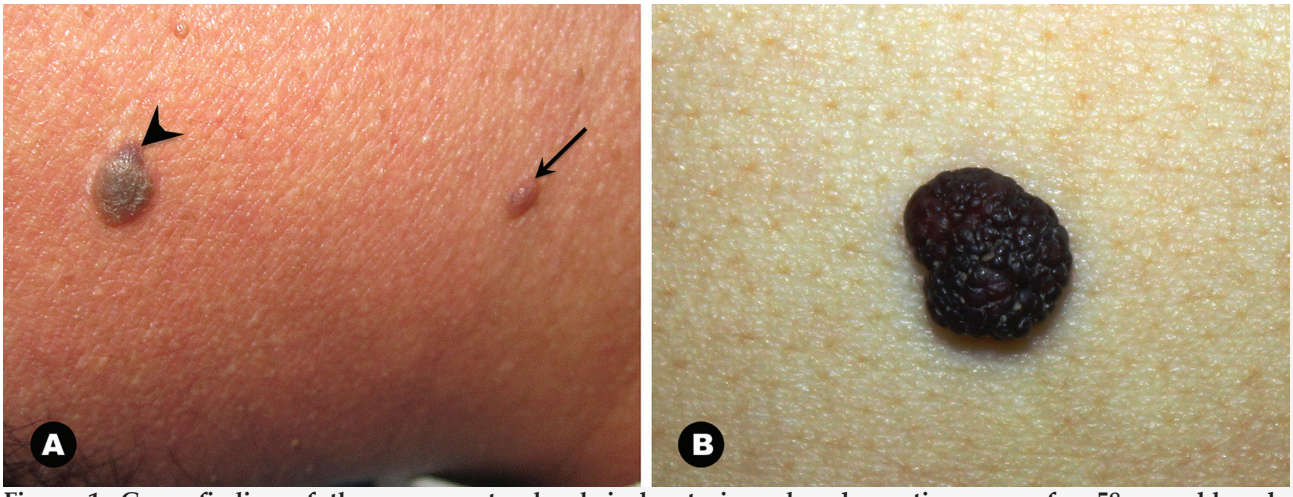

Figure 1. Gross finding of the concurrent seborrheic keratosis and melanocytic nevus of a 58-year-old male patient (Case 1) and a 36-year-old female patient (Case 4). (A), A 0.6 - 0.5 cm-sized, oval brown pigmented papule with superficial scale is noted on the posterior side of the neck of the first patient. Focal area of slightly dense pigmentation is seen within the lesion (Arrowhead). Another popular lesion, pathologically confirmed as seborrheic keratosis later, is also noted in the lower part of the neck (Arrow). **(B),** A mulberry-shaped, black pigmented, polypoid mass, measuring 1.0 - 0.7 cm, is found on the abdomen of a 36-year old female patient. It seems to be hard to define two components in this lesion grossly.

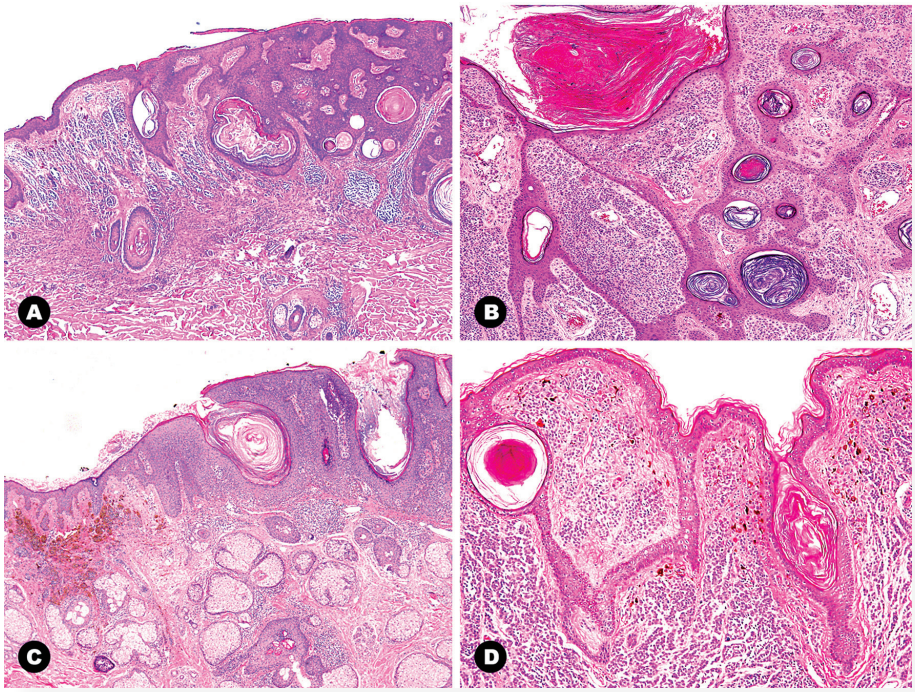

Figure 2. Microscopic finding of concurrent seborrheic keratosis (SK) and melanocytic nevus (MN) (H&E stain). (A), Intradermal nevus is located just beneath the SK in Case 1 (× 40). **(B),** Compound type nevus is found beneath the SK in Case 2 (×100). **(C),** Intradermal nevus is found juxtaposed to the SK in Case 3 (×40). **(D),** Intradermal nevus is found beneath the SK in Case 4 (×100).

Discussion

Combined SK and MN in the same lesion was first described by Requena et al. [3] in 1989 and another case of compound nevus and SK followed by Wagner et al. [4]. In 1994, Boyd and Rapini [5], in a retrospective study of 40,000 cutaneous biopsies, reported 14 cases of MN juxtaposed with SK. Three additional reports, in total less than 20 cases, have been reported since then [6-8]. The clinicopathological findings of the cases are summarized in Table I.

Although the number of reported cases is limited and the clinicopathologic information of the 14 cases in Boyd and Rapini's report [5] is lacking, there seems to be no predominant clinicopathologic features among the cases. Both male and female patients can be affected, the age of the patients widely varies from 14 up to 82, and all parts of the skin, especially exposed sites to sunlight, can be involved as seen in usual SK.

Year	Authors	No. of Cases	Age (yrs) / Sex	Site	Size (mm)	Type of nevus	Intertumoral positioning	Other associated tumors
1989	Requena et al. [2]	1	45/Male	Face (cheek)	Unspecified	Junctional	Overlapped	
1991	Wagner [4]	1	36/Female	Ankle		Compound	Overlapped	
1994	Boyd et al. [5]	14	Unspecified	Unspecified	Unspecified	Unspecified	Juxtaposed	Unspecified
2001	Betti et al. [6]	1	54/Male	Back	30	Junctional and compound	Overlapped	Basal cell carcinoma
2003	Kim et al. [7]	1	82/Male	Face (canthus)	5	Intradermal	Overlapped	
2005	de Giorgi et al. [8]	1	38/Female	Hip	13	Compound	Juxtaposed	Basal cell carcinoma
2008	Gonzalez-Vela et al. [9]	1	39/Female	Back (scapular)	13	Intradermal	Overlapped	
2013	Present case 1	1	58/Male	Neck	6	Intradermal	Overlapped	
	Present case 2	1	39/Female	Arm	10	Compound	Overlapped	
	Present case 3	1	62/Male	Face	12	Intradermal	Juxtaposed	
	Present case 4	1	36/Female	Abdomen	10	Intradermal	Overlapped	
	Present case 5	1	14/Female	Back (upper)	9	Compound	Overlapped	

Table I. Summary of the 8 reports with collision tumor of seborrheic keratosis and melanocytic nevus.

Intradermal, junctional and compound types of MN can be involved with SK either in overlying or juxtaposed manner. Additional remarkable clinicopathological findings were not otherwise described.

Among 25 cases including present three cases, 2 cases were accompanying basal cell carcinoma in part of the lesions [6,8]. One of them, reported by Betti et al. [6] in 2001, revealed a junctional nevus and separately-found compound nevus underneath a part of the SK while another part of the SK showed complexes of a typical superficial basal cell carcinoma arising within. The authors carefully suggested the possibility of involvement of the multipotential follicular germ in the pathogenic mechanisms of SK and accompanying basal cell carcinoma in this case. Furthermore, giving the examples of several cutaneous tumors associated with melanocytic lesions, the authors suggested the idea that nevi might interact with stromal elements to induce epithelial growths. However, they concluded their case as a chance association because of its rarity in comparison with the frequency of SK and MN. De Giorgi et al.[8], in the other report, focused on the dermoscopic features and did not mention about the pathogenic mechanism of this collision tumor.

In this report, we found the *BRAF* mutation status of SK and MN in one of these collision tumors differs from each other, suggesting the possibility of independent pathogenic mechanisms of each component. Although this finding might be not enough to explain the different pathogeneses of these tumors, juxtaposed presentation in some of the reported cases and relatively low frequency of these collision tumors favor the coincidental occurrence of these tumors. Taking into account that the most commonly associated tumors to SK was MN and vice versa in Boyd and Rapini's retrospective study [5], it seems to have more persuasive power. Because of relatively low clinical significance of SK and MN, both dermatologists and pathologists may not notice these collision tumors frequently. With an extension of this idea, it seems to be more relevant to take UV exposure for the common pathogenic trigger in both tumors as in usual SK and MN. For a clearer explanation, additional cases and more studies on the known pathogenic causes of SK and MN, such as *BRAF* mutation are required.

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DOI: 10.7241/ourd.20142.45

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MELKERSSON-ROSENTHAL SYNDROME ASSOCIATED WITH *PSORIASIS VULGARIS* AND *OROFACIAL IMPETIGINIZATION*

Ryszard Galus[1], Katarzyna Borowska[2], Marian Jędrych[3], Barbara Jodłowska-Jędrych[4], Longin Niemczyk[5], Marek Antiszko[6], Stanisław Zabielski[7]

[1]*Department of Histology and Embryology, Center for Biostructure, Medical University of Warsaw, Chalubinskiego 5 Str., 02-004 Warsaw, Poland*
[2]*Department of Cosmetology, The Bronisław Markiewicz State Higher School of Technology and Economics in Jarosław, 16 Czarnieckiego Str., 37-500 Jarosław, Poland*
[3]*Department of Mathematic and Biostatistic, Medical University of Lublin, Jaczewskiego 4 Str., 20-090 Lublin, Poland*
[4]*Department of Histology and Embryology with Experimental Cytology Unit, Medical University of Lublin, Radziwiłowska 11 Str., 20-080 Lublin, Poland*
[5]*Department of Nephrology, Dialysotherapy and Internal Medicine, Medical University of Warsaw, Banacha 1a Str., 02-097 Warsaw, Poland*
[6]*La Beauté, Gabinet Dermatologii i Medycyny Estetycznej, Waszyngtona 45/51 Str. app. 133, 04-008 Warsaw, Poland*
[7]*School of Economics, Law and Medical Sciences in Kielce, Jagiellońska 109A Str., 25-734 Kielce, Poland*

Corresponding author: Dr Ryszard Galus, MD PhD *rkgalus@wp.pl*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 183-184 Date of submission: 30.01.2014 / acceptance: 13.03.2014

Abstract
Melkersson-Rosenthal syndrome (MRS) is a disease of unknown etiology, usually restricted to the orofacial region, characterized by reccurent orofacial swelling, relapsing facial palsy and plicated tongue. We report case of MRS associated with psoriasis in a 25-year-old woman. The patient has been treated with satisfying results with a combination of Cetirizine, Cefuroxime axetil and Mupirocin ointment; psoriatic eruptions were successfully treated with 10 % salicylic-sulphuric ointment twice a day. MRS syndrome is a rare disease and should be considered in the differential diagnosis of labial swelling and facial palsy.

Key words: Melkersson-Rosenthal syndrome; psoriasis; plicated tongue

Cite this article:
Galus R, Borowska K, Jędrych M, Jodłowska-Jędrych B, Niemczyk L, Antiszko M, Zabielski S. Melkersson-Rosenthal syndrome associated with psoriasis vulgaris and orofacial impetiginization. Our Dermatol Online. 2014; 5(2): 183-184.

Introduction

Melkersson-Rosenthal syndrome (MRS) is a rare disorder of unknown etiology, characterized by recurrent orofacial swelling, relapsing facial palsy and plicated tongue. Diagnosis is usually made by clinical and histopathologic criteria. Furthermore, diagnosis of the condition can be difficult, as incomplete forms are not infrequent [1].

Case Report

In this paper we present a 25-year-old Caucasian girl presenting with a 2 -year history of swelling of the upper lip and biopsy-proven psoriasis.

On examination, there was cheilitis with local angioedema, persistent swelling and considerable enlargement of the upper lip. The lower lip was slightly swollen and perioral bacterial infection was observed. Moreover, there was lower motor neuron right-sided facial palsy (Fig. 1)

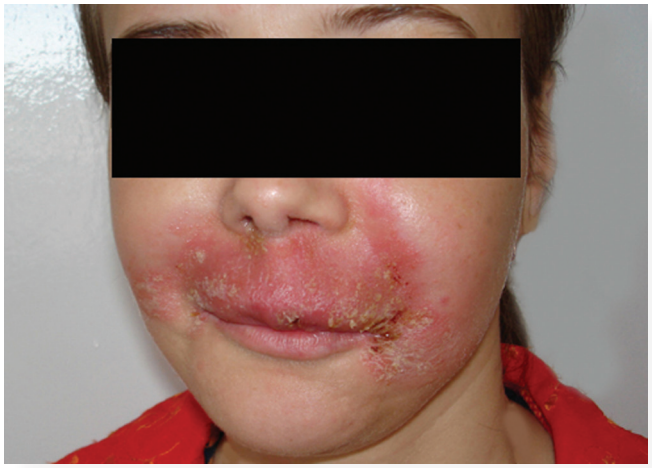

Figure 1. A 25-years-old woman with right-sided facial palsy, swelling of the lips and orofacial impetiginization.

The tongue was fissured. On extensor surfaces the patient exhibited psoriatic eruptions represented as an erythematous, scaly inflamed patches and papules. The patient had no history of atopy or inflammatory bowel disease and there were no gastrointestinal symptoms. Laboratory tests, including blood examinations, sedimentation rate, complement levels, anti-DNA, anti-nuclear antibodies, thyroid function test, C-reactive protein, IgE and chest roentgenogram were normal. Sections from biopsy of the lower lip showed edematous squamous mucosa with underlying fat. The submucosa was edematous with dilated blood vessels and inflammatory cellular infiltration - composed of lymphocytes, plasma cells - mainly marked around blood vessels and no sarcoid-like granulomas were identified.

Discussion

Although facial edema is usually nonresponsive to antihistamines [2], we have administered a combination of Cetirizine, Cefuroxime axetil and topically Mupirocin, which have produced satisfactory improvement of bacterial lesions, but mild enlargement of the upper lip has persisted. Psoriatic lesions were successfully treated with topical 10% salicylic-sulfuric ointment twice a day. Pharmacological treatment was sufficient, thus lip reduction cheiloplasty was unnecessary [3].

Biopsy did not reveal granulomas, which are present in classic picture of MRS [4], but granulomatic changes not always occur in MRS, and nonspecific edema and inflammation might dominate in the early phase [1].

Our case confirms previous observations which suggest association of MRS with psoriasis [5]. Although psoriasis is a relatively common chronic skin disease (affects 2-3 % of the US population) [6], we think psoriasis in association with the MRS is not coincidental. Plicated tongue, which is believed to be a physiological variant (incidence is estimated about 10-15 % of normal population) [4] – is at the same time a part of the classic MRS triad and is more frequent in psoriatic patients [7].

Melkersson-Rosenthal syndrome is a rare disorder and should be considered in the differential diagnosis of labial swelling and facial palsy.

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DOI: 10.7241/ourd.20142.46

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LINEAR SCLERODERMA: A SERIES OF ALL CLINICAL VARIANTS

Keerthi Jampani, Akshaya Nagaraja, Srilakshmi Peddireddy, Shiva Kumar V.

Department of Dermatology, Venereology & Leprosy, P.E.S Institute of Medical sciences and Research, Kuppam, AP, India

Source of Support: Nil
Competing Interests: None

Corresponding author: Dr. Keerthi Jampani, MD *Keerthi.jampani88@gmail.com*

Our Dermatol Online. 2014; 5(2): 185-187 Date of submission: 22.01.2014 / acceptance: 15.03.2014

Abstract
Morphea is a fibrosing disorder of the skin and subcutaneous tissues, wherein the overabundant collagen deposition destroys adnexal structures and hair follicles. In linear morphea erythematous or violaceous patches or plaques are seen with central sclerosis and active red border distributed in linear configuration which over time become sclerotic, white or hypopigmented. We report a series of cases encompassing all the three clinical variants of linear morphea. Case one had en coup de sabre deformity, case two had progressive facial hemiatrophy and case three had linear limb morphea with involvement of the face. This series is being reported for its rarity.

Key words: Morphea; En coup de sabre; Parry Romberg syndrome; Linear limb morphea

Cite this article:
Jampani K, Nagaraja A, Peddireddy S, Kumar VS. Linear scleroderma: a series of all clinical variants. Our Dermatol Online. 2014; 5(2): 185-187.

Introduction

Morphea, also known as localized scleroderma, is a fibrosing disorder of the skin and subcutaneous tissues, wherein the overabundant collagen deposition destroys adnexal structures and hair follicles [1]. The common clinical variants are circumscribed, generalized, bullous, linear and deep [2]. Plaque-type morphea is the most common type affecting adults in the mid-40s. The most common variant in children is linear morphea, with equal sex distribution, presenting as erythematous or violaceous patches or plaques with central sclerosis and active red border distributed in linear configuration which over time become sclerotic, white or hypopigmented.

Case Report

Case 1

A 16-year-old male patient presented to our outpatient department with an asymptomatic, right-sided-facial atrophy and alopecia involving frontal region of scalp since 2 years (Fig. 1). Skin over the involved areas was smooth in texture and could be pinched up easily on palpation. There was no history of seizures, visual abnormalities or trauma. Examination showed a linear depressed groove on the frontoparietal region extending onto scalp, producing a linear zone of alopecia. This case was managed with topical corticosteroids.

Case 2

A 46-year-old female patient presented with a hyperpigmented depression over the left side of the face progressing upwards onto the scalp and downwards to involve the mandibular area since 20 years (Fig. 2). There was history of trauma to the head following which lesions started. History of three episodes of seizures was present since 1 year. She also had mild blurring of vision in the left eye. The patient was managed with intralesional corticosteroid injections.

Case 3

A 26-year-old female patient came with depressed groove over the left-side of the face, left arm and left forearm since 10 years (Fig. 3A, B). It initially started over the face and gradually progressed on to arms and forearms involving the elbow joint which restricted her joint mobility. The case was managed with topical calcipotriol and corticosteroids.

Skin biopsy was done in all 3 cases which showed histopathological features suggestive of morphea. Epidermis showed basket-weave keratosis with ironed out rete ridges and follicular keratosis (Fig. 4). Dermis showed thick collagen bundles paralleled to one another extending from papillary dermis to deeper dermis with lymphocyte infilteration around blood vessels and sweat ducts. Features suggestive of morphea.

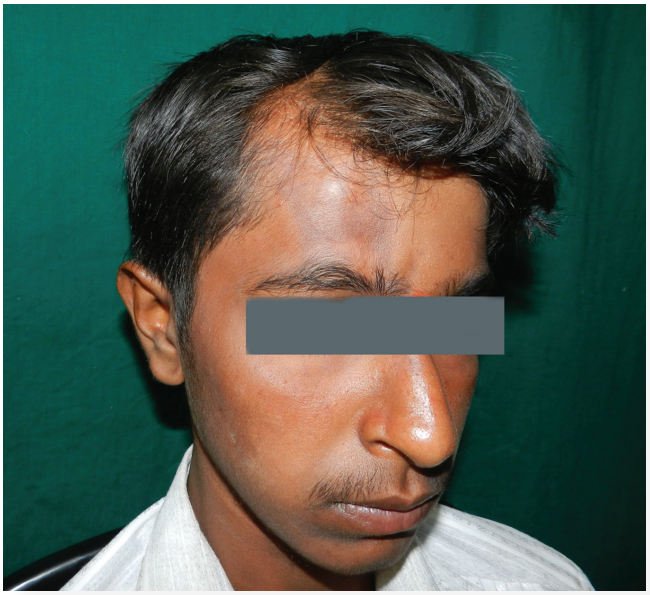

Figure 1. En coup de sabre with a linear depressed groove on the frontoparietal region extending into the scalp, producing a linear zone of alopecia.

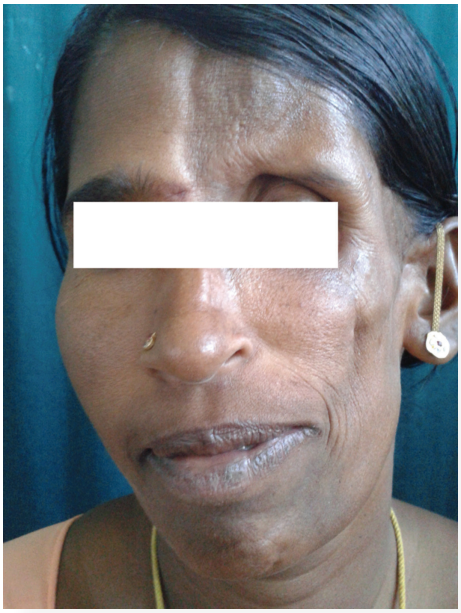

Figure 2. Parry Romberg syndrome with progressive facial hemiatrophy extendind from left side of forehead upwards to the left side of the cheek downwards.

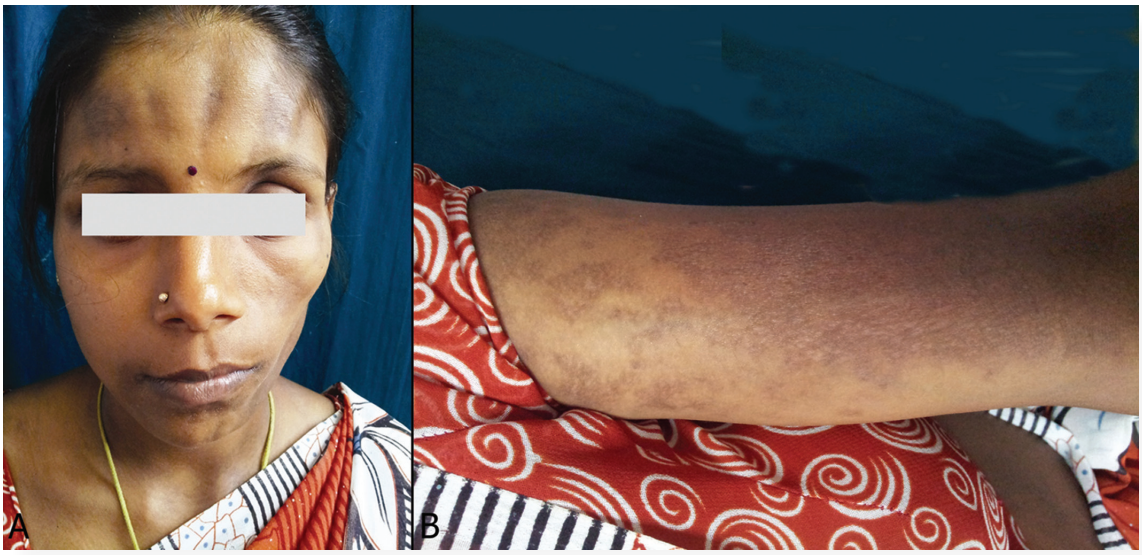

Figure 3A and B. Facial hemiatrophy with linear limb morphea.

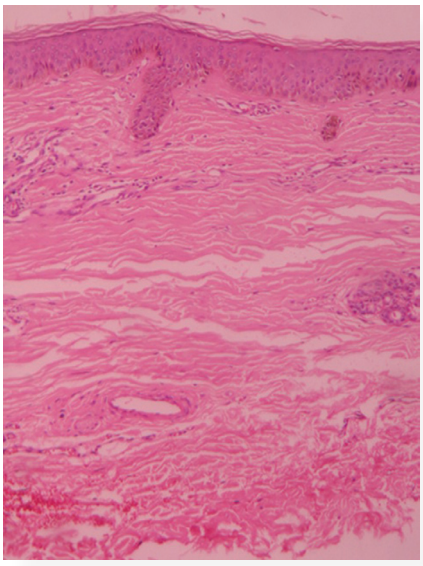

Figure 4. Epidermis showed basket-weave keratosis with ironed out rete ridges and follicular keratosis. Dermis showed thick collagen bundles paralleled to one another extending from papillary dermis to deeper dermis with lymphocyte infilteration around blood vessels and sweat ducts.

Discussion

Linear morphea which is the most common type in children involves the lines of blaschko, suggesting genetic mosaicism. The three clinical variants are en coup de sabre (Fig. 1), progressive hemifacial atrophy (Fig. 2), and linear limb morphea (Fig. 3), all of which can be associated with underlying tissue atrophy. This case series represents all the varieties of linear morphea.

En coup de sabre

The term en coup de sabre morphea refers to a lesion of linear morphea generally located in the frontoparietal scalp and/or the paramedian forehead, often resembling a stroke from a sword [3]. It usually occurs on the paramedian forehead. It can be associated with underlying ocular and central nervous system (CNS) involvement, including headaches and seizures. It typically follows Blaschko lines [4]. It can be associated with alopecia and present (less commonly) with more than 1 lesion.

Progressive hemifacial atrophy (also known as Parry-Romberg syndrome)

It is an infrequent, acquired disorder characterized by progressive hemiatrophy of the skin and soft tissue of the face and, in some cases, results in atrophy of muscles, cartilage, and the underlying bony structures. It was first described by Parry in 1825 and Romberg in 1846 [5]. It can have overlap with en coup de sabre; thought to be different ends of the same condition. It may have underlying seizures [1].

Linear limb morphea

It is associated with muscle atrophy, limb length discrepancies, and joint contractures. It is usually unilateral. Most likely to have extracutaneous manifestations with linear morphea. Linear morphea found to be associated with the following complications:

Articular disease (47.2%), neurologic (17.1%), vascular (9.3%), ocular (8.3%), gastrointestinal (6.2%), respiratory (2.6%), cardiac (1%), and renal (1%).

Treatment

Various treatment modalities for linear morphea are tried like [6];

Topical corticosteroids: High-potency topical steroids can be applied once or twice daily to affected areas; lower-potency steroids should be used on the face or folds; care should be taken to prevent atrophy of the uninvolved skin.

Topical vitamin D analogues: Calcipotriene ointment 0.005% under occlusion twice a day has been used, with good results.

Topical calcineurin inhibitors: Tacrolimus ointment (0.1%) is another effective topical treatment.

Intralesional corticosteroids: Triamcinolone, 5 mg/mL can be injected intralesionally once a month for 3 months.

Oral corticosteroids and Methotrexate given at 0.5 mg/kg weekly. It might be helpful to initiate a 1- to 2-month course of oral corticosteroids at the same time because of the slow onset of action for methotrexate.

Phototherapy: UVA and NB UVB is also tried with varied response.

Conclusion

Because of the rarity of en coup de sabre morphea and parry-romberg syndrome,there is still much to be learned about them. Both en coup de sabre and Parry-Romberg syndrome are types of localised scleroderma that may have a similar pathogenesis. Neurological abnormalities, particularly seizures have been described in association with en coup de sabre and Parry-Romberg syndrome.

Antimalarials like hydroxychloroquine and methotrexate were found to be most effective of all.

Acknowledgement

We gratefully acknowledge the help of;

1. Principal, Pesimsr, Kuppam
2. Dr Vijayashankar Metikurke, Professor, Department Of DVL, Pesimsr, Kuppam.

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DOI: 10.7241/ourd.20142.47

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ACTINIC LICHEN PLANUS IN A CHILD – A RARE ENTITY

Neerja Puri

Department of Dermatology and Venereology, Punjab Health Systems Corporation, Ferozepur, Punjab, India

Corresponding author: Dr. Neerja Puri *neerjaashu@rediffmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 188-189 Date of submission: 05.12.2013 / acceptance: 19.02.2014

Abstract
Lichen Planus actinicus (LP actinicus) is a variant of lichen planus often confined to individuals in tropical and subtropical regions. The lesions involve sun-exposed areas and are characterized by well-defined nummular patches which have a deeply hyperpigmented centre surrounded by a hypopigmented zone. It mainly involves teenagers with an Asian racial profile. We report a rare case of a 10 year old male child who reported to the department of dermatology with multiple annular pigmented patches on the face, forearms and shins which developed slowly over a period of one year.

Key words: Lichen planus; actinic; variants; pigmented; histopathology; children

Cite this article:
Puri N. Actinic lichen planus in a child – a rare entity. Our Dermatol Online. 2014; 5(2): 188-189.

Introduction

Actinic lichen planus (ALP), also known as lichen planus tropicus, is a rare variant of Lichen planus that typically affects children or young adults with dark skin that live in tropical or subtropical regions [1]. It is important to identify certain conditions like melasma which may mimic actinic lichen planus [2]. Melasma occurs more in females and it is oestrogen dependent.

Case Report

We report a rare case of a 11 year old male child who reported to the department of dermatology with multiple annular pigmented patches (Fig. 1) on the face, forearms and shins which developed slowly over a period of one year. The patient had history of sunexposure since 4 years. Dermatological examination showed skin phototype IV. Examination of the patient's nails and oral mucosa was normal. There was no lymphadenopathy and the patient was generally well. All the routine investigations of the patients were normal. The patient was examined for hepatitis B and hepatitis C antigens and they were negative. Histological findings showed compact hyperkeratosis, wedge-shaped hypergranulosis, saw-toothed hyperplasia, coarse basal cell vacuolization, and civatte bodies. A bandlike inflammatory cell infiltrate (Fig. 2) in the papillary dermis invading the lower layers of the epidermis with liquefaction of basal cells and presence of melanin in the dermis was found. Direct imunofluorescence of the exposed skin was negative. A diagnosis of actinic lichen planus was made and laboratory investigations revealed no inflammatory syndrome and no antinuclear antibodies. The patient received topical corticosteroids of intermediate level for a short time associated with sunblock. His symptoms partially improved within 3 months with a relapse of pigmented lesions following sun exposure.

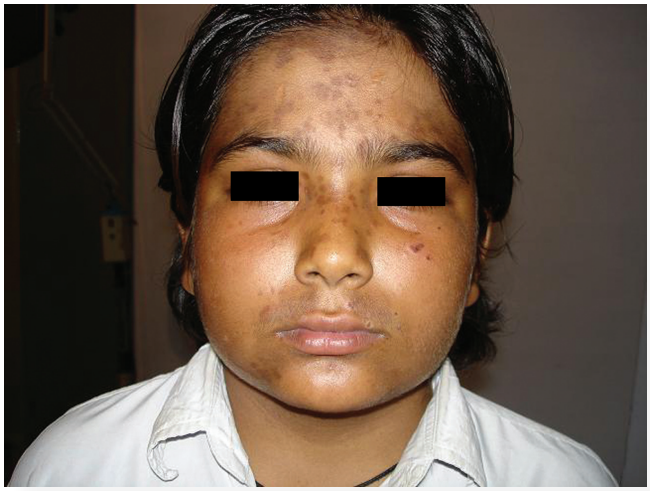

Figure 1. Actinic lichen planus in a 11 year old child.

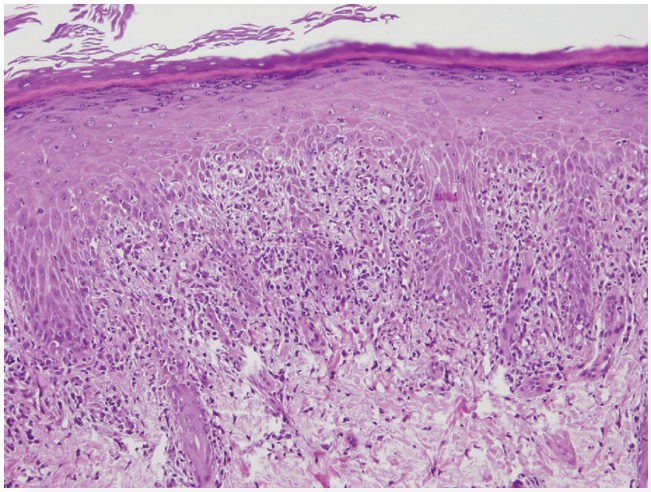

Figure 2. Acanthosis, lichenoid mononuclear dermal infiltrate and colloid bodies. (H& E stain 100x)

Discussion

Lichen planus actinicus is a photosensitive variant of lichen planus that can present with annular, melasma-like, dyschromic, or violaceous plaques in sun-exposed areas. A racial predilection to Asians with dark complexions and patients living in tropical and subtropical countries has been noted. The eruption usually appears during spring and summer, and improvement or complete remission takes place during the winter, leaving hyperpigmented patches [3]. However, relapses may occur during subsequent sunny seasons. There are three forms of actinic lichen planus including annular, pigmented and dyschromic. The most common form is the annular type, which consists of erythematous brownish plaques with an annular configuration, with or without atrophy. The pigmented type consists of hypermelanotic patches, with a melasma-like appearance. The pathogenesis of ALP is still unknown. Sunlight appears to be the major precipitating factor, probably under the influence of genetic or other factors (hormonal, toxic, or infectious factors, etc.). Treatment strategies for lichen planus actinicus are based primarily on anecdotal reports but should include the use of sunscreens and sun avoidance [4]. Hydroxychloroquine, intralesional glucocorticoids, and acitretin with topical glucocorticoids have been used successfully in patients with lichen planus actinicus. 0.1% pimecrolimus cream has been tried in some patients with good results [5]. In recalcitrant cases, treatment has been tried with intense pulse light (IPL) [6]. The case is rare and hence being reported.

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DOI: 10.7241/ourd.20142.48

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FORGIVE SINS: RISE OF THALIDOMIDE

Yugandar Inakanti, Shiva Kumar

Department of Dermatology Venerology Leprosy, P.E.S. Institute of Medical Sciences and Research, Kuppam, AP, India

Corresponding author: Dr Yugandar Inakanti *dryugandar@gmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 190-196 Date of submission: 12.02.2014 / acceptance: 30.03.2014

Abstract
Thalidomide was originally used as a Wonder Drug to treat morning sickness and insomnia in pregnant women in late 1950s. It became apparent in early 1960s that thalidomide treatment resulted in severe birth defects in thousands of children. Then it was banned in most of countries. Later on discovered anti-inflammatory and anti-angiogenic properties of Thalidomide proved to be useful for treatment of leprosy and multiple myeloma. A series of immunomodulatory drugs created by chemical modification of thalidomide have been developed to overcome the original devastating side effects. It's being investigated extensively as a treatment for many other severe cutaneous disorders and advanced cancers.
We briefly review pharmacological and the therapeutic profile of thalidomide.

Key words: Amelia; Contegran; ENL; Phocomelia; Teratogenetic defects; Thalidomide.

Cite this article:
Inakanti Y, Kumar S. Forgive sins: rise of thalidomide. Our Dermatol Online. 2014; 5(2): 190-196.

Introduction

Thalidomide is a synthetic glutamic acid derivative was synthesized in 1954, by Chemie Grunenthal under the brand name of Contergan and was subsequently licensed in 46 other countries worldwide, covering all continents. It is an odourless white crystalline compound with low solubility in water [1-3]. We briefly review here pharmacological, therapeutic properties and side effects of thalidomide in Dermatology.

History

Thalidomide is potent hypnotic, antiemetic and used as a Sedative. Because of as an antiemetic, thalidomide was often administered on pregnant women [1].
It became an attractive alternative to barbiturates in view of its rapid speed of onset, lack of hangover effect and apparent safety after overdose [4,5].
Dr. Heinrich Muckter accidentally identified sedative property of thalidomide in 1954.The drug was first marketed in Germany in 1957 under the name Contergan [1], and in the UK in April 1958 as Distaval. Later, compound preparations which combined thalidomide with other drugs were marketed for a wide variety of indications: Asmaval for asthma, Tensival for hypertension, Valgraine for migraine, and so forth.
However, soon after its release, there was a marked increase in cases of phocomelia (congenital limb foreshortening). In 1961, after reports linking this to in-utero thalidomide exposure, the drug was withdrawn leaving a legacy of about 10,000 affected children [5].
In November 1961, Lenz suggested that these deformities resulted from the mothers having taken thalidomide. By a remarkable coincidence, the same suggestion was made at much the same time by McBride [3] in Australia.
In some countries, e.g. Belgium, Brazil, Canada, Italy and Japan, thalidomide continued to be sold for several months (after withdrawal of the drug from West German and British markets).
The individual type of thalidomide malformation depends on the time of intake. Thalidomide does not produce malformations if only taken before the 34th day after the last menstruation and usually no malformation of taken only after the 50th day [3].
Within the sensitive period from day 35 to day 49 there is the following sequence [3]:
1. Absence of ears and deafness: 35th - 37th day
2. Absence of arms: 39th - 41st day
3. Phocomelia with 3 fingers: 43rd - 44th day
4. Thumbs with 3 joints: 46th - 48th day.

About 40 per cent of thalidomide victims died before their first birthday. Thalidomide was withdrawn in Germany by the end of November 1961 and In Japan, it was finally withdrawn in September 1962.

Sheskin, an Israeli physician, administered some old supplies of thalidomide to his patient with mania and leprosy for inducing sleep. There was a dramatic and complete resolution of the patient's cutaneous symptoms and Sheskin published this in 1965. This observation maintained the interest in thalidomide and it was soon obvious that the drug has important contribution in the treatment of erythema nodosum leprosum.

In 1997, however, the Food and Drug Administration (FDA) allowed thalidomide to be used on erythema nodosa leprosum (ENL), largely thanks to Sheskin's work in 1965 [4].

In 1991, thalidomide's anti-tumour necrosis factor-α (TNF-α) activity was discovered and this virtually intensified the interest in the potential uses of this unique drug [5]. Currently it is being evaluated or used on a compassionate use basis in more than 30 conditions including dermatologic, infectious, autoimmune and malignant disorders.

Pharmacology

Thalidomide is a nonpolar synthetic glutamic acid derivative. Chemically, it is an α -[N-phthalmido]-glutarimide consisting of a single central asymmetric carbon atom with a left pthalidimide ring and a right glutarimide ring. The pthalidimide ring is thought to be responsible for the teratogenic effects whereas the glutarimide ring, which is structurally similar to other sedatives, mediates sedation. It exists as optically active R (+) and S (-) enantiomers, which interconvert rapidly in vivo [4] (Fig. 1).

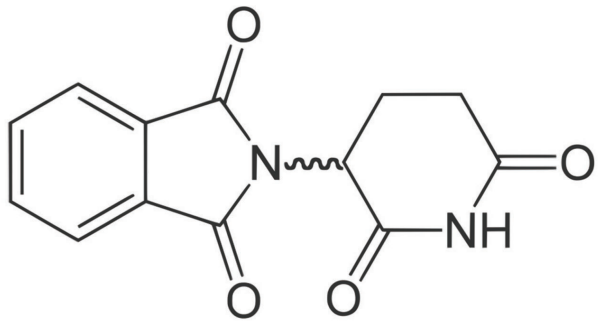

Figure 1. thalidomide are aromatic polycyclic compounds, contain one isomer responsible for treating morning sickness, another isomer responsible for Teratogenetic effects. Chemical formula is C13H10N2O4.

Pharmacokinetics

Thalidomide is slowly absorbed from the gastrointestinal tract. Peak levels in blood are reached within 2–6 hours, which could be delayed with a high-fat meal. It is extensively distributed in all the tissues and fluids with higher concentrations in skin and kidneys. Bioavailability of thalidomide cannot be ascertained owing to its poor water solubility. It is primarily metabolized by nonenzymatic hydrolytic cleavage of its amide bonds. Cytochrome P-450 enzymes may have some role in metabolizing the anti angiogenic metabolite [4]. The mean elimination time is 5-7 hours, and it is not excreted in renal system; less than 0.7 percent of the drug is found in the urine [2,6].

Mechanism of Action

The exact mechanism of thalidomide actions is not determined. However, various theories have been proposed.

Anti inflammatory

It inhibits the chemotaxis, phagocytosis by Neutrophils, lymphocytes, and macrophages, stabilizes the lysosomal membranes and decreases the generation of superoxide and hydroxyl radicals [1,4].

Anti tumour effects

Thalidomide has been tested in a variety of haematological and solid malignancies. It has shown remarkable efficacy in patients with advanced multiple myeloma [17]. The exact basis for thalidomide's anti-tumour activity is not well-understood. It may be related to its anti angiogenic action, immunomodulatory effects, TNF-α- regulation, effect on cytokines and anti-adhesion effects.

Immunomodulatory effects

Thalidomide's immunomodulatory properties are complex. Multiple mechanisms of action have been reported.The best recognised action is its ability to inhibit the production of TNF-α, inhibit synthesis of IL-6, IL-12 and interferon-γ (IFN-γ). It reduces expression of intracellular adhesion molecule-1 and vascular cell adhesion molecule [5].

Anti angiogenesis

Many tumours require new vessel formation (angiogenesis) in order to support their continuous growth. Thalidomide inhibits basic fibroblast growth factor (bFGF) (induces angiogenesis) and vascular endothelial growth factor (VEGF) [4-6]. Thalidomide-induced antiangiogenic action is mediated by ceramide through depletion of VEGF receptors [7,17]. Angiogenic inhibition also results from antagonism between the following elements: E2 and F2 prostaglandins, histamine, serotonin and acetylcholine [1].

Sedative properties

It activates the forebrain sleep centre and therefore does not cause respiratory depression, in coordination, or hangovers [4].

Miscellaneous Actions

Thalidomide Reduces cellular proliferation, myelin phagocytosis and subperineural oedema. There is decrease in the capacity to release elastase and lactoferrin by lipoteichoic acid-stimulated granulocytes granulocytes [8].

Indications

In Table I was described therapeutic uses of Thalidomide and in Table II Contraindications.

Uses in Dermatology

Dermatological conditions have been grouped into the following categories:

(a) Very effective: ENL, aphthous stomatitis, Behcet's disease, LE, and prurigo nodularis;

(b) Moderately effective: Actinic prurigo, Langerhans cell histiocytosis, cutaneous Sarcoidosis, erythema multiforme, graft-vs.-host disease (GVHD), Jessner's infiltrate, and uremic pruritus;

(c) Possibly effective: Kaposi's sarcoma, lichen planus, melanoma, and pyoderma gangrenosum;

(d) Contraindicated: Toxic epidermal necrolysis (paradoxical increase in TNF-α activity).

	List of Therapeutic Uses		List of Therapeutic Uses
A	**Autoimmune disorders:** * Rheumatoid arthritis * Systemic lupus erythematosis * Discoid lupus erythematosis * Sjögren's syndrome * Sarcoidosis * Multiple sclerosis	E	**Miscellaneous:** * Graft versus host disease * Neuropathic pain * Diabetic retinopathy * Macular degeneration
B	**Gastrointestinal:** * Recurrent aphthous oral ulceration * HIV associated oral and oesophageal ulceration * Crohn's disease	F	**Haematological malignancies:** * Multiple myeloma * Myelodysplasia * Myelofibrosis with myeloid metaplasia
C	**Dermatological:** * Leprosy * Behçet's disease * Actinic prurigo * Prurigo nodularis * Uraemic pruritus * Pyoderma gangrenosum	G	**Solid tumours:** * Malignant glioma * Kaposi's sarcoma * Prostatic carcinoma * Colorectal carcinoma * Renal cell carcinoma * Carcinoma of breast
D	**Cachexia and weight loss:** * Cancer cachexia * HIV-associated wasting * Tuberculosis associated wasting		

Table I. Therapeutic indications of Thalidomide.

List of contraindications
· accidental exposure · blood donation · breast-feeding · children · driving or operating machinery · dysfunctional uterine bleeding · females · human immunodeficiency virus (HIV) infection · intrauterine fetal death · leukopenia · TEN

Table II. Contraindications of thalidomide.

The only FDA-approved indication for thalidomide is the acute treatment and suppression of the cutaneous manifestations of erythema nodosum leprosum (ENL). Rest of indications are off-labeled dermatological uses.

Erythema nodosum leprosum (ENL)

ENL is a lepra reaction that occurs in lepromatous patients on multiple drugs or from interferon-γ (IFN-γ) intradermal injections. It usually presents within the first year of multidrug therapy with both cutaneous and visceral manifestations. Skin reactions are erythematous nodules associated with arthralgia, fever, iritis, malaise and neuritis. Visceral manifestations can include hepatosplenomegaly, nephritis, orchitis and pleuritis [8].

It is both a cell-mediated immune response as well as an immune complex mediated disease. Patients have raised INF-γ, TNF-α and IL-12.Thalidomide's effectiveness is due to its anti-cytokine properties. After therapy, there is marked reduction in TNF-α along with down regulation of intracellular adhesion molecule-1 [2].

The response rates for thalidomide have been greater than 90 percent, with improvement seen within days and complete resolution within 2 weeks. The other symptoms of ENL also responded rapidly. The most common side-effects were somnolence and constipation [6,8]. Although thalidomide is considered first-line for ENL, no trials have compared it with corticosteroids or clofazimine [8].

Sheskin reviewed 4522 patients treated with thalidomide for ENL, and found that 4479 (99%) improved while only 43 (1%) had no change or worsened. The best initial dose seemed to be 400 mg daily, with a maintenance dose of 50–100 mg daily. The duration of therapy ranged from sporadic use to continuous use for greater than 6 years [8].

In Parikh et al study, where the dosing solely depended on the clinical response of the patient.

They started thalidomide at 100 mg four times a day and then the dose was reduced to thrice, twice and once per day depending on the patient's clinical improvement. The duration of this study ranged from 12 to 643 days and the maintenance dose was 50 mg/day [10,11]. The recommended dosage is to begin with 100-400 mg at night and continue with this dose until the symptoms subside. Thereafter, tapering by 50mg every 2-4 weeks is recommended. Patients can be maintained on 25-200 mg a day to prevent an ENL recurrence [6,10].

Lupus Erythematosus

The first reported successful thalidomide treatment of chronic cutaneous lupus erythematosus (CCLE) was in 1977 in a case series of 20 patients. One large clinical trial of 60 patients with CCLE reported complete or marked responses in 54 patients (90%), but 71% of patients relapsed after discontinuing treatment.

Patients with relapse again responded when therapy was reinitiated [2,8].

Pelle and Werth reviewed 8 separate case series that reported a total of 171 patients with various forms of cutaneous lupus treated with thalidomide.The overall response rate was 85%, with complete resolution in 59%; the response rates for discoid lupus erythematosus and subacute cutaneous lupus erythematosus were comparable at 90.3% and 82.4%, respectively [2].

Thalidomide has also been used to effectively treat refractory tumid lupus erythematosus [2,9], but the drug has not been as successful in treating lupus panniculitis [2], Coelho and colleagues reported a complete or partial response in 99% of patients with all types of cutaneous lupus treated with thalidomide (100mg daily tapered to 50mg daily or less when clinically feasible). Two thirds of patients with lupus panniculitis, however, had no response to treatment [2].

Aphthous stomatitis

The first report of thalidomide for recurrent aphthous stomatitis was in 1979. Six patients had scrotal and mouth ulcers and were treated with thalidomide 100mg daily. The lesions were painless after 2–3 days and completely resolved after 7–10 days. Thalidomide is also beneficial for human immunodeficiency virus (HIV)-associated aphthous ulcers [8].

One mechanism by which thalidomide works in aphthous stomatitis is by inhibiting the increased chemotactic response of Neutrophils [6].

Behcet's syndrome

Behcet's disease is a systemic disorder with various skin lesions, ocular disease (panuveitis), arthritis, intestinal bleeding, and recurrent aphthous orogenital ulcers.

After successful reports of the efficacy of thalidomide in treating aphthous ulcers, thalidomide was used for Behcet's syndrome.Thalidomide was given at 400mg daily for the first 5 days, followed by 200mg daily for the next 15–60 days. Oral and genital lesions healed very rapidly, with milder and shorter recurrences.

Thalidomide may work in Behcet's syndrome by reducing the production of hydroxyl and superoxide radicals that cause tissue damage at sites of inflammation [12,14].

Prurigo nodularis

Prurigo nodularis is a pruritic type of neurodermatitis with skin-colored, erythematous, or hyperpigmented cutaneous nodules. Patients with Prurigo nodularis can be difficult to treat, and standard therapies with corticosteroids and antihistamines may be ineffective.

The initial report of thalidomide's efficacy in treating Prurigo nodularis was in 1965 by Sheskin. A more recent retrospective study presented 12 patients with Prurigo nodularis who were given thalidomide for at least 1 month at an initial dosage of 100mg daily. Response was noted in 8 of 12 patients, ranging from mild to moderate improvement, with complete resolution in 1 patient [2].

Several theories have been proposed about the mechanism of thalidomide in prurigo nodularis. Thalidomide may have a local effect on proliferated neural tissue in prurigo nodularis. A central effect of thalidomide may be the secondary peripheral neuropathy (to lose the sensation to scratch) and the sedation. The sedative properties of thalidomide may disrupt the itch–scratch cycle [8].

Actinic prurigo

In a study 1970, 34 patients treated with thalidomide and obtained good results in 30 cases over a period varying from one to two months. There was recurrence of the condition after the drug was halted1. This was also confirmed by other authors. actinic prurigo also may require ongoing, maintenance drug to prevent relapse of disease [2].

Graft-versus-host disease

The case reports and clinical trials have not been conclusive, as some demonstrate efficacy while others do not. Thalidomide has shown beneficial effects in both acute and chronic forms of graft-versus-host disease [15].

Chao et al. performed a randomized, double-blind, placebo-controlled study with 59 patients to evaluate the efficacy of thalidomide as a prophylactic agent in the prevention of chronic GVHD. The treatment group received 200mg of thalidomide twice a day beginning 80 days following allogeneic bone-marrow transplantation. The treatment group actually developed chronic GVHD more often than the placebo group. A recent study showed that thalidomide can be beneficial in the treatment of chronic GVHD in patients refractory to prednisone and cyclosporine [6].

Sarcoidosis

The treatment with thalidomide (200mg daily for two weeks, followed by 100mg daily for 11 weeks) improved the cutaneous lesions, hilar lymphadenopathy and Kaposi's sarcoma [1,17].

Sarcoidosis involves a Th1-type immune response characterized by increased levels of interferon-γ (IFN-γ),interleukin (IL)-2, and IL-12.Also, tumor necrosis factor a (TNF-a) plays a major role by escalating macrophage recruitment into granulomatous lesions [2]. This response was attributed to macrophage inhibition. No benefit attributed in treatment of Pulmonary Sarcoidosis [13].

Langerhans cell histiocytosis (histiocytosis X)

There are various reports on thalidomide's therapeutic effect here, but treatment doses and time have fluctuated according to various authors. In many instances, however, patients relapsed after cessation of treatment and ultimately required maintenance dosages [1,6].

Jessner's lymphocytic infiltrate

Guillaume studied 28 patients. Thirteen patients received thalidomide and 15 placebos. Of the 13 treated, 11 had remission where as the 15 who received the placebo showed no improvement [1].

Lichen Planus

Thalidomide has been used in the treatment of lichen planus, but only case reports exist. TNF-α has been implicated in mediating the effects of lichen planus, so thalidomide's ability to suppress this cytokine has led to its use in this disease [6]. In a 25-150 mg daily dose, thalidomide produced a regression of the oral lichen planus lesions with in 4 months of treatment [1].

Cicatricial Pemphigoid

There has been limited experience, just a small series and a case report have been published. Duong et al. reported the use of thalidomide in a patient with cicatricial pemphigoid, an autoimmune blistering disorder affecting the mucous membranes and occasionally the skin. Cicatricial pemphigoid is usually treated with dapsone or immunosuppressants. Because the patient's oral and cutaneous lesions had not responded to these treatments, he was treated with 100mg of thalidomide a day and improvement was noted after just 5 months. The disease remained stable after a taper of the thalidomide [6].

Pyoderma gangrenosum

Pyoderma gangrenosum is a non-infectious skin disorder that begins as painful pustules or papulonodules that enlarge and ulcerate. Several case reports have reported thalidomide's effectiveness in Pyoderma gangrenosum unresponsive to other treatments. One recent case of Pyoderma gangrenosum related to myelodysplastic syndrome had dramatic improvement of massive ulcerovegetative lesions after 4 months of combination therapy with IFN- α2 a and thalidomide (200mg daily) [2].
Farrell and cols. treated two cases with corticosteroids and minocycline. One of latter associated with thalidomide in a 100mg daily dose for five days, with an improvement of the condition [1].

Necrobiosis lipoidica

A case of necrobiosis lipoidica that was unresponsive to therapy was treated with thalidomide (150mg daily). Four months after initiation of therapy, there was clinical improvement in all lesions, and thalidomide was tapered to 50mg daily.

Postherpetic neuralgia

Treatment with thalidomide is effective, although with recurrence three weeks after halting the drug [1].

Erythema multiforme

Various cases were treated with thalidomide (100mg daily), showing good results, but with posttreatment recurrence [1].

Uremic Pruritus

For uremic patients receiving hemodialysis, pruritus occurs in 80% to 90% of patients at some point. The cause remains unclear, and no standard treatments have yet been established. In a crossover, randomized, double-blind trial,
thalidomide (100mg daily for 7 days) wascompared with placebo for treating refractoryuremic pruritus in 29 patients. Of 18 patients finishingthe study, approximately 55% showed a response to thalidomide whereas none responded to placebo. Although promising, additionalinvestigation is needed to evaluate thalidomide's efficacy for management of uremic pruritus [2].

Human Immunodefiency Virus

HIV has been treated with thalidomide because it does have some proven anti-retroviral effects assiciated with its inhibition of TNF-α production.TNF-α stimulates a cellular transcription factor that induces the expression of HIV from chronically infected cell lines [16]. Blocking of TNF-α- stimulated HIV replication by thalidomide has been demonstrated both in vitro and ex vivo [6].

Wasting and cachexia

Thalidomide has been shown to retard or reverse the weight loss associated with a number of conditions i.e. HIV infection, active pulmonary tuberculosis and advanced malignancies. Cachexia, in these disorders, is mediated through a Th1 immune response with increased production of TNF-α, IL-1ß and IL-6, all of which are reversed by thalidomide [1].

Toxic epidermal necrolysis

The pathogenesis of toxic epidermal necrolysis was believed to be related to an increased level of TNF- α [8]. 12 patients were treated with thalidomide (400mg daily for five days).However, 10 had a lethal outcome. In the 10-patient placebo group, three died [1]. This is not a good indication for the therapeutic use of thalidomide. Thalidomide is known to be a powerful inhibitor of TNF- α.

Adverse effects

Common adverse effects reported during treatment with thalidomide are summarized in Table III. Common side-effects are sedation and constipation. The degree of sedation decreases with continued administration at a constant bedtime dosing. Fortunately, any 'hang-over' effect is minimal. Constipation is a significant problem with doses around 400 mg/d or more. The most serious adverse effect is teratogenicity.

Teratogenicity:

Thalidomide's most severe toxicity is teratogenicity. This agent should never be used by pregnant women or anyone who could become pregnant, because it is labeled pregnancy category X.
Severe birth defects can result from only a single dose of thalidomide, with teratogenic risk at its highest during the critical period of 35 to 50 days after the last menstrual period.
It has become possible to delineate wide spectrum of malformations attributable to the drug [3,6] (Fig. 2A - D).

<u>These were:</u>

1. Absence of the auricles with deafness.
2. Defects of the muscles of the eye and of the face.
3. Malformations of the heart, the bowel, the uterus, and the gallbladder.
4. Absence or hypoplasia of arms, preferentially affecting the radius and the thumb.
5. Thumbs with three joints i.e. Triphalangy.
6. Defects of the femur and of the tibia.

Amelia totalis: Complete absence of four limbs.
Phocomelia: Arm, forearm in upper limb and thigh, leg absent in lower limb. So hands and feet sprout directly from trunk.
Ectrocheiria: Total or partial absence of hand.
Ectromelia: Total or partial absence of fingers or toes.
Ectrophalangia: Absence of one or more phalanges.
Ectropodia: Total or partial absence of foot.
Hemimelia: Absence of one of the paired bones of limbs.
Polydactyly: Presence of Extra digits.
Syndactylyl: Fusion of fingers.
Oligodactyly: Presence of fewer fingers or toes less than five.

	List of Adverse effects		List of Adverse effects
A	**Teratogenicity:** * A single dose of 50mg is adequate to produceserious defects	E	**Macular rash:** * Self-limiting on stopping treatment * More common in HIV-positive patients
B	**Peripheral neuropathy:** * Predominantly sensory * Axonal degeneration * Occasionally permanent	F	**Neutropenia:** * Rare * More common in HIV-positive patients
C	**Somnolence:** * Virtually universal * Administer at bedtime to reduce effect * Tolerance develops	G	**Miscellaneous:** * Xerostomia * Weight gain * Oedema of face / limbs * Decreased thyroid hormone production * Hypotension
D	**Constipation:** * Occasionally severe * Laxatives commonly needed		

Table III. Adverse effects of Thalidomide.

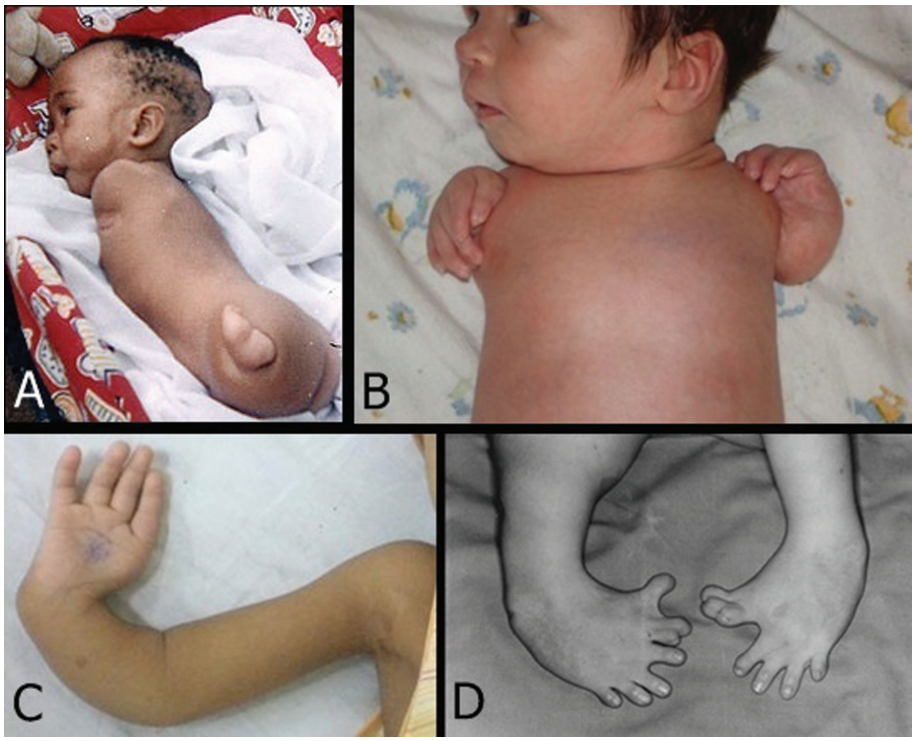

Figure 2A. Bilateral Complete Absence of upper and lower limbs. (Amelia totalis) (Courtesy of www. news.bbc.co.uk); **B.** Absence of arms and forearms. (Phocomelia) (Courtesy of www.duke.edu); **C.** Absence of thumb, shortening of distal end of radius, angulation of radius bone i.e. radial club hand. (Courtesy of www. medibird.com); **D.** Presence of Multiple fingers (Polydactyly). Fusion of digital fingers (Syndactylyl) (Courtesy of en.wikipedia.org).

They are also readily prevented by taking precautions and following guidelines for avoiding pregnancy while on thalidomide. Due to teratogenic potential, the manufacturer requires all physicians prescribing thalidomide to follow the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.). Thalidomide can be prescribed for only 28 days at a time with no refills. Prescriptions are valid for 1 week only, and monthly pregnancy tests are required [2].

Peripheral Neuropathy

Thalidomide may cause irreversible peripheral neuropathy presenting as symmetric painful paresthesias of extremities with sensory loss in the lower extremities with or without muscle cramps or weakness. Electophysiologic findings show an axonal neuropathy with reduced sensory nerve action potentials, and loss of large-diameter nerve fibers without segmental demyelination is seen on biopsy [4].

There was a significant correlation between neuropathy and cumulative doses for patients receiving more than 20g of thalidomide. The severity of neuropathy was also dose related for this group. For patients given less than 20g, neuropathy occurred less often [2].

Thromboembolic effects

Thromboembolic complications due to thalidomide are mostly associated with thalidomide's use in the cancer setting, especially when given concomitantly with chemotherapeutic agents [2]. Venous thromboembolism has emerged as the single most important complication of thalidomide in the setting of malignancy especially multiple myeloma. Venous thromboembolism was noticed in less than 5% of advanced myeloma patients taking thalidomide as a single agent [5].

It is also an emerging toxicity of thalidomide in the dermatologic setting, however. There are at least 15 cases of thalidomide-related thromboses in the noncancer setting, including among cases of sarcoidosis, lupus erythematosus, and atopic dermatitis. The risk increases when thalidomide is combined with corticosteroids (such as dexamethasone). It may be advisable to screen patients for possible thrombotic predisposition before thalidomide treatment [2].

Thalidomide derivative

Thalidomide analog includes lenalidomide (phase-II and -III clinical trials), revimid, and actimid, and are very potent in the treatment of multiple myeloma and other oncologic conditions.

Conclusion

Thalidomide is a double-edged weapon. After thalidomide use, it was prohibited due to its teratogenic effects (SINS). The 1961 tragedy remains as a bitter lesson in our minds and serves as a reminder to exercise extreme caution and vigilance when using any new drug. Anyone using thalidomide should follow the S.T.E.P.S. program and closely monitor for side effects in treated patients. Thalidomide should be considered when the underlying conditions are disabling or disfiguring and recalcitrant to other therapies.Thalidomide attracting growing interest because of Anti inflammatory and Immunomodulatery effects. Despite the major drawbacks of thalidomide - teratogenicity and peripheral neuropathy,now it has been administered for diverse dermatoses with relative success where standard anti inflammatory or immunosuppressive therapies have failed.So we described it a title name, "FORGIVE SINS OF THALIDOMIDE: RISE OF INDICATIONS OF THALIDOMIDE IN DERMATOLOGY ".

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DOI: 10.7241/ourd.20142.49

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DIFFUSE CUTANEOUS LEISHMANIASIS IN HIV POSITIVE WOMAN

Niloofar Mehrolhasani

Department of Dermatology, Kerman Medical University, Iran

Corresponding author: Dr Niloofar Mehrolhasani *mehrolhasaniniloofar@gmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 197 Date of submission: 23.01.2014 / acceptance: 28.02.2014

Cite this article:
Mehrolhasani N. Diffuse cutaneous leishmaniasis in HIV positive woman. Our Dermatol Online. 2014; 5(2): 197.

A 29 years old woman was come to our dermatology clinic with a 1 month history of lesions on her face and extremity.
She was diagnosed with HIV from 6 months ago and since then she was on treatment for HIV. Clinical examination was notable for painless indurated erythematous plauqe on her face and erythematous papule on her extremities (Fig. 1, 2). The Patient was from Bam (Iran), in which cutaneous leishmaniasis is endemic.
She has history of cutaneous leishmaniasis 4 years ago. In that time she was treated successfully with injections of sodium stibogluconate.
After skin biopsy and smear she was diagnosed with diffuse cutaneous leishmaniasis in the setting of HIV.
Leishmaniasis is a protozoal infection transmitted primarily by sandflies and is due to organisms of the genus Leishmania. Individuals who were positive for HIV and born in endemic areas may also develop disease, pointing to recrudescence of a previously controlled latent infection. In HIV-infected patients, amphotericin B (which acts by T-cell-independent mechanisms) typically has better efficacy than pentavalent antimonials [1].
After treatment with amphotericine B leasons on her face and extremity got much better.

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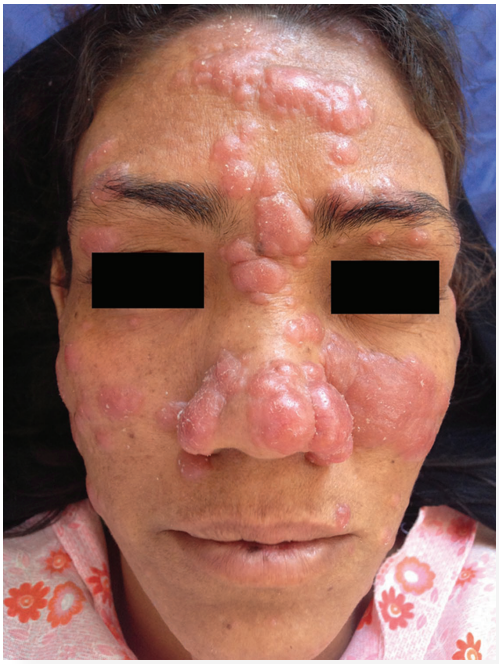

Figure 1. Indurated erythematous plaques on the face.

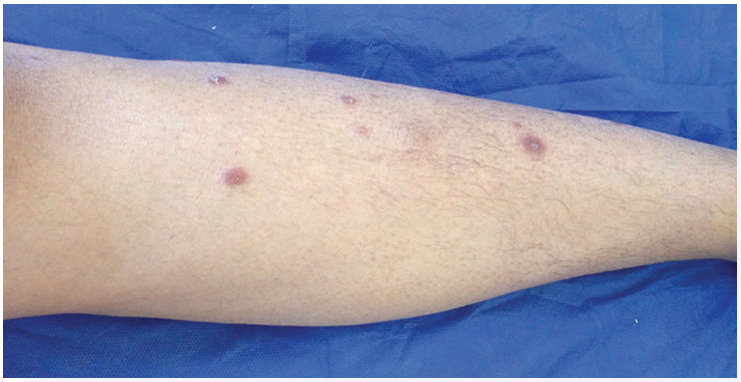

Figure 2. Erythematous and scaly papule on the leg.

DOI: 10.7241/ourd.20141.50

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BEAU´S LINES DUE TO CYTOSTATIC DRUGS IN A PATIENT WITH BREAST CANCER

Patricia Chang[1], Monica Vanesa Vásquez Acajabón[2]

[1]*Department of Dermatology, Hospital General de Enfermedades IGSS and Hospital Ángeles, Guatemala*
[2]*Hospital General de Enfermedades IGSS and Hospital Ángeles, Guatemala*

Corresponding author: Patricia Chang, MD PhD *pchang2622@gmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 198-200 Date of submission: 14.09.2013 / acceptance: 29.11.2013

Cite this article:
Chang P, Vásquez Acajabón MV. Beau´s lines due to cytostatic drugs in a patient with breast cancer. Our Dermatol Online. 2014; 5(2): 198-200.

Female patient, 47 years old who was hospitalized due to urinary tract infection, during her hospitalization bullous lesions appeared on her left limb and interconsultation to the Dermatology Department was made.

The patient has been treated by breast cancer with docetaxel, doxorubicin and cyclophosphamide; she had received 5 cycles of chemotherapy

Clinical examination showed vesicles on an erythematous base of the left arm following a linear pattern and the diagnosis of herpes zoster was done. The rest of the clinical examination of the patient showed black color and transverse lines was observed on finger and toenails predominantly on both big toenails seeing four Beau lines on each one (Figs. 1A - J). The diagnosis of Beau´s lines and melanonychia of finger and toenails due to cytostatics drugs was done.

The present case shows the normal evolution of the nails after therapy with cytostatics drugs and each transverse line correspond to each cycle of cytostatics drug.

Beau's lines are deep grooved lines in the nail plate [1,2]. They result from a sudden interruption of nail keratin synthesis and grow distally with the nail plate. In severe cases if the activity of the matrix is inhibited for 1 to 2 weeks the nail becomes detached (onychomadesis) [3]. It was named after a French physician, Joseph Honoré Simon Beau (1806–1865), described their evolution in typhoid fever and other systemic disorders, in 1846 [4].

It can be caused by chemotherapy (Fig. 2A - E), drug reactions (Fig. 3A - G) (antibiotics like moxifloxacina [5], retinoids, dapsone [3,6] and carbamazepine [6], idiopathic (Fig. 4a - c), trauma and local or systemic diseases [2]. Some of the illness where Beau's Lines had been described include malnutrition, zinc deficiency, pemphigus, Kawasaki disease [2,3], renal failure and infections [4]. Also a nervous habit of repeatedly pushing back the cuticle on one or several finger can cause "washboard nails", due to an obsessive compulsive disorder [3].

The cytotoxic chemotherapeutic agents can induce temporary arrest of proliferative function of the nail matrix, which can be clinically observed as Beau's lines in the nail plate [3,7]. This has been observed in patients who received chemotherapy with placitaxel and docetaxel, this last one being the most frequently responsible for nail matrix damage. Beau's lines are typical signs of acute toxicity to the nail matrix with transient arrest in nail plate production [7].

Beau's lines can vary based upon the width or depth of the depression, reflecting the duration or extent of the damage. The involvement of multiple nails may suggest a systemic cause, including a side effect from medication. Other causes may also be due to metabolic, inflammatory or trauma [3].

As the nail grows (at the rate of 1mm/month for toenails and 3mm/day for fingernails) [8], the Beau's lines can disappear [1]. And the time course of the illness can be estimated from the position of the Beau's line from proximal nail fold [2]. All Nails can be equally affected, but deformities are frequently noted on thumbnails and toenails due to the slower growth rate [3]. It is important to mention that Beau's lines are normal in neonates, and they have been seen in infants of 8 to 9 weeks. They may disappear around the 14th weeks of life [9].

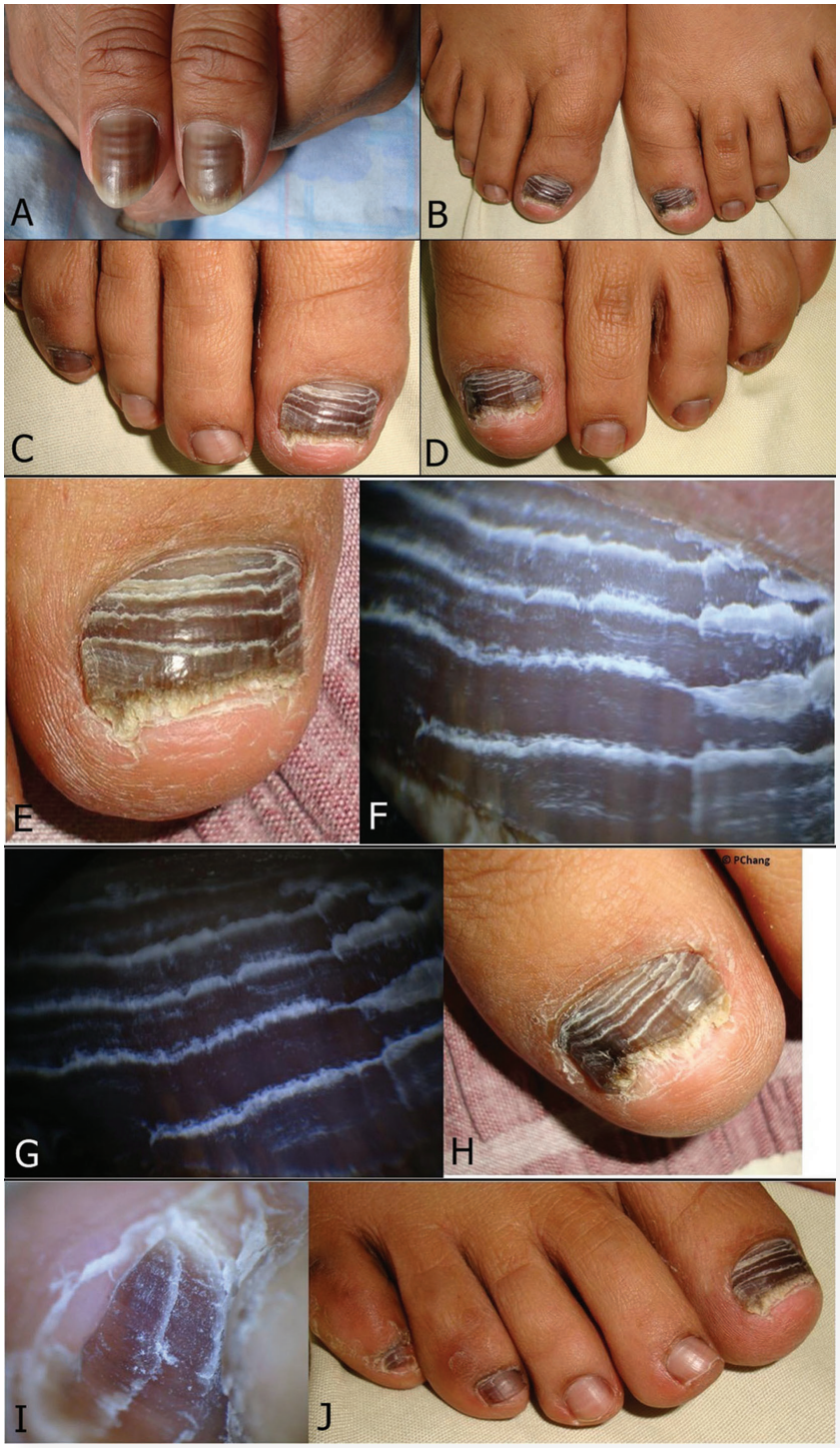

Figure 1A. Beau´s lines and melanonychia on fingernails due to docetaxel, doxorubicin and cyclophosphamide in a patient with breast cancer. **B.** Panoramic view of toenail nail disease. **C.** Close Up of the Beau´s lines on her right foot. **D.** Close up of the Beau´s lines on her left foot. **E and F.** Dermatoscopic view of the right big toenail with 4 Beau´s lines. **G and H.** Dermatoscopic view of the left big toenail with 4 Beau´s lines. **I and J.** Dermatoscopic view of the Beau´s lines on the fifth toenail.

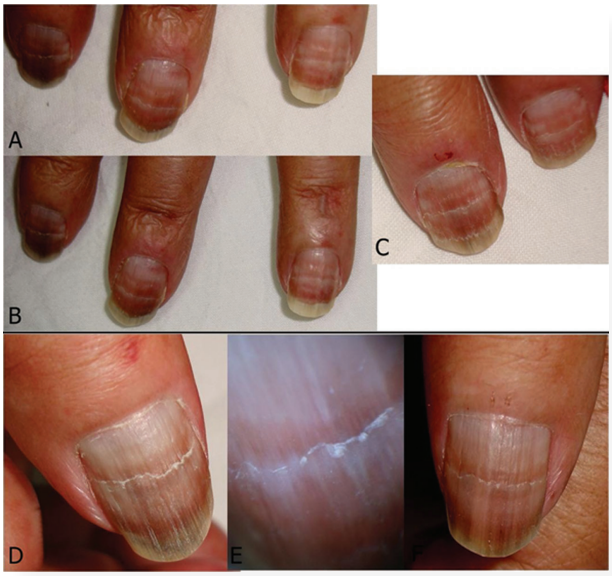

Figure 2A - E. Beau´s lines on finger nail in a patient with breast cancer treated with docetaxel.

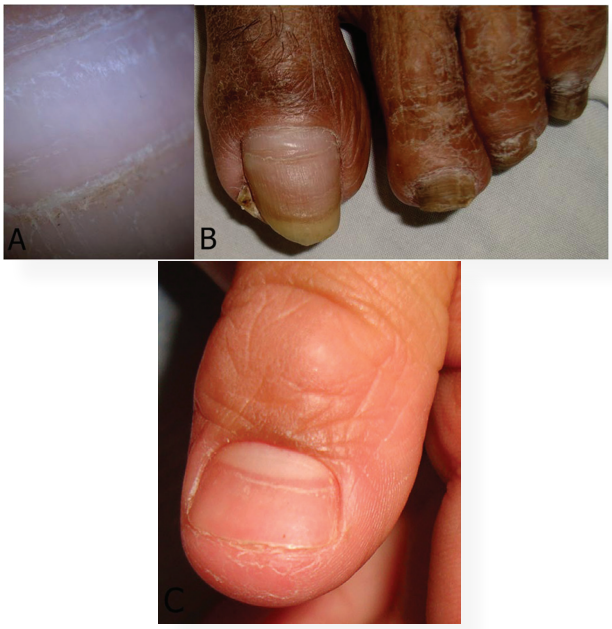

Figure 4A - C. Idiopathic causes of Beau´s lines.

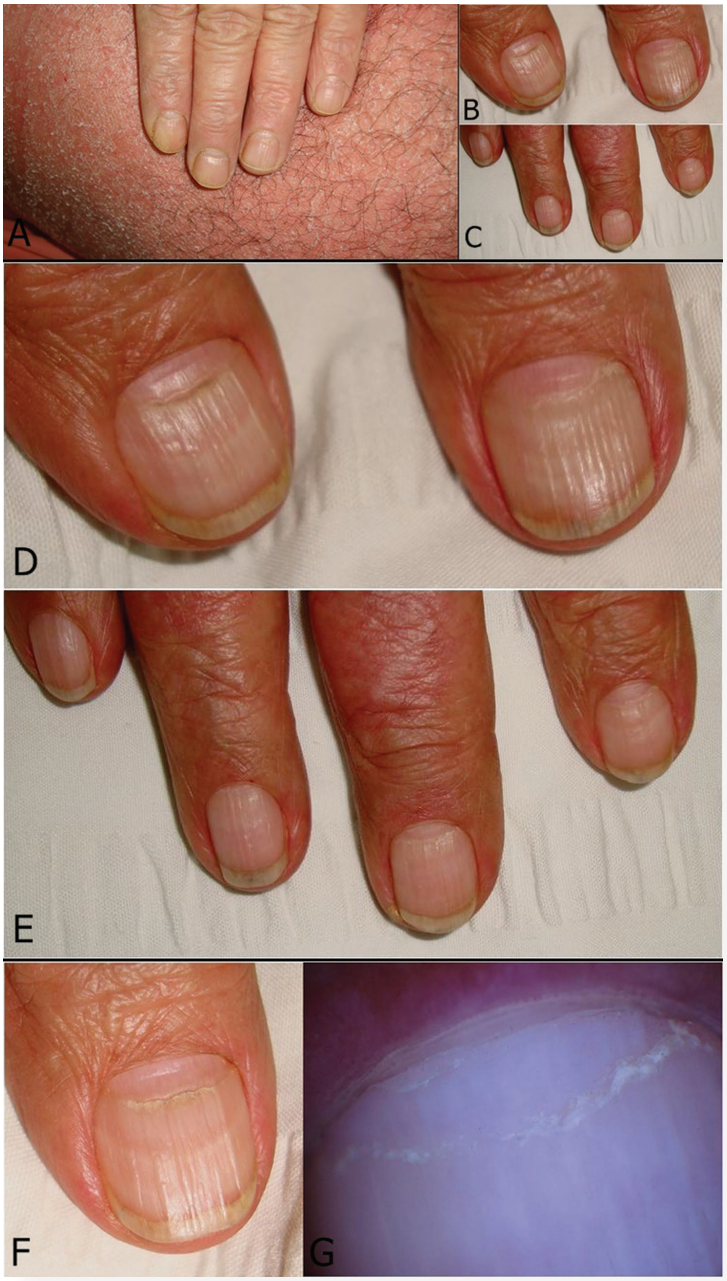

Figure 3A - G. Beau´s lines on fingernails in a patient with erythroderma exfoliative due to carbamazepin.

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DOI: 10.7241/ourd.20142.51

NASZA DERMATOLOGIA Online
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ONYCHOLYSIS DUE TO TRAUMA

Patricia Chang[1], Monica Vanesa Vásquez Acajabón[2]

[1]*Department of Dermatology, Hospital General de Enfermedades IGSS and Hospital Ángeles, Guatemala*
[2]*Hospital General de Enfermedades IGSS and Hospital Ángeles, Guatemala*

Corresponding author: Patricia Chang, MD PhD *pchang2622@gmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 201-204 Date of submission: 15.09.2013 / acceptance: 03.12.2013

Cite this article:
Chang P, Vásquez Acajabón MV. Onycholysis due to trauma. Our Dermatol Online. 2014; 5(2): 201-204.

Female patient, 35 years old who came to the private office due to discoloration of her left thumbnail and little pain since 1 month ago.

Clinical examination shows nail disease on her left thumbnail with onycholysis and dyschromia, dermatoscopy showed white-yellowish discoloration (Fig. 1A, B).

The rest of the clinical examination was normal.

Patient use to using acrylic nails since 2 years ago and denied some trauma at the nail.

The diagnosis of onycholysis due to trauma was done and recommended her not to use acrylic nail, maintain the nail short and avoid wetness.

Onycholysis is the detachment of the nail from its bed at distal end or/and its lateral attachments [1,2]. The pattern of separation sometimes resembles the damage from a splinter under the nail, extending proximately along a convex line, giving the appearance of a half moon. Normal physiologic onycholysis is seen at the distal free margin of healthy nails as they grow. It is more frequently seen in women, particularly in those with long fingernails [3-7].

Usually the nail acquires a grayish tone -with coloration due the presence of air under the nail, but the color may vary from yellow to brown depending on the etiology. In fungal infections and psoriasis, there is usually a yellow margin between the pink normal nail and the white separated area, due to the accumulate of serum like exudates [1,3]. Green discoloration indicates the presence of pseudomonas. Red discoloration is typical for drug-induced onycholysis or photoonycholysis [6].

Involvement of the lateral edge of the nail alone is less common [1]. Onycholysis creates a subungual space that gathers dirt and keratin debris. Water accumulates beneath the nail plate and a secondary infection by yeasts or bacteria may occur [1,2]. When the process reaches the matrix, the onycholysis is complete [1].

It can be primary (Idiopathic) or secondary. The onycholysis primary is painless and occurs without an apparent cause; generally the affected nail grows quickly, and returns to its normal state/condition after a few months. Pain occurs if the detachment is caused by a trauma or an infection supervenes (Fig. 2A -C). The secondary one can be classified into: dermatological causes, drug-induced (Fig. 3A - D) (the most frequent cause [5]), systemic, onychomycosis (Fig. 4A - G), others cause (Fig. 5A, B) [2].

Numerous dermatologic conditions may cause onycholysis, as lichen planus and psoriasis (Fig. 6A, B) [1,2]. Other causes can be neoplasm, inflammatory skin diseases, thyroid disease, pregnancy, anemia and allergies [7].

In the drug-induced kind/type/one the onset of this disease may be sudden, as in photoonycholysis, where there may be a triad of photosensitization, onycholysis and dyschromia [1]. In this affection, the lateral margins of the nails are never involved and thumbs are rarely affected. The nail is tender and painful in tetracycline or psoralen-induced photo-onycholysis [2]. Tetracycline, aripripazole, olanzapine and chemotherapy with docetaxel and paclitaxel can cause onycholysis or photoonycholysis [3,4].

Onycholysis may also appear in persons who come into contact with chemical irritants such as nail polish, nail wraps, nail hardeners and artificial nails. Also the frequent contact with water can cause this disorder. Traumatic onycholysis can be caused by a lack of appropriate nail care on the toenails, common trauma
(Fig. 7A - G) tight and high heel shoes (Fig. 8A - C). In hands the habitual finger sucking or the use of fingernails as a tool can induce onycholysis (Fig. 9A, B) [7].

The goal of the management is to keep the growing nail attached, and include keeping the nails dry and clipped short, sparingly use of nail polish [7], meticulous nail care and possible use of topical antifungal [1]. It is necessary treat the underlying cause if there is one, and to avoid contact with irritant substances, traumas or the wetness (Fig. 10) [3,7]. The photoonycholysis resolve spontaneously [3], with the complete recovery within 3 to 4 months after the suspension of the responsible drug. Nevertheless it could evolve to a partial or complete nail dystrophy [5].

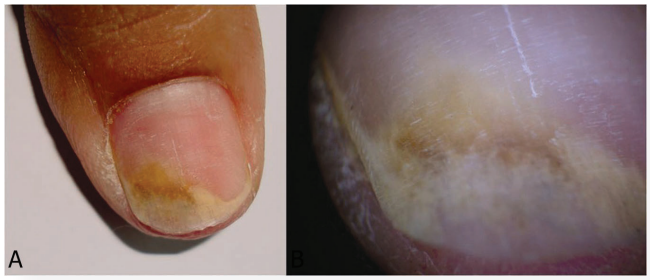

Figure 1A and B. Onycholysis on left thumbnail due to trauma.

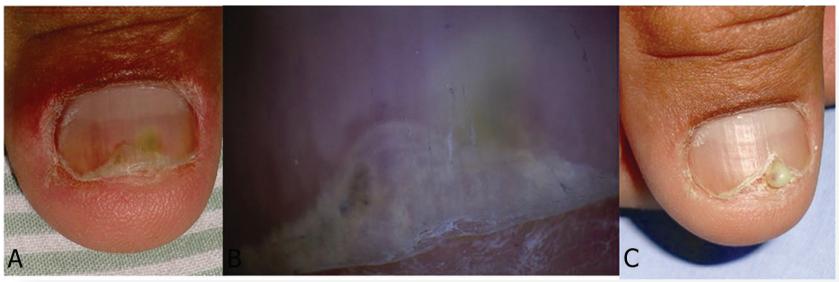

Figure 2A - C. Onycholysis due to sub ungueal infection.

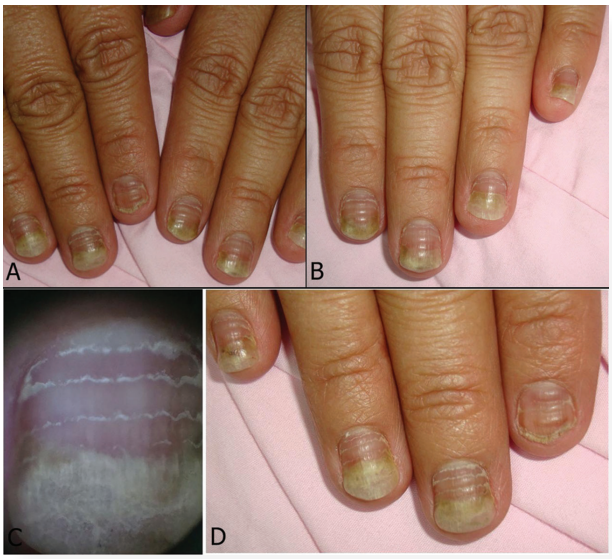

Figure 3 A. Panoramic view of fingernails due to docetaxel female breast cancer. **B.** Close up of nail lesions onycholysis and Beau´s lines due to docetaxel female breast cancer. **C and D.** Clinical and dermatoscopic nail changes due to docetaxel female breast cancer.

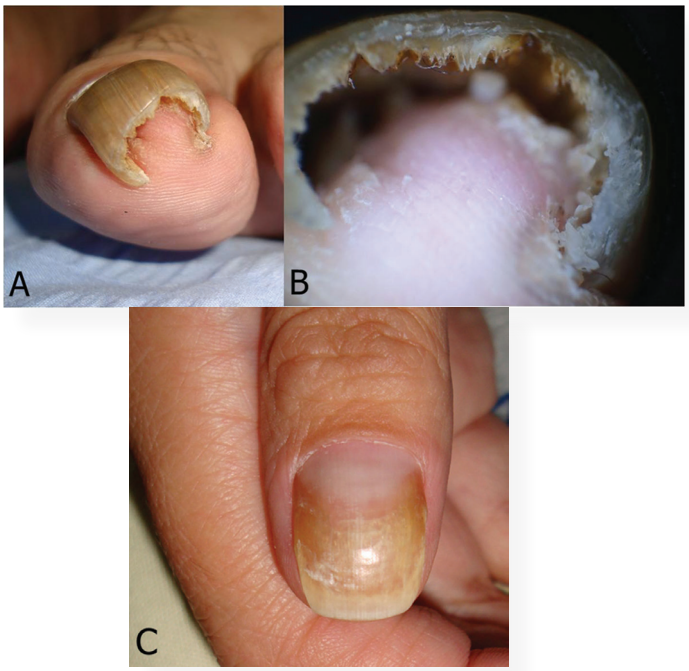

Figure 5 A and B. Onycholysis due to pincer nail. **C.** Onycholysis due acrylic nails.

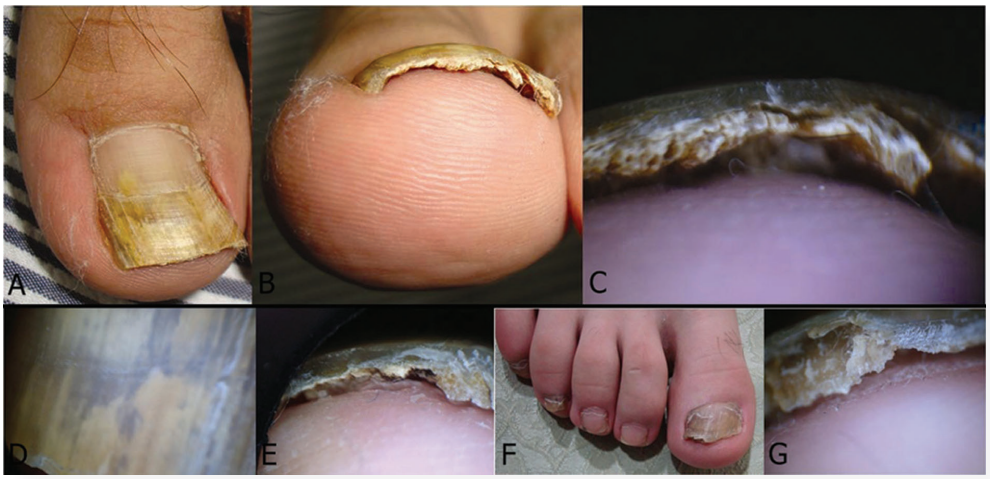

Figure 4 A - G. Onycholysis due to onychomycosis.

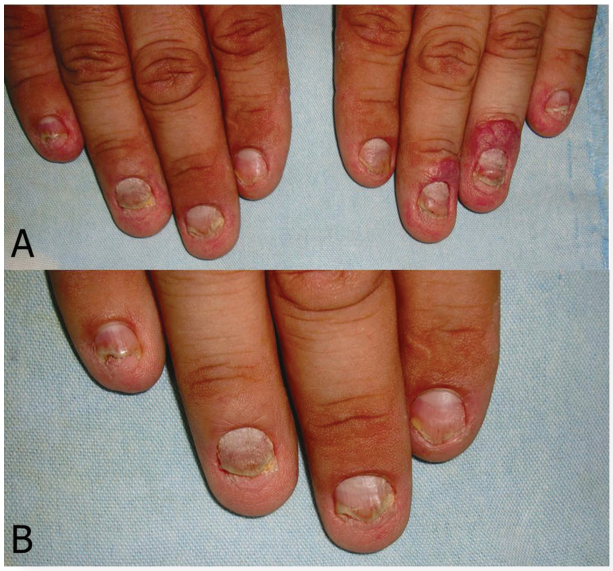

Figure 6. A and B. Onycholysis due to psoriasis.

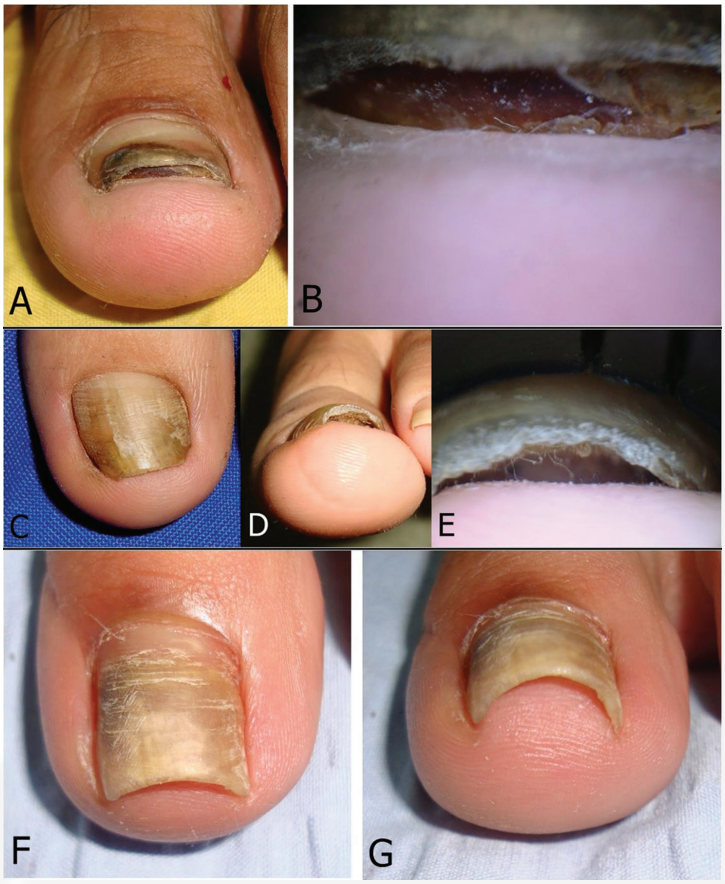

Figure 7. A - G. Onycholysis due to trauma foot ball soccer.

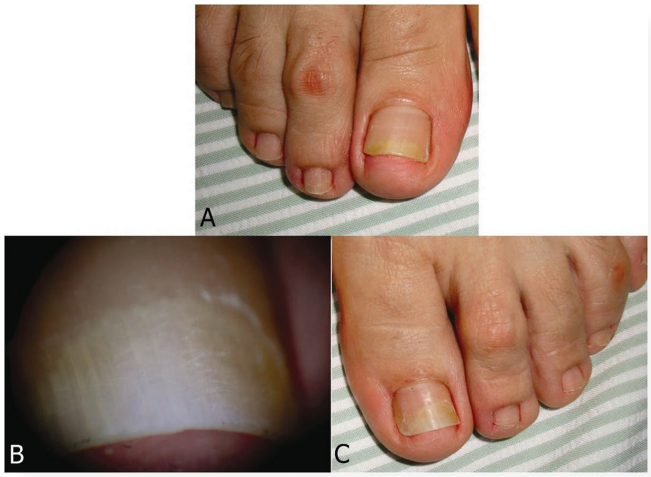

Figure 8. A - C. Onycholysis due to tight and high heel shoes.

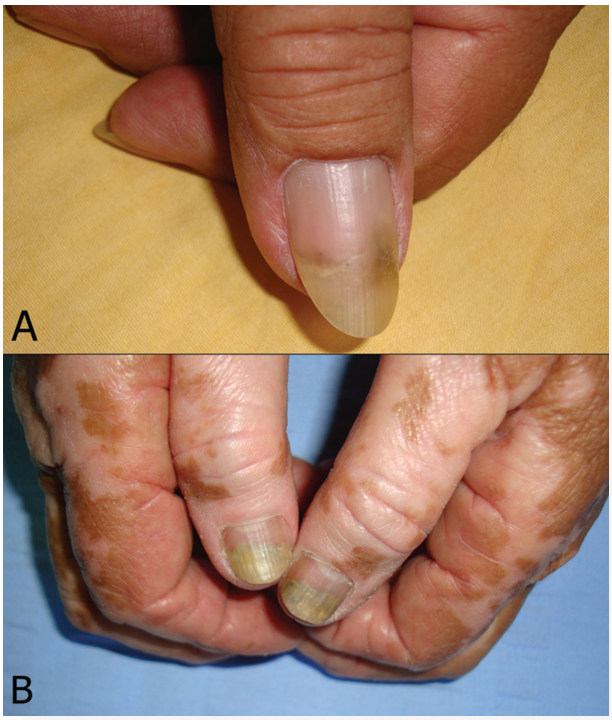

Figure 9. A and B. Onycholysis due to use fingernails as tools.

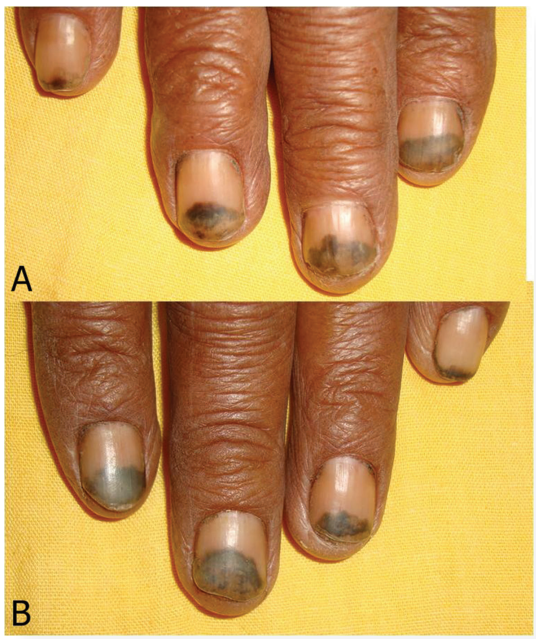

Figure 10. A and B. Onycholysis due to minor trauma.

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DOI: 10.7241/ourd.20142.52

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A CASE OF SYMMETRICAL DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA CAUSED BY VALACYCLOVIR

Masataka Satoh, Toshiyuki Yamamoto

Department of Dermatology, Fukushima Medical University, Fukushima, Japan

Corresponding author: Dr Masataka Satoh, MD masataka@fmu.ac.jp

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 205-206 Date of submission: 29.01.2014 / acceptance: 02.03.2014

Cite this article:
Satoh M, Yamamoto T. A case of symmetrical drug-related intertriginous and flexural exanthema caused by valacyclovir. Our Dermatol Online. 2014; 5(2): 205-206.

Introduction

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) has recently been separated from baboon syndrome and proposed as a unique type of drug eruption [1], which appears only on intertriginous or flexural folds and in gluteal areas in the absence of systemic involvement. Antibiotics including amoxicillin and cephalosporins are the most common drugs causing SDRIFE [2]. We report herein a case of SDRIFE showing symmetrical erythema predominantly on major flexural areas, rapidly developed after taking valacyclovir, which was suggested as a causative drug by skin patch test.

Case Report

A 79-year-old man was diagnosed with herpes simplex of the lip a few days prior to presentation. Oral administration of valacyclovir at a daily dose of 1000mg was started. About 3 hours after the patient had initially taken the tablets (500mg), freshly erythematous, prupuric rash appeared symmetrically on the neck, as well as in axillary, inguinal, intergluteal areas (Fig. 1a, 1b) with mild dysphoria. There were no mucous membrane lesions. Laboratory tests including peripheral blood counts, and C-reactive protein were within normal limits. After 1 week of the treatment with predonisolone (40 mg/day) and olopatadine hydrochloride (10 mg/day), the skin symptoms dramatically improved. Two months later, skin patch tests on the right upper arm inside part were performed with valacyclovir 1%, 10% pet. The results were positive for valacyclovir 10% pet (Fig. 2), while negative on the uninvolved back skin. Unfortunately, histological examination, drug-induced lymphocyte stimulation test (DLST) and provocation test were not performed, because the patient did not agree.

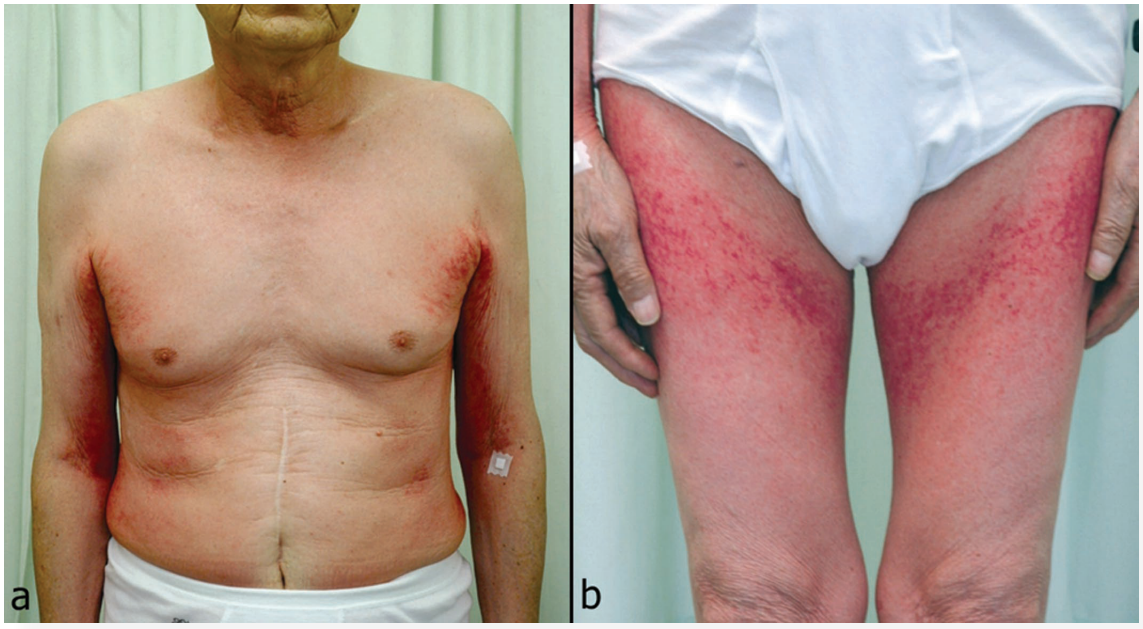

Figure 1. Clinical findings on the first examination.
Fresh erythematous prupuric rash was observed symmetrically on the neck, and the axillar (1a), inguinal areas (1b).

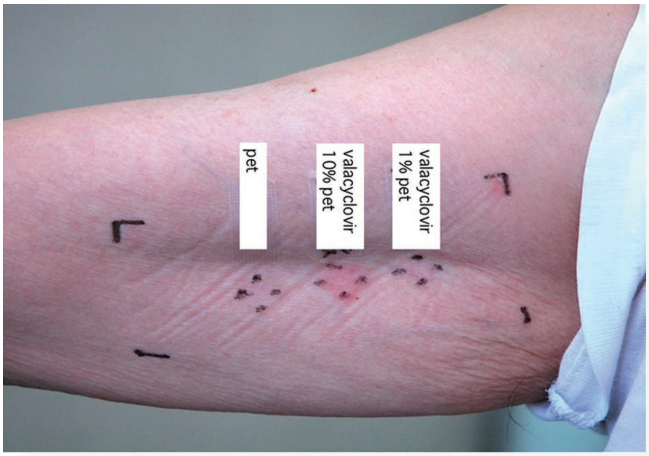

Figure 2. Skin patch test.
Skin patch testing on involved arm skin was positive for valacyclovir 10% pet, and negative for petrolatum and valacyclovir 10% pet.

Discussion

SSDRIFE, proposed as a drug-associated baboon syndrome [1], is an uncommon type of drug eruption. This condition is characterized by five clinical criteria: occurrence after exposure to systemic drugs, sharply-demarcated erythema of the buttocks and/or V-shaped erythema of the thighs, involvement of at least one other flexural fold, symmetry, and the absence of systemic symptoms. The precise pathogenesis of SDRIFE is still unknown. It occurs after the systemic administration of drug-related allergens, regardless of known prior sensitization. Amoxicillin is the most common drug causing SDRIFE, followed by cephalosporins, mitomycin C and radio contrast media [1,2]. We report the typical case of SDRIFE, met all of the criteria, induced by valacycrovir, a L-valine ester of acyclovir used for the treatment of herpetic infection.

Although patch testing is essential for the diagnosis of SDRIFE, the rate of positive tests is not high and estimated at approximately 50% [1,3]. In our case, results of patch testing with valacyclovir 10% pet on involved arm skin was positive, which was however negative on the uninvolved back skin. In the previous report of valacycrovir-induced SDRIFE [3], the patch testing with valacyclovir 20% pet on the uninvolved back skin resulted in negative. Although there has been no evidence on the most suitable site for patch testing in SDRIFE, we showed the usefulness of skin patch test on the lesional skin to provoke a positive response as in fixed drug eruption.

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DOI: 10.7241/ourd.20142.53

NASZA DERMATOLOGIA Online
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CONFUSION BETWEEN VASCULAR MALFORMATIONS AND HEMANGIOMAS-PRACTICAL ISSUES

Anca Chiriac[1,2], Meda Bradeanu[3], Piotr Brzezinski[4]

[1]*Department of Dermatology, Nicolina Medical Center, Iasi, Romania*
[2]*Department of Dermato-Physiology, Apollonia University Iasi, Strada Muzicii nr 2, Iasi-700399, Romania*
[3]*Department of Neonatology, Obstetrics and Ginecology Hospital Elena Doamna, Iasi, Romania*
[4]*Department of Dermatology, 6th Military Support Unit, Ustka, Poland*

Corresponding author: Assoc. Prof. Anca Chiriac ancachiriac@yahoo.com

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 207-209 Date of submission: 07.01.2014 / acceptance: 04.03.2014

Cite this article:
Chiriac A, Bradeanu M, Brzezinski P. Confusion between vascular malformations and hemangiomas-practical issues. Our Dermatol Online. 2014; 5(2): 207-209.

Sir,

A lot of confusion exists in daily practice regarding the terminology of vascular anomaly diagnosed in infants!

Hemangioma is a vascular tumor and it is NOT a vascular malformation!

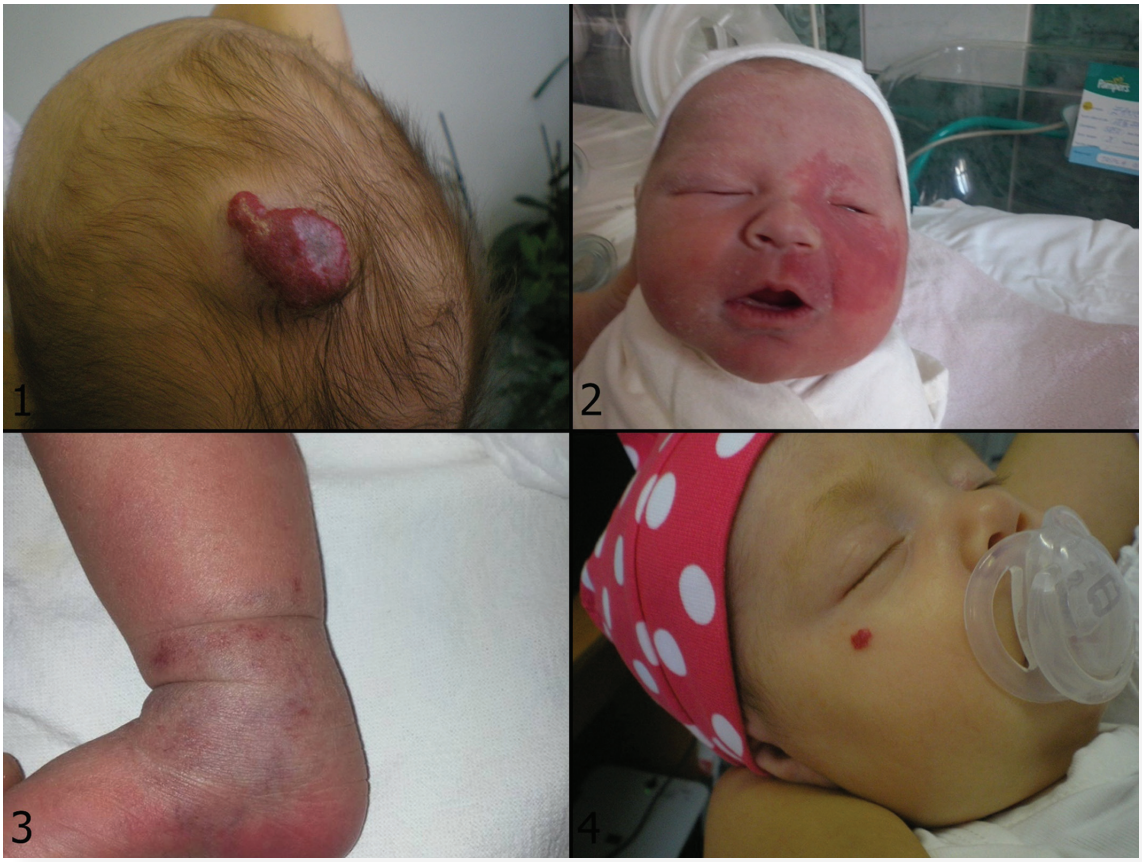

Figure 1. Case 1: Ulcerated hemangioma on the scalp in a 2month old female child;
Figure 2. Case 2: Congenital vascular malformation on the face (type capillary malformation);
Figure 3. Case 3: Congenital vascular malformation on the inferior limb (type venous malformation);
Figure 4. Case 4: Small hemangioma on the face in a 4month old female child.

We present 4 cases just to express the importance of the differential diagnosis of these two entities with great impact on clinical practice (Fig. 1 - 4).

In French literature there is the terminology of "angiomes cutanés"(cutaneous angiomas) that includes both hemangiomas and vascular malformations. The persistence of using this medical term creates confusions among physicians of different specialties and within member of the families.

Also the name "angiome plane" (plane angioma) is still widely used to describe capillary malformations.

It is of great importance to clearly delineate hemangiomas from vascular malformations based on origin, pathogenic mechanisms, clinical aspect, with impact on therapeutic approach, follow-up and evolution (Tabl. I).

Tumors	Vascular malformation
Haemangioma Other tumours	Capillary malformation (CM) Lymphatic malformation (LM) Venous malformation (VM) Arterio-venous malformation (AVM)

Table I. International Society for the Study of Vascular Anomalies. Classification of vascular anomalies, 1996 [1].

For a more clear delineation of hemangiomas and vascular malformations a few practical criteria are summarized in Table II, just to be of great help in front of a vascular anomaly seen in an infant or child.

A few hints are important to sustain the diagnosis of hemangioma: onset in early neonatal period, more frequent than vascular malformations, most seen in girls, with a "self-limited" evolution, diagnosis based on clinical aspect and spontaneous resolution.

Hemangioma	Vascular malformation
appears in the early neonatal period	presents at birth
incidence of 2-3% in newborns and 10% by the end of first year of life [6]	incidence of 1.2% [7]
sex ratio: female/male is 3-5:1	sex ratio: equal
has a growth cycle with two phases [1]: · rapid growth induced by proliferation · slow regression induced by involution of hemangioma by the age of 5-10 (in great majority of cases) or three phases [4]: · rapid proliferating phase (0-1year) · involuting phase (1-5 years) · involuted phase (5-10 years)	continues to grow at a rate proportional with the growth rate of the body, with no involution
"self-limited" tumor spontaneous regression can occur with or without sequels: telangiectases, scars, anetoderma or epidermal atrophy, hypopigmentation and/or redundant skin [3]	"self-perpetuating" embryologic tissue with malformed vessels [5] never involutes
is a vascular tumor: endothelial cells proliferation	vascular abnormalities due to defects of embryogenesis (vasculogenesis/angiogenesis) with two subtypes: · extratruncular-the defect appears during earlier stage of embryogenesis (before formation of vascular trunk) · truncular - embryogenetic defect is produced later [2]
the absence of recurrence phenomenon	recurrence can occur in extratruncular forms due to persistence of mesenchymal cells (angioblasts) that can proliferate triggered by trauma, pregnancy, surgical interventions
Duplex sonography and/or MRI in case of deep hemangioma mimicking vascular malformation	Duplex sonography and MRI attest the malformations

Table II. Differences between hemangiomas and vascular malformations [1].

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DOI: 10.7241/ourd.20142.54

NASZA DERMATOLOGIA Online
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EPIDERMOTROPIC PAGETOID SPREAD AND SQUAMOUS CELL CARCINOMA *IN SITU* IN THE OVERLYING EPIDERMIS OF MERKEL CELL CARCINOMA

Toshiyuki Yamamoto

Department of Dermatology, Fukushima Medical University, Fukushima 960-1295, Japan

Source of Support:
Nil
Competing Interests:
None

Corresponding author: Prof. Toshiyuki Yamamoto *toyamade@fmu.ac.jp*

Our Dermatol Online. 2014; 5(2): 210-211 Date of submission: 07.01.2014 / acceptance: 11.02.2014

Cite this article:
Yamamoto T. Epidermotropic pagetoid spread and squamous cell carcinoma in situ in the overlying epidermis of Merkel cell carcinoma. Our Dermatol Online. 2014; 5(2): 210-211.

Sir,

A 71-year-old female visited the Department of Dermatology at Tokyo Metropolitan Bokuto Hospital, complaining of a nodule in the face. She was diagnosed as Merkel cell carcinoma by a skin biopsy in another clinic, and referred to our hospital for operation. A physical examination revealed a dome-shaped reddish nodule, sized 1-cm in diameter, in the center of the left cheek. Cervical lymph nodes were not palpable. The nodule was totally removed with a margin. Histological examination revealed the tumor nests extending from the dermoepidermal junction into the deep dermis. The tumor cells had uniform small round or spindle-shape cells with hyperchromatic nuclei and numerous mitoses, which were consistent with Merkel cell carcinoma (Fig. 1, 2). Tumor cells were immunoreactive for neuron-specific enolase (NSE). Also, tumor nests were scattered within the overlying epidermis (Fig. 3). In addition, bowenoid changes were recognized within the overlying epidermis or at the border of MCC, showing many atypical disarrayed cells and clusters of large hyperchromatic nuclei (Fig. 4).

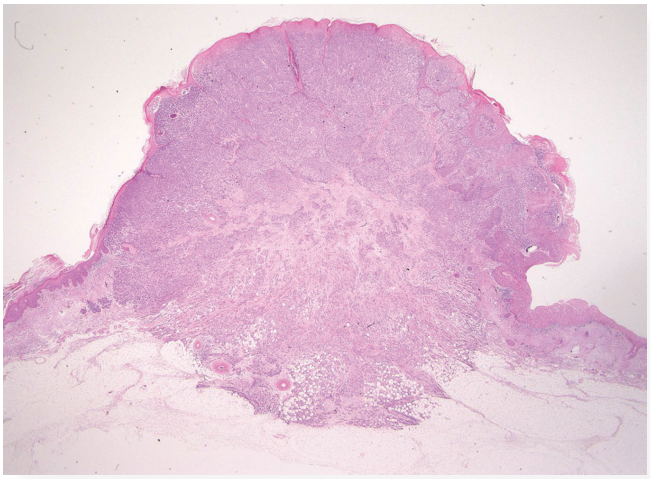

Figure 1. Overview of the histological features.

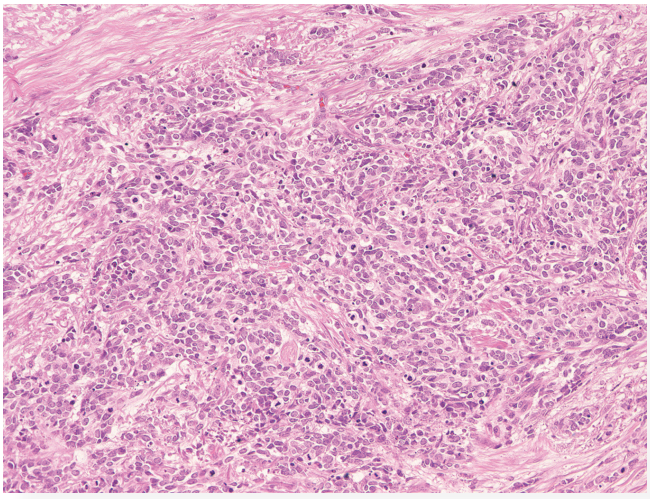

Figure 2. Higher magnification of the tumor nests showing nuclear molding, scant cytoplasm and a high mitotic rate.

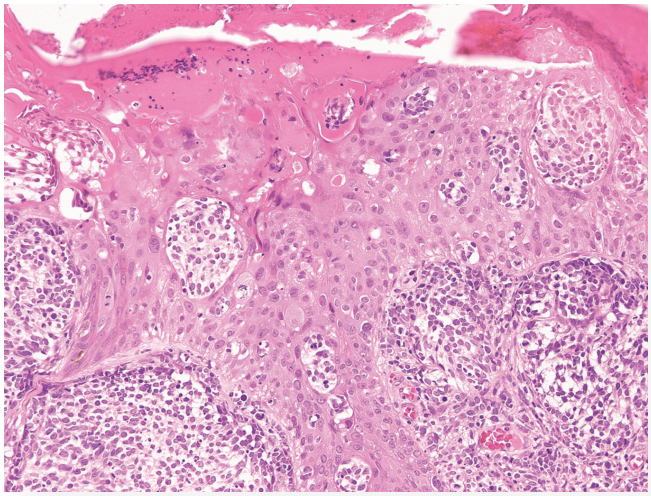

Figure 3. Pagetoid spread of MCC tumor cells in the overlying epidermis, as well as proliferation of MCC tumor nests beneath the epidermis.

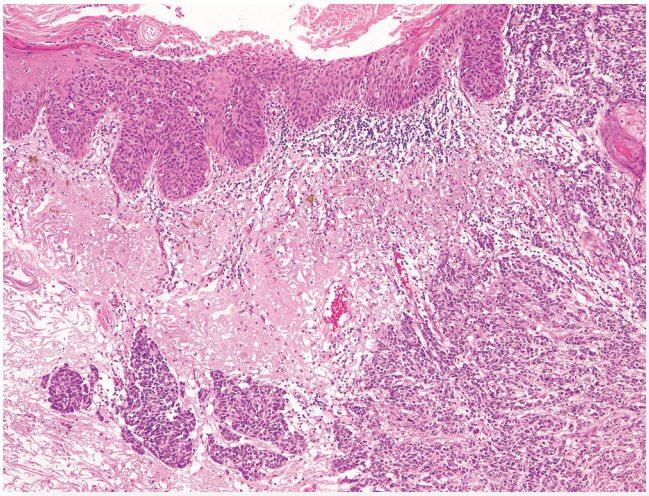

Figure 4. Bowenoid features within the overlying epidermis of MCC in the dermis.

Our case was a typical Merkel cell carcinoma (MCC). The most interesting feature in this case is the presence of Merkel tumor cell nests in the overlying epidermis. Epidermal involvement is occasionally seen in MCC including ulceration; however, true epidermal involvement exhibiting pagetoid or Pautrier-like pattern is relatively rare. An epidermotropic growth pattern is an uncommon feature in malignant skin neoplasms, and several cases of MCC which showed pagetoid spread in the overlying epidermis have been reported until now [1]. The mechanism of epidermotropism in MCC still remains unknown; however, affinity of tumor cells with keratinocytes is speculated, possibly *via* adhesion molecules. Pagetoid MCC cells show enhanced expression of epithelial membrane antigen (EMA) as compared with those located in the dermis [2], which may play a role by interfering with adhesion of the neoplastic cells with epithelial cadherin. Alternatively, epidermotropism in MCC may be related to transepidermal elimination. In our case, tumor cells were predominantly located in the dermis, extending into the deep dermis and subcutaneous tissues. Also, MCC was proliferated just beneath the epidermis without grenz zone, which may be related to epidermal invasion.

The origin of MCC has not been clarified, and proposed origins include Merkel cells, pluripotent stem cells within epidermis or adnexal epithelium, and dermal neuroendocrine cells. Previous cases in which most tumor cells exist in the epidermis suggest that MCC may arise from intraepidermal Merkel cells [3]. Further, a case of intraepidermal MCC with no dermal involvement was also reported [4]. Although examination of cytokeratin expression was not performed in our case, different staining pattern was reported between invasive MCC tumors cells and *in situ* zone [2,5].

Another interesting finding in the presented case is the association with Bowen's disease. MCC is often associated with squamous differentiation, and overlying epidermis showing SCC in situ and invasive SCC have been reported in approximately more or less 10%. Cases of MCC showing both pagetoid epidermal involvement and bowenoid changes were rare [6,7]. A similar case was recently reported in an organ-transplant recipient [7]. Although our case was not immunosuppressed, intraepidermal MCC tumor nests were intermingled with bowenoid changes in the overlying epidermis, and the bowenoid changes were also found in the border epidermis. These epidermal involvements in MCC may suggest a relationship to the epidermal or appendageal epithelia or their stem cells.

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DOI: 10.7241/ourd.20142.55

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EARLY DIAGNOSIS OF THE COLON CARCINOMA DURING THE TREATMENT WITH ACITRETIN

Ilteris Oguz Topal[1], Yunus Topal[2], Nilgun Bahcetepe[1], Sule Gungor[1]

[1]*Department of Dermatology, Okmeydani Research and Training Hospital, Istanbul, Turkey*
[2]*Department of General Surgery, Taksim Research and Training Hospital, Istanbul, Turkey*

Corresponding author: Dr Ilteris Oguz Topal *drilteris@yahoo.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 212 Date of submission: 14.02.2014 / acceptance: 10.03.2014

Cite this article:
Topal IO, Topal Y, Bahcetepe N, Gungor S. Early diagnosis of the colon carcinoma during the treatment with acitretin. Our Dermatol Online. 2014; 5(2): 212.

Sir,

Acitretin is a systemic retinoid drug used in the treatment of severe psoriasis and various other skin disorders, such as lichen planus, ichthyosis, lupus erythematosus. The mechanism of action of acitretin is still incompletely understood although, like retinoic acid, it is thought to interfere with the terminal differentiation of keratinocytes. The most frequent adverse reactions associated with this drug are the mucocutaneous effects on the lips, eyes, mouth, and other epidermal surfaces [1]. Herein, we present a case of a 54-year old man who developed rectal bleeding and detection of early stage colon carcinoma during the treatment with systemic acitretin for psoriasis vulgaris. A 54-year old man with 15-year history of psoriasis vulgaris, resistant to several topical agents, was presented to our out-patient clinic. He had generalised erythematous plaques. His only other medical problem was diabetes mellitus. Routine laboratory tests were normal. Therapy with oral acitretin (25 mg/day) was initiated. A month after starting the acitretin treatment, he developed symptoms of rectal bleeding which was intensified by defecation. He also complained of cheilitis, xerosis, and eye dryness. The patient was referred to department of general surgery. Abdominal examination was unremarkable. Pelvic ultrasonography did not revealed any abnormalities. Stool examination for occult blood was negative, and tumor markers (CEA, CA19.9) were normal. The colonoscopy was performed and this revealed a flat polyp measuring 2,5×1,7x1,5 cm located in the sigmoid colon. Snear polypectomy was performed. A histological evaluation revealed a well differentiated adenocarcinoma penetrating the submucosa. Histologically, the tumor was composed of neoplastic cells that had invaded the lamina propria without venous or perineural invasion. Abdominal computed tomography (CT) and CT scanning with positron-emission tomography (PET-CT) showed no evidence of primary lesions or distant metastasis. Based on clinical and histopathological features, a diagnosis of early stage colon carcinoma was made. We suspected that the acitretin was causing the complaints and recommended discontinuation of the drug. Once this occurred, the problems subsided gradually over the next two weeks.

Acitretin is a retinoid drug used for systemic treatment of severe cases of psoriasis and keratinization disorders. The most common side-effects of acitretin are dry lips and cheilitis, occuring in up to 75-100 % of patients. Other mucocutaneous effects include conjunctivitis, dry nose, epistaxis and sticky skin [1,2]. Rectal bleeding are not commonly documented side effects in dermatological practice. Previously, Erpolat et al. reported a case who developed anal fissures, rectal bleeding soon after receiving systemic retinoid therapy [3]. But detection of occult malignancy after the use of acitretin has never been documented. Interestingly, our patient had a malignancy but he was not aware of this condition. Because the tumor was very small and did not caused any symptoms, we think that the rectal bleeding was caused by the acitretin as it related to the dryness of the rectal mucosa. Rectal bleeding can be occured as a result of trauma, such as forceful defecation in xerotic, fissured rectal mucosa.

As a result, the use of the acitretin in our patient caused the rectal bleeding and provided early diagnosis of the colon carcinoma. It can be said that clinicians should be aware of the possible mucocutaneous side effects of acitretin. These side effects sometimes may provide detection of occult malignancy.

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DOI: 10.7241/ourd.20142.56

NASZA DERMATOLOGIA Online
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REMARKS ON THE PRESCRIPTIONS AND THE DISPENSING OF THE MEDICATIONS

Khalid Al Aboud

Department of Public Health, King Faisal Hospital, Makkah, Saudi Arabia

Corresponding author: Dr Khalid Al Aboud *amoa65@hotmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 213-214 Date of submission: 27.02.2014 / acceptance: 30.03.2014

Cite this article:
Al Aboud K. Remarks on the prescriptions and the dispensing of the medications. Our Dermatol Online. 2014; 5(2): 213-214.

Sir,

Several researchers have called for reforms in drug naming, labeling, and packaging standards.

Giving the patients the medications remains the most important stage in patients care.

There are medical errors associated with this stage. In the following disquisition, we shall highlights on some points on the prescriptions and the dispensing of the medications. We wish that these points encourage further discussions by the readers.

Enhancing and strengthening the knowledge of the health care providers about the medications.

One way to achieve this is by creating a websites for this purpose and teaching the health care providers how to utilize these websites efficiently.

It will be very helpful, also, if all pharmaceutical firms establish and maintain a drug information centers for their products.

Important resources such as medication guides and Physicians' Desk Reference (PDR) should be readily available to the practitioners. PDR is a commercially published compilation of manufacturers' prescribing information (package insert) on prescription drugs, updated annually. PDR is available in many forms, including the annual publication, online (PDR.net), and integrated directly into electronic health record (EHR) systems. The 2011 version is the 65th edition, and has information on over 1,116 of the most commonly prescribed drugs [1]. It is hoped that there will be PDR edition for each specialty. There is already published PDR for ophthalmology.

Practitioners should know also how to deal with incidences of drug poisoning and should have training programs on the knowledge of basic poison management. Establishing Drug and Poison Information Center (DPIC) should provide support in this regards [2].

Improving drug packaging

The pharmaceutical packaging including secondary packaging items (cartons, labels, and package inserts), is an essential constituent of medical products because it guarantees its stability and integrity. Important details like expiry date should be printed clearly and should not be easily erased from the packages. An easy-to-use pharmaceutical packaging also guarantees the good use of medicinal products and promotes patient compliance (for example, pack and calendar blisters).It is also a safety guarantee when it uses specific methods, such as single-dose packaging or safety caps for children.Pharmaceutical packaging also help to recognize the drug, which in itself is part of the safety process all along supply chain. Indeed, drug packaging's major role is to avoid confusion with other drugs among professionals and patients alike [3].

Improving the drug labeling

Drug labeling refers to all of the printed information that accompanies a drug, including the label; the wrapping and the package insert (PI) [4-6]. The labeling of medications encompasses the provision of information and instructions to ensure the safe and effective use of the products by patients. The labels of dispensed medications represent one of the most important sources of information available to patients. Legitimately, labeling information includes but is not limited to the following categories: patient identification, medication name, dosage, frequency, route of administration, production and expiration date and some medication storage requirements [4].

Good medication labeling practices are imperative to ensure safe medication use. International standards such as labeling guidelines issued by in the Institute for Safe Medication Practices (ISMP) should be followed.

PI (formally prescribing information in the United States; in Europe, Patient information leaflet for human medicines or Package Leaflet for veterinary medicines) is a document provided along with a prescription medication to provide additional information about that drug [7,8]. In January 2006, the FDA released a major revision to the patient PI guidelines.

The new requirements include a section called Highlights which summarizes the most important information about benefits and risks; a Table of Contents for easy reference; the date of initial product approval; and a toll-free number and Internet address to encourage more widespread reporting of information regarding suspected adverse events [7].

In each country the PI is available in one or two languages only. Language Localization System is a one-year effort by the European Commission to produce a prototype tool which will support the creation of various kinds of medical documentation simultaneously in multiple languages, by storing the information in a database and allowing a variety of forms and languages of output [2].

International organizations such as World Health Organization are encouraged to establish standards for writing PI.There are many initiatives to improve the quantity and quality of information in PI as well as accessibility and readability of PI.Proper use of colors, diagrams in PI might be helpful. Information in PI should be comprehensible, understandable by the patients and not misleading. South Africa has taken the initiative of making all package inserts available electronically via the internet, and Canada is working on a similar capability. The UK-based electronic Medicines Compendium provides freely-available online access to both Patient Information Leaflets (intended for consumers) and Summary of Product Characteristics (aimed at healthcare professionals) for products available in the UK [2].

In November 2005, aimed to replicate these leaflets in more accessible formats, including Braille, large print and on CD-ROM. It is a venture by the Royal National Institute of the Blind, the National Library for the Blind and Datapharm Communications [3].

Increasing the communication between health care providers (physician and pharmacist) and the patients regarding the drugs

It has been shown that personal recommendation from health care providers is more helpful and more accepted by the patient than PI [4].

Computerizing the labeling and the dispensing of the medications

It is expected that computerized systems in medical fields could prevent prescription errors by automatically checking prescriptions. In contrast to PI, the computer-generated leaflets can be personalized and thus irrelevant information can be omitted and only age-specific information included, leading to a shorter but more relevant leaflet. Another major advantage of electronically generated leaflets is that they can instantly updated [5].

The proper use of technology throughout the medication use process was shown to possibly improve medication safety and minimize medication errors.

Effective implementation of laws regarding proper dispensing of medications

The laws mandate that medications purchased from a community pharmacy are dispensed in their original packages with PI inside it. However, it is a common observations in many countries that the pharmacists is selling the patients one strip of the drugs as a patient cannot afford to buy the complete course. Drugs should be dispensed in a child resistant containers instead of envelops. The patients should be warned for the hazards of careless storage of drugs inside homes.

Only Over-The-Counter (OTC) medications could be given without prescription. Violating this rule had led to serious complications particularly to dermatology patient from misuse of potent topical steroids. Self-medication should be forbidden [6].

Adherence to the proper uniform for pharmacy staff

It is well known that white coat symbolize professionalism, and represent provider-patient fiduciary relationship. A good appearance of the staff increases the trust of patients in them.

Acknowledgement

The author wishes to thank the administrators of King Faisal hospital. Hospital Director, Dr Ahmad Faden, and Medical Director, Dr Raef Qutob, for their support to the public health department and to the author.''

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DOI: 10.7241/ourd.20142.57

NASZA DERMATOLOGIA Online
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Hairy ears; Revisited

Daifullah Al Aboud

Dermatology Department, Taif University, Taif, Saudi Arabia

Corresponding author: Dr. Daifullah Al Aboud *dalaboud@hotmail.com*

Source of Support:
Nil
Competing Interests:
None

Our Dermatol Online. 2014; 5(2): 215-216 Date of submission: 25.01.2014 / acceptance: 06.03.2014

Cite this article:
Al Aboud D. Hairy ears; Revisited. Our Dermatol Online. 2014; 5(2): 215-216.

Hair can grow in areas which are not usually hairy in human skin. The Online Mendelian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/omimhave) some entries in this regards. These include (%139600 - HAIRY ELBOWS, #605130 - HAIRY ELBOWS, SHORT STATURE, FACIAL DYSMORPHISM, AND DEVELOPMENTAL DELAY, 139630 - HAIRY NOSE TIP, 139500 - HAIRY EARS, and 425500 - HAIRY EARS, Y-LINKED).

Hairy ears, (Fig. 1), are uncommon trait and it is rare to see a person with very long hair on the ears. There is already Guinness World Record for the longest hair on the ears.

This trait is commonly seen in people from some parts of India [1-6] and Sri Lanka [7]. However, it has been observed in other ethnic groups. There are reports of its occurrence in persons from Malta [8], Australia [9], Egypt [10], Malaysia [11], Nigeria [12], and Japan [13].

The increased hair on the ears can involve meatal opening, pinnae (Hypertrichosis pinnae auris) or the external rim. The type of hair can be lanugo or terminal type of hair.

It was originally described as a Y chromosome-linked trait 1 [5,15]. However, it is believed now that it is not linked to it.

Hairy ears is mainly of a cosmetic concern. However, hairy ears have been described in infants born of diabetic mothers [16,17], a baby with congenital malformation [18], in association with human immunodeficiency virus (HIV) infection [19], in patient with cancer (lanugo hair) [20] and after using some medications [21-23]. There is also report of infection of the ear being precipitated by increased hair on the ears [23].

Increased hair on the ears can be also a feature of conditions and syndromes with generalized hypertrichosis [24,25].

In (Fig. 2), I proposed a clinical scheme to approach a person with hairy ears.

Long hair on the ears can be cut by trimming and can also be removed by shaving, waxing and laser.

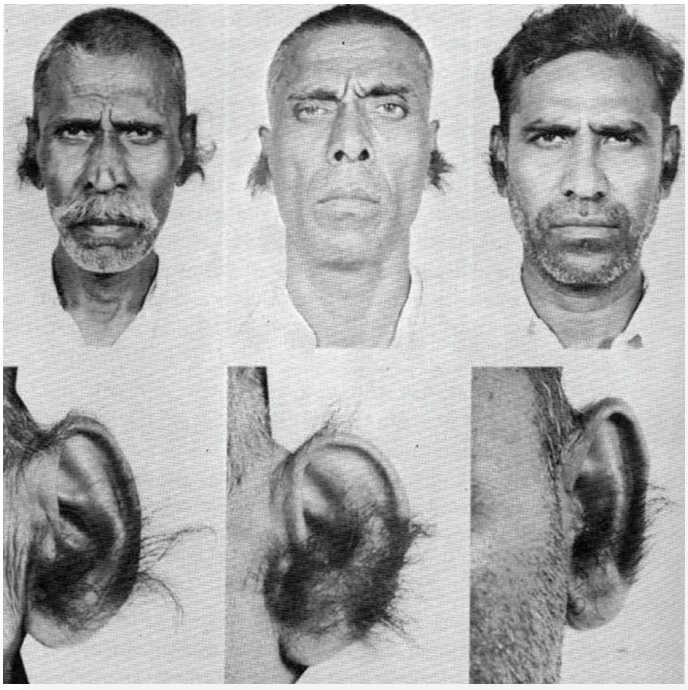

Figure 1. Hairy ears.Available online at; http://www.mun.ca/biology/scarr/Hairy_Ears.html. Courtesy of Dr Steven M Carr, Professor of Biology, Dept. of Biology, Memorial University of Newfoundland, St John's NL A1B 3X9, Canada.

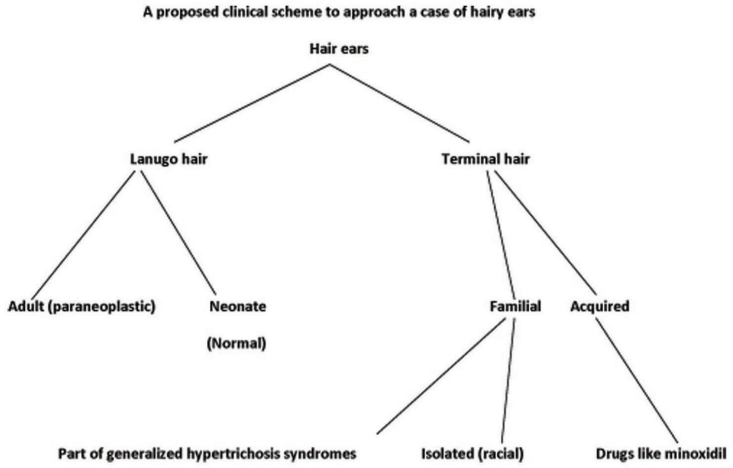

Figure 1. A proposed clinical scheme to approach a person with hairy ears.

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DOI: 10.7241/ourd.20142.58

NASZA DERMATOLOGIA Online
OUR DERMATOLOGY Online

DERMATOLOGY EPONYMS – SIGN – LEXICON – (L)

Piotr Brzeziński[1], Anca Chiriac[2,3], Roberto Arenas[4], Geme Urge Dori[5], Rodrigo Monteiro[6], Sandy Cairncross[7], Gilles Safa[8], Essam El Toukhy[9]

[1]*Department of Dermatology, 6th Military Support Unit, Ustka, Poland*
[2]*Department of Dermatology, Nicolina Medical Center, Iasi, Romania*
[3]*Department of Dermato-Physiology, Apollonia University Iasi, Strada Muzicii nr 2, Iasi-700399, Romania*
[4]*Departments of Dermatology, "Dr Manuel Gea González", General Hospital, Mexico City, Mexico*
[5]*Addis Ababa University, Faculty of Medicine, School of Medical Laboratory Sciences, Addis Ababa, Ethiopia*
[6]*Dermatology Service, Hospital Regional de Presidente Prudente, Universidade do Oeste Paulista, Presidente Prudente, SP, Brazil*
[7]*Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom*
[8]*Department of Dermatology, Centre Hospitalier de Saint-Brieuc, Saint-Brieuc, France*
[9]*Cairo University & Director, National Eye Centre, Cairo, Egypt*

Corresponding author: Piotr Brzezinski, MD PhD brzezoo77@yahoo.com

Source of Support: Nil
Competing Interests: None

Our Dermatol Online. 2014; 5(2): 217-230 Date of submission: 07.02.2014 / acceptance: 31.03.2014

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 (L) 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:
Brzezinski P, Chiriac A, Arenas R, Dori GU, Monteiro R, Cairncross S, Safa G, El Toukhy E. Dermatology Eponyms – Sign – Lexicon – (L). Our Dermatol Online. 2014; 5(2): 217-230.

LA CROSSE SIGN [Wisconsin, 1963]

Fever and nausea that can progress in children to include seizures, coma, paralysis, and brain damage, caused by a viral encephalitis (La Crosse virus (LACV) [1]. This zoonotic disease is spread by the bite of the mosquito. La Crosse virus (LACV) is one of the most common causes of viral encephalitis in children in the United States. LACV is historically transmitted by the native mosquito Aedes triseriatus (*Ochlerotatus triseriatus*) [2] (Fig. 1).

Figure 1. Aedes triseriatus (Ochlerotatus triseriatus).

LAFORA SIGN
Picking of the nose regarded as an early sign of cerebrospinal meningitis [3,4].

GONZALO RODRÍGUEZ LAFORA
Spanish neuropathologist, (1887-1971) (Fig. 2). Gonzalo Rodriguez Lafora studied in his native city of Madrid and finished his neuropathological training in the Nervenklinik in Munich, together with Alois Alzheimer (1864-1915). He received his doctorate in Madrid in 1908. He subsequently spent his internship in Madrid and 1910-1912 was histopathologist at the Government Hospital for the Insane in Washington. After returning to Madrid he was habilitated for neuropathology, becoming professor extraordinary in 1916, and subsequently headed the institute of brain physiology at the Instituta Cajal. In 1923 he lectured in Buenos Aires. Lafora was particularly interested in child psychopathology and mental hygiene, and in 1917 he published the book "Mentally abnormal children". In 1925 he was co-founder of the journal Archivos de neurobiologia, psichologia, fisiologia, histologia, neurologia y psiquiatria, now titled Archivos de neurobiologia [5].

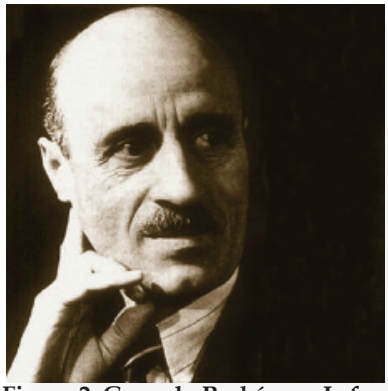

Figure 2. Gonzalo Rodríguez Lafora.

LANCET SIGN
Dicrocoeliasis from injestion of raw liver or ants containing the zoonotic fluke. Dicrocoeliasis (Lancet liver fluke disease) is caused by *Dicrocoelium dendriticum*, a trematode living in bile ducts of sheep, cattle and other mammals including man. Human infection is asymptomatic or mild to moderately severe, but being sporadic or rarely reported [6]. The life cycle proceeds through two intermediate hosts: the land snail and the field ant [7].

KARL ASMUND RUDOLPHI
Swedish scientist, l77I-1832 (Fig. 3). He is credited with being the „father of helminthology". He was awarded his doctorate in 1795, from the University of Greifswald, where he was appointed Professor of Anatomy. He worked widely across the fields of botany, zoology, anatomy and physiology. He investigated the anatomy of nerves, carried out studies of plant growth and was an early champion of the view that the cell is the basic structural unit of plants. In 1804, Karl Rudolphi, along with J.H.F. Link were awarded the prize for „solving the problem of the nature of cells" by the Königliche Societät der Wissenschaft (Royal Society of Science), Göttingen, for proving that cells had independent rather than common walls.
His first great publication was a study of parasitic worms, the „Enterozoorum Sive Vermium Intestinalium Historia Naturalis". This is the first publication to describe the Nematoda. His second, the „Synopsis cui accedunt mantissima duplex et indices locupletissima" was the first work to detail the life cycle of important nematode parasites of humans, such as Ascaris lumbricoides.
In 1810 he was appointed Professor of Anatomy and Physiology at the University of Berlin, a position he held until his death. He served two terms as rector of the University, and founded the Berlin Zoological Museum. In 1816, he was elected a foreign member of the Royal Swedish Academy of Sciences.
In 1821, Rudolphi published his „Grundriss der Physiologie", where he argued that the human genus should be divided into species, not into races. His work therefore predates „scientific" racism the Nazi period in German and Scandinavian countries [8].

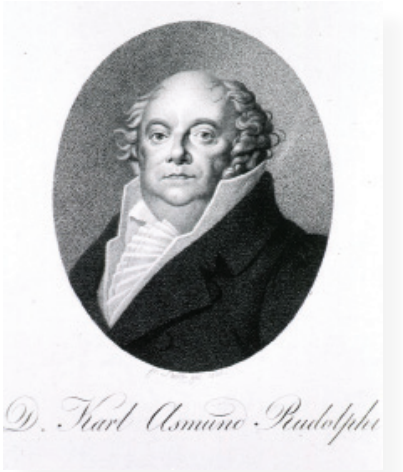

Figure 3. Karl Asmund Rudolphi.

LANDOUZY'S SIGN
Severe leptospirosis (Fig. 4A, B); also called Weil's sign and Fiedler's sign. Leptospirosis is an infectious disease caused by the pathogenic spirochete Leptospira interrogans. There is a large range of clinical manifestations in leptospirosis, and infected people can present with asymptomatic illness, self-limited systemic infection or severe and potentially fatal disease [9].
The severe form is characterized by jaundice, acute kidney injury (AKI) and hemorrhage, and is mainly caused by the serovars Icterohaemorrhagiae, Copenhageni and Lai. There are also severe forms of the disease that occur without jaundice or renal failure, such as hemorrhagic pneumonitis.

LOUIS THÉOPHILE JOSEPH LANDOUZY
French physician, 1845-1917 (Fig. 5). He commenced medical studies in Reims but in 1867 moved to Paris where he completed his studies and became hospital resident – interne des hôpitaux - in 1870. Landouzy obtained his doctorate in 1876 for a thesis on the sequel of meningo-encephalitis and subsequently published on a variety of neurological topics.

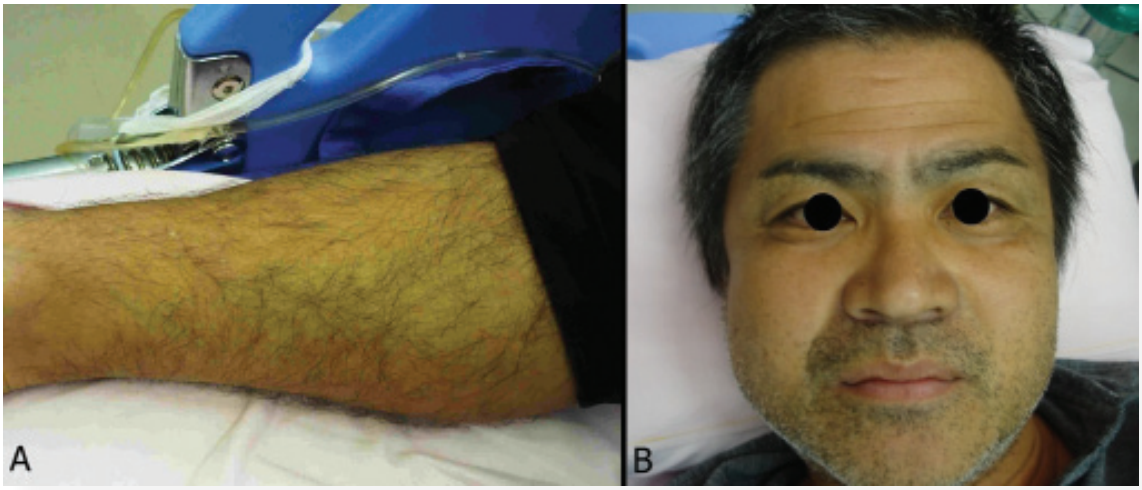

Figure 4A and B. Landouzy's sign.

He became chef de clinique with Alfred Hardy (1811-1893) at the faculty in 1877, and in 1879 médecin des hôpitaux, 1880 professeur agrégé.
Landouzy was appointed professor of therapy in 1893 and dean of medicine of the University of Paris in 1901.
Although Landouzy is chiefly remembered for his description of facio-scapulo-humeral muscular dystrophy, his main area of research was tuberculosis in which he had had a special interest. Landouzy demonstrated that lesions from erythema nodosum in patients with tuberculosis would produce the disease when injected into guinea pigs. He was one of the foremost workers in recognising that tuberculosis was a social disease and campaigned vigorously for its eradication by education of the lay public [10].

Figure 5. Louis Théophile Joseph Landouzy.

ADOLF WEIL
German physician, 1848-1916 (Fig. 6). Adolf Weil studied at Heidelberg, receiving his doctorate in 1871, and completed his education in Berlin (1818-1876). From 1872 to 1876 he was Frerichs' assistant, and was habilitated for internal medicine at his alma mater in 1872, becoming ausserordentlicher professor in 1876. While Friedreich was sick, and after his death, Weil was deputy of the medical clinic. In 1886 he was called to Dorpat as ordentlicher professor of clinical medicine. Already in 1887 he had to resign from his teaching duties because of tuberculosis of the larynx, also abandoning his scientific activities. For some years he practiced in the winter in Ospedaletti and San Remo, in the summer in Badenweiler, and in 1893 settled Wiesbaden.
He collaborated with Emil Abderhalden (1877-1950) and isolated norleucine in 1913. He was professor of medicine at Tartu, Estonia, and Berlin. He described four cases of the disease which he had observed in Heidelberg [11].


Figure 6. Adolf Weil.

KARL LUDWIG ALFRED FIEDLER
German physician, 1835-1921 (Fig. 7). Studied in Leipzig, as a student of Karl Reinhold August Wunderlich (1815-1877). He received his doctorate in 1859, was assistant physician at the medical clinic at Rostock, and from 1868 chief physician at the municipal hospital – the Stadtkrankenhaus – in Dresden. He became professor, and was also privy medical counsellor and royal life physician [12].

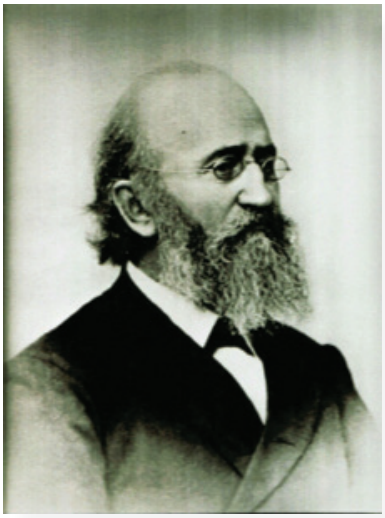

Figure 7. Karl Ludwig Alfred Fiedler.

LANTERN JAW SIGN
Acromegaly [13].

CONDICT WALKER CUTLER, JR.
American surgeon. Former President of American Society for Surgery of the Hand.

LASSA SIGN [Africa]
Severe swelling of the head and neck, with muscle pain and fever, there will also be heart and lung effusions. Caused by the zoonotic Lassa arenavirus spread by rodent waste or huiman contact [14].

LAUGHING DEATH 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. Also known as Kuru 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 [15].

DANIEL CALLON GAJDUSEK
Hungarian-Slovak-American physician and medical researcher (virologist and paediatrician) (1923-2008) (Fig. 8). In 1976 won the Nobel Prize for his work on kuru [15-16].

Figure 8. Daniel Calton Gajdusek.

MICHAEL PHILIP ALPERS
Australian medical researcher (Fig. 9), 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.
Trembling, loss of the ability to walk, talk and eat. Eventually ending with death. A sign of the falal brain disease Kuru caused by cannibalism. Kuru means trembling with fear in the Fore language. Also known as Kuru sign [15-17].

Figure 9. Michael Philip Alpers.

LAST MEMBRANE SIGN

de Duncan Buckley membrane (piel muy fina). In psoriasis. When all scales are removed formed moist, thin, translucent layer of skin covering the lesions (Fig. 10). Known also as de Duncan Buckley sign [18].

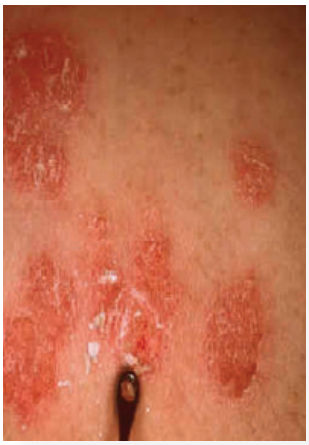

Figure 10. Last Membrane sign.

LUCIUS DUNCAN BULKLEY

American physician, 1845-1928 (Fig. 11). Bulkley wrote extensively on the dangers of biopsies. In 1885, Dr. Bulkley organized the New York Skin and Cancer Hospital (NYSCH). This distinguished physician gradually became convinced that surgery was useless, and that a careful, nourishing diet was the answer. Criticizing surgery and advocating natural methods. In 1924, he published the results of 250 cases of breast cancer eliminated without surgery [18].

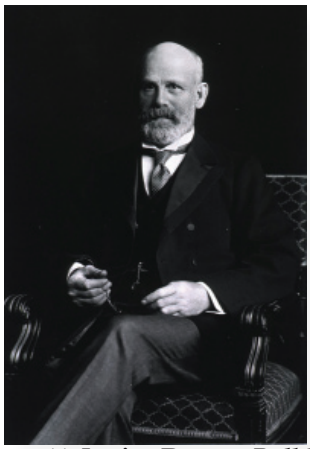

Figure 11. Lucius Duncan Bulkley.

LEATHERY PALM SIGN

A classic sign of arsenical poisoning, in which the palms and the soles of the feet have a leathery texture (Fig. 12). Also known as Arsenic sign [19].

LENNHOFF'S SIGN

A furrow appearing on deep aspiration below the lowest rib and above the liver. A sign of an echinococcus cyst of the liver [20].

RUDOLF LENNHOFF

German physician, 1866-1933 (Fig. 13). Was one of the best known medical authorities in Berlin (Germany). He was the publisher of a library for social hygiene and of medical statistics and was recognized as an authority in the fields of heart, stomach and kidney [21].

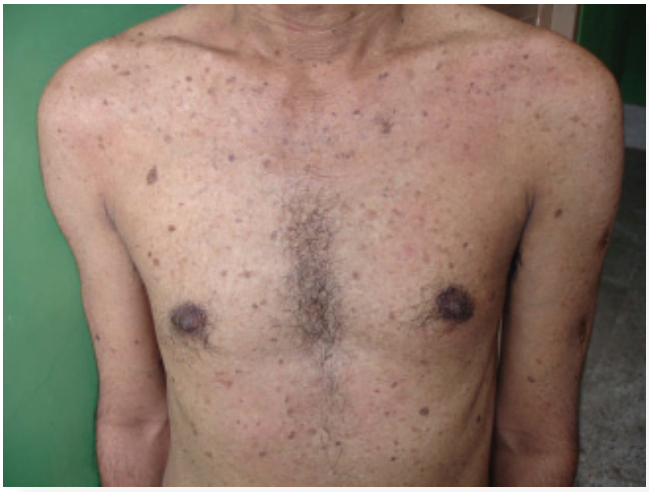

Figure 12. Leathery Palm sign.

Figure 13. Rudolph Lennhoff and Wilhelm His, Jr. in 1912 in Manhattan.

LENTICULAE SIGN

Purpura followed with free flowing bright red sputum, early signs of the Black Death, the infection with the Bubonic plaque bacterium Yersinia pestis. Also called vulgar freckels or lentiggini [22].

JUSTUS FRIEDRICH KARL HECKER

German physician and medical writer, (1795-1850) (Fig. 14). He particularly studied disease in relation to human history, including plague, smallpox, infant mortality, dancing mania and the sweating sickness, and is often said to have founded the study of the history of disease. He studied medicine at the University of Berlin, graduating in 1817 and becoming a Privatdozent and then (in 1822) Extraordinary Professor.

In 1834, he became the university's „ordinary professor" for the History of Medicine. He also cooperated with the professors of the „Medical Faculty of Berlin" on the encyclopaedic dictionary of the medical sciences [23].

Figure 14. Justus Friedrich Carl Hecker.

LEOPARD SKIN SIGN

Intense itching and a mottling of the epidermis caused by the microfilariae worms from the zoonotic Onchocera volvulus parasite (Fig. 15A, B) [24].

Figure 15A. Leopard Skin sign.

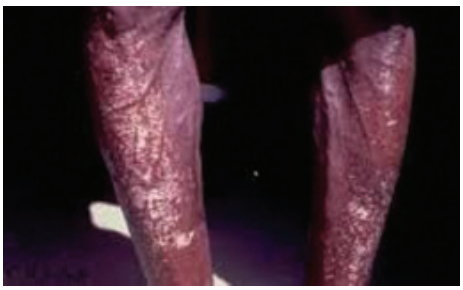

Figure 15B. Leopard Skin sign.

LESIEUR-PRIVEY SIGN

Tuberculous albumin reaction [25]. Mantoux tuberclin skin test is used for routine screening of individuals with a high risk of Tuberculosis infection and also for diagnosis of tubercular etiology in various illness. A standardized 5 tuberculin units (TU) of purified protein derivative (PPD) is injected intradermally into the volar aspect of the left forearm and the delayed hypersensitivity reaction is noted by measuring the induration after 48-72 hours.

C. LESIEUR

French physician.

PAUL PRIVEY

French physician.

LESER-TRÉLAT SIGN

Telangiectases, warts, and pigmented spots that appear suddenly and increase rapidly in number, usually associated with pruritus and is considered as a marker of internal malignancy (Fig. 16). It may take the form of acanthosis nigricans, dermatomyositis, amyloidosis, herpes zoster, or senile keratoses [26].

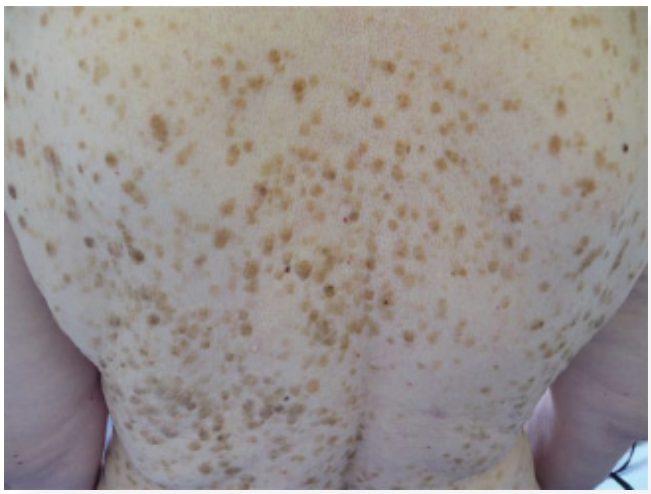

Figure 16. Leser-Trélat sign.

EDMUND LESER

German surgeon, 1853-1916. Edmund Leser first studied law in Bonn, then participated in the Franco-Prussian war, after which he continued service as an artillery officer. He commenced the study of medicine in 1876 in Leipzig, where he obtained his doctorate in 1880, before he became assistant to Volkmann in Halle. He was habilitated for surgery in 1884, becoming titular professor in 1894. Leser practised in Halle, and later in Frankfurt [27].

ULYSSE TRÉLAT

French physician, 1828-1890 (Fig. 17). Ulysse Trélat was the son of the army physician of the same name (1795-1879). He received his scientific and practical education from his father, Philippe-Frédéric Blandin (1798-1849), Philibert Joseph Roux (1780-1854) and Auguste Nélaton (1807-1873).

He became assistant of anatomy in 1853, he was conferred doctor of medicine in 1854 and in 1855 took over as prosector. He became agrégé in 1857, chirurgien des hôpitaux in 1860, chirurgien-en-chef at the Maternité in 1864. Following extensive practice at the other major Paris hospitals, he became professor of clinical surgery at the Hôpital Necker in 1860, and in 1872 was elected member of the academy [28].

Figure 17. Ulysse Trélat.

LGE SIGN

Linear gingival erythema, an erythematous band al the free gingiva that follows the contour with a reddish chevron appearance (Fig. 18). An indication of HIV disease [18,29]. Also called ANUG, HiVR and NUP signs.

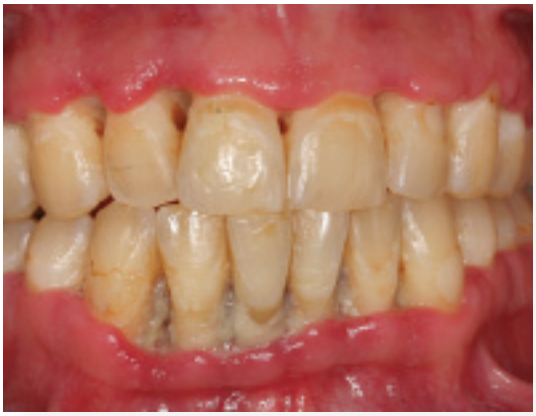

Figure 18. LGE sign.

LIGATURE SIGN

In hematuria, the development of ecchymoses in the distal part of a limb to which a ligature has been applied [29].

LIMBURGER SIGN

Strong smell of Limburger cheese, present in wounds, bandages or bed linens. An indication of gangrene infection [30,31].

LION FACE SIGN

The leonine facies presentation of leprosy, includes the thickened skin on the ears and nose, as well as, the thickening of the brows, producing the lion appearance (Fig. 19) [32,33].

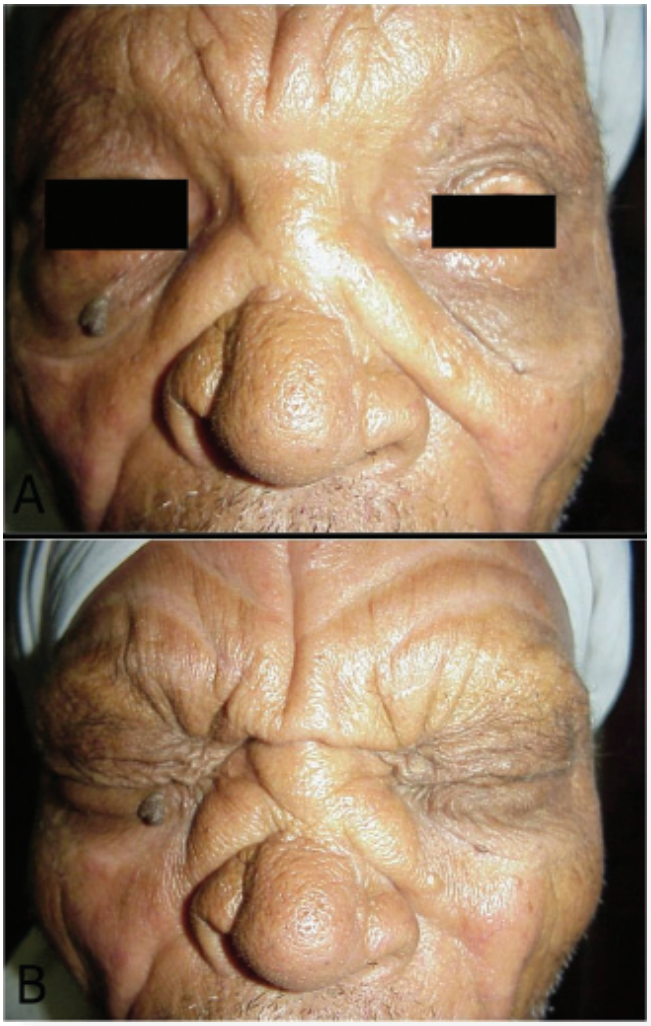

Figure 19. Lion Face sign.

LITTLE DRAGONS SIGN

Vesicular skin lesion that ruptures to reveal a worm (Fig. 20A - D). Caused by the zoonolic *Dracunculus medinensis* nematode. Also known as the Guinea or Medina worm infection [34-36].

LIVING ANGEL SIGN

Anomalous bronze discoloration of the skin with hairs surrounded by a darker color. The skin in these areas has a colored secretion with the distinct smell of mice and a garlicky odor.

…. Galtier described a man born in Switzerland the latter part of the last century, calling himself Joseph Galart. He presented the following appearance: The skin of the whole posterior part of the trunk, from the nape of the neck to the loins, was of a bronze color.

This color extended over the shoulders and the sides of the neck, and this part was covered with hairs of great fineness and growing very thick; the skin of the rest of the body was of the usual whiteness. Those parts were the darkest which were the most covered with hair; on the back there was a space of an inch in diameter, which had preserved its whiteness, and where the hairs were fewer in number, darker at their bases, and surrounded by a very small black circle; the hair was thinner at the sides of the neck; there were a great many individual hairs surrounded by circles of coloring matter; but there were also many which presented nothing of this colored areola. In some places the general dark color of the skin blended with the areola surrounding the roots of the hair, so that one uniform black surface resulted. In many places the dark color changed into black. The irides were brown. The man was of very unstable character, extremely undecided in all his undertakings, and had a lively but silly expression of countenance. A distinct smell, as of mice, with a mixture of a garlicky odor, was emitted from those parts where the excessive secretion of the coloring matter took place. In those places the heat was also greater than natural... [37].

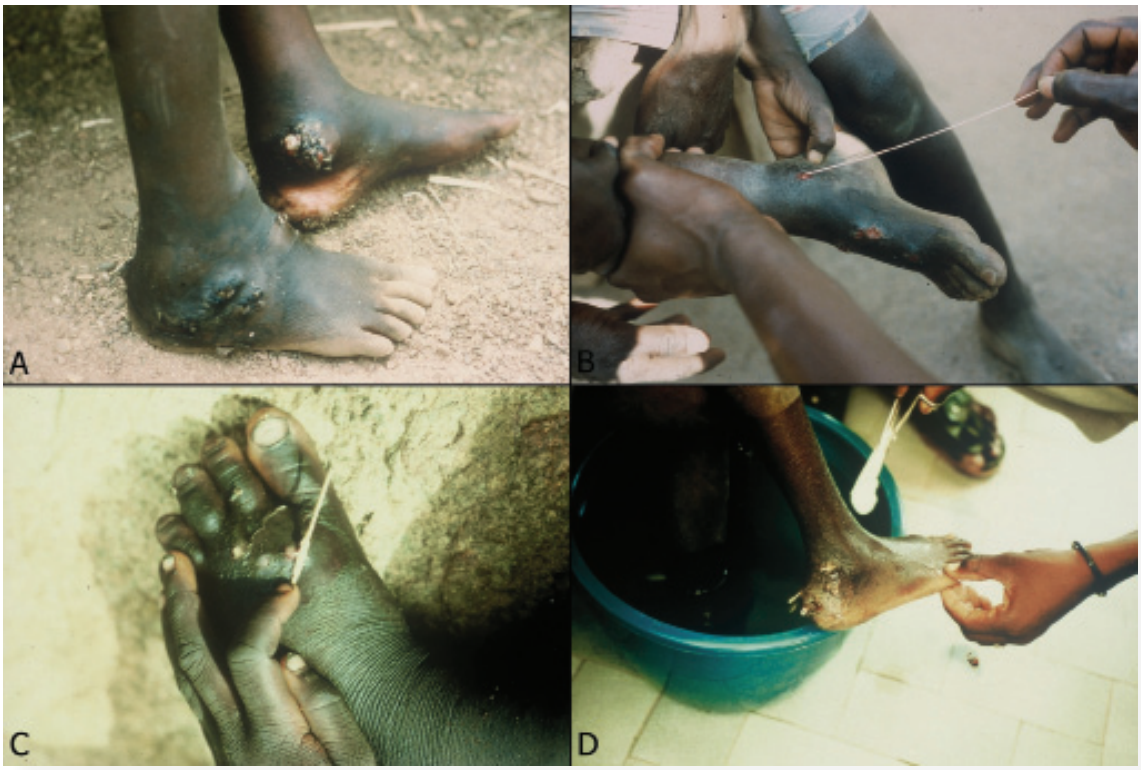

Figure 20. Little Dragons sign.

LONESTAR SIGN
A zoonotic Borrelia disease in Southern USA, also called Southern tick-associated rash illness [38].

LONG SCAR SIGN
Livid white blotches and scars on the shins and ankles from constantly scratching. A sign of onchocerciasis [24].

"LOOP HAIR" PHENOMENON
Pinkus described the phenomenon of a "loop hair" in pseudofoliculitis barbe. As a hair grows out of the skin in the extrafollicular pathway, it forms an arc or loop when it re-enters the skin. As the hair continues to grow, the loop becomes larger [39].

JULIUS POHL
German pharmacologist and biochemist, 1861-1942. He served from 1897 to 1911 as a professor of pharmacology at the German University in Prague and then to 1928. Professor of Pharmacology at the University of Breslau.
Julius Pohl was born in 1861 in Prague and graduated in his hometown and high school as well as from 1879 to 1883 to study medicine at the German University of Prague. He received his Ph.D. in November 1884 and was then at the Pharmacological Institute of the University Assistant at Franz Hofmeister. In March 1892 he obtained the Habilitation in Experimental Pharmacology, three years later, the appointment would come to associate professor.
After the change of tutor at the University of Strasbourg Julius Pohl was appointed in January 1897 his successor as professor of pharmacology. In the winter semester 1911, he moved to the University of Breslau, where he took over the chair of pharmacology in succession by Wilhelm Filehne and worked until his retirement in 1928.

Julius Pohl published about 50 scientific publications and dealt among other things with the breakdown and excretion of methanol, ethanol, and drugs, which he regarded as the founders of the pharmacokinetics. In further studies, the results were important for the later postulated by Hans Horst Meyer and Ernest Overton lipid theory of narcosis, he devoted himself to the distribution and metabolism of chloroform. He also explored the purine metabolism and the protein balance of the organism, in particular catabolic reactions in diseases, as well as the detoxification of mineral acids and organic acids [40].

FELIX PINKUS

German-American dermatologist, 1868-1949. He studied at the Friedrich Wilhelm University in Berlin and at the University of Freiburg, in 1894, he received his PhD dissertation on the basis of „Die Hirnnerven des Protopterus annectens." From 1892 to 1894 years, he was studying the nervous system in Wiedersheim. From 1895 until 1898 in Neisser in Breslau dermatology clinic. In 1898, he practiced as a dermatologist in Berlin. In 1921 he became an associate professor. In 1941 he emigrated to the United States. The scientific achievements of Pinkus are primarily works on dermatopathology. In 1901, first described the disease known as lichen nitidus [41].

LOUPING SIGN, [United Kingdom]

Meningoencephalitis caused by the bite of the *Ixodes ricinus* tick that is infected with the zoonotic Louping ill flavivirus [42].

LOVE'S SIGN

Exact localization of tenderness with the help of pin head in glomus tumor is called as Love's sign [43,44]. A classic triad of paroxysmal pain, cold sensitivity and point tenderness has been described. Love's test consists of eliciting point tenderness with a fine instrument such as the tip of a pencil or pinhead.

LUCIO PHENOMENON

Hemorrhagic infarcts; Latapi's lepromatosis. Lucio phenomenon (LP) or erythema necroticans was first described by Rafael Lucio and Ignacio Alvarado in 1852, in Mexico („A Short Treatise on the Disease of San Lazaro, or Elephantiasis of the Greeks") and later confirmed by Latapi and Zamoraas in 1948 a vasculitis occurring in diffuse non-nodular form of leprosy, which they called as "pure and primitive." (Fig. 21A, B and 22A - C) It is a relatively rare, peculiar reaction pattern occurring in untreated lepromatous or borderline lepromatous leprosy cases. LP is endemic in Mexico although cases have been reported from USA, Spain, South and Central America, including Brazil, and Asia [45-47].

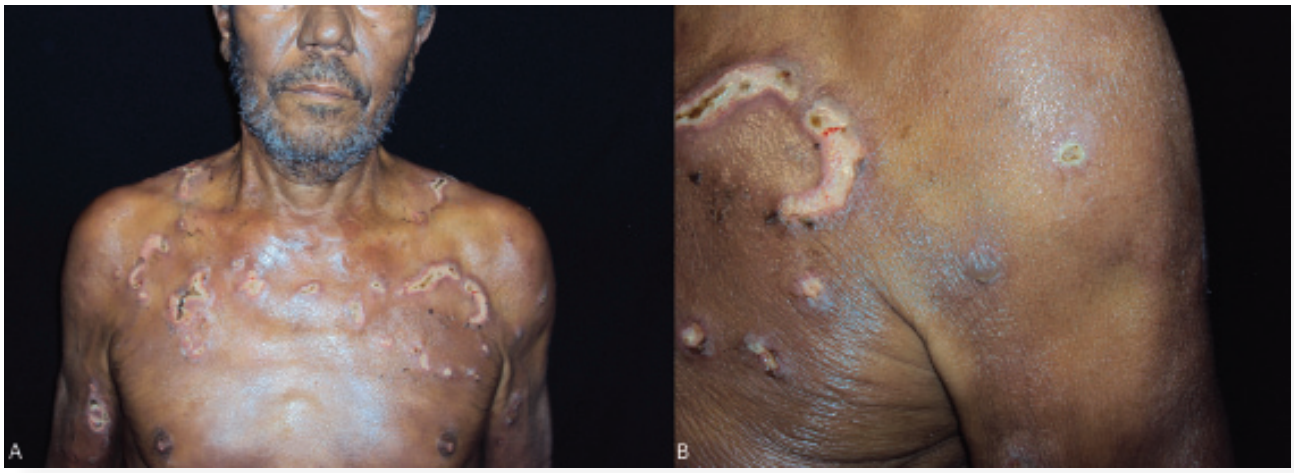

Figure 21. Lucio Phenomenon.

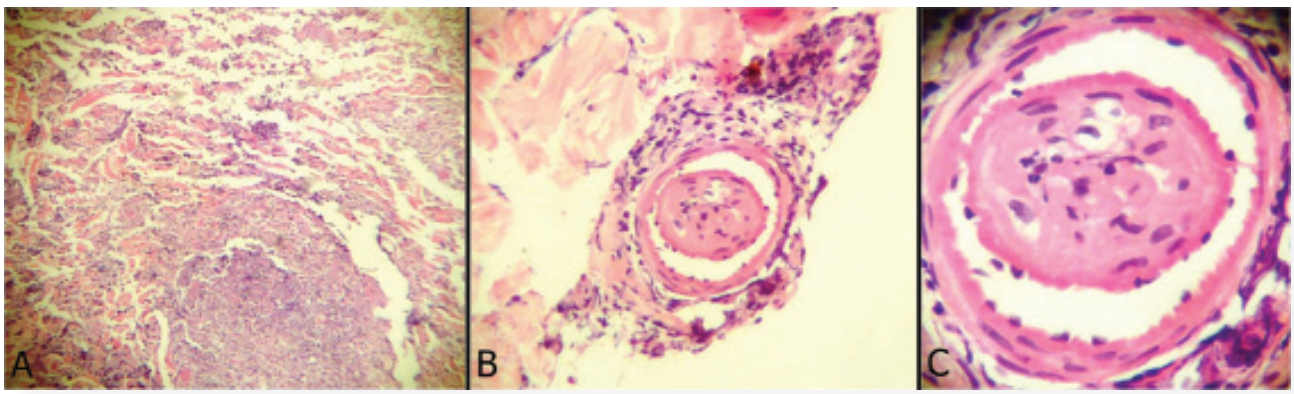

Figure 22. ***Photos represent pathological vascular obstruction, etiological factor of patient injury and characteristics of the phenomenon of Lucio.*** **This is the obstruction small vessels granuloma formed by mycobacteria and by itself by mycobacteria that can be found in the wall vase and in light of blood vessel, facts that lead to obstruction, ulceration ischemia and injuries. Therefore be interesting photo in coloring ziel-nilsen (faraco) where clearly view mycobacteria inside wall vase and light vessel.**

RAFAEL LUCIO NÁJERA

A physician, scientist and Mexican scholar, 1819-1896 (Fig. 23). He devoted many years of his life to research on leprosy. Rafael Lucio began his studies in Xalapa. In San Luis Potosi he continued his schooling and surfaced his vocation for medicine. In 1838, he enrolled in the Establishment of Medical Sciences in Mexico City, where he obtained the place of practical exercises of operative medicine. He completed his entire career with notable success in 1842 and earned his medical degree, having sustained bright exam. Months later, when the young doctor had just twenty-four, he was appointed director of the San Lazaro Hospital in the very capital of the Republic, a post he held for seventeen years always with great dedication, efficiency and humanitarianism. During his tenure at the San Lazaro Hospital was dedicated to the study and research of a disease that was very common among patients attending that institution, and at that time it was known under the name wrong of Saint Lazarus or elephantiasis of the Greeks, the disease first manifested with ardent reddish spots on the skin, later changed to a red wine and finally became ulcerations. Dr. Rafael Lucio gave this name wrong Leprosy manchada.

In 1845 Dr. Lucio was appointed assistant professor at the Faculty of Medicine and, two years later, gives the chair of legal medicine and then kind of internal pathology.

In 1851, discloses the National Academy of Medicine observations and research on this disease.

His work was so clear and comprehensive that formed the basis and motivation for other notable physicians, as Latapí and Faget, continue the research for a cure for this terrible disease, a goal that was achieved in this century in the early years forty. In recognition of the valuable contribution of Dr. Rafael Lucio, the disease was named Lucio and Fuzzy lepromatosis Latapí.

Throughout his life , this man of science devoted to the study of medicine. In 1855 and 1868 he traveled to Europe to study the progress of medical science in those countries. Upon his return, on both occasions, implemented and spread what he learned, especially in surgery and everything related to it. The reforms introduced in this area represented a significant advance in medical practice in our country.

Dr. Rafael Lucio was a long- time professor at the Faculty of Medicine. In addition to his wisdom and his vast experience showed in class ease of expression and remarkable clarity in their exhibitions; to this must be added his unassuming manners, his kindness and his spotless morality, all qualities that made him a exemplary teacher. In the private practice of medicine was widely recognized altruism, humanitarianism. Tended with the same care and dedication to all patients regardless of social class to which they belonged, or whether or not they afford to pay their fees.

Among his colleagues, enjoyed much prestige and recognition, therefore, often required it to get their opinion on difficult cases, and always got him a wise and generous response. Dr. Rafael Lucio made his profession of medicine a true ministry of service, support and comfort to anyone who needed it, and in response people gave their love and respect. In recognition of his high virtues as a man and citizen, and his outstanding work as a physician and scientist, in Mexico City it was erected a statue in the Paseo de la Reforma [47,48].

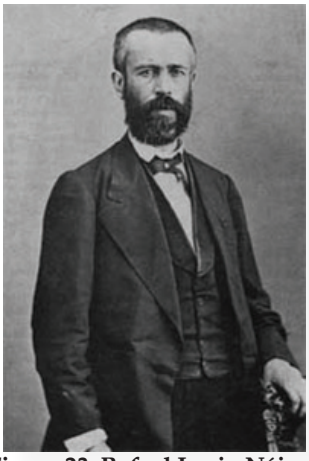

Figure 23. Rafael Lucio Nájera.

FERNANDO LATAPI

Mexican dermatologist, teacher and author, 1902–1989 (Fig. 24). He is the founder of the Mexican Society of Dermatology, and the Mexican School of Leprology. He changed the way leprosy was perceived, classified different types of leprosy patients, and made important contributions to both syphilis and a disease called pinta. He attended elementary school at Instituto Franco Inglés, and then went to the Nacional Preparatoria de la Universidad Nacional, where he studied medicine. After graduating from medical school in August 11, 1928, he was not originally interested in pursuing a career in dermatology. However, as it was the only vacant position at a local clinic, he started working in the field. When the Mexican Association of Action Against Leprosy (AMAL for its abbreviation in Spanish) was founded in 1948, Fernando Latapí donated a few books and promoted the establishment of a library.

On January 2, 1937, Fernando Latapí founded the Mexican School of Leprology that has as main goals the abolishment of drastic laws against people with leprosy, as well as the integral and respectful treatment towards them. Dr. Latapí contributed to the eradication of the traditional concept of leprosy, in which people that suffered from this condition were social misfits since people considered them impure and they thought leprosy was highly contagious. To change this misconception, he and his team crusaded for the training of medical personal in the disease. Later on, he and his team created brigades which diagnosed more than seven thousand patients in three years which was more people than what had been diagnosed in thirty years prior. At AMAL, he always promoted equal treatment for all patients, and he successfully treated most of them, giving a revolutionary twist to the history of this disease that had no cure before.

He also demonstrated that chaulmoogra oil, which at the time was thought to be an efficient treatment, was actually not beneficial, but harmful to the treatment of the disease. Instead, in 1944 he was the first one to use promin, as a treatment for leprosy in Mexico. He also made significant contributions for a disease called pinta, specifically about its diagnosis with early buds.

The AMAL Center of Leprosy served as a hospital for all cases of leprosy and some years later became a dermatological center, which is now Ladislao De La Pascua Dermatological Center.

The Center was founded by Dr. Latapí and strongly contributes to the role of teaching and qualification of personal in the Mexican dermatological area since successful specialists have studied there and have developed futures institutions based on the teachings of their alma mater.
Due to his contributions during his career, he received national and international recognition. In 1956 he organized the 3rd Ibero Latin-American Congress of dermatology as well as the 11th edition of the same one In 1960, he received the Gaspar Viana of CILAD, the highest award in the Mexican medicine. In 1978 he organized the XI International Congress of Leprosy. He also received the Damián Dutton award for his contributions in the field of leprology in 1978. He served as the president of the XI International Congress of Leprosy celebrated in Mexico in 1978 as well.
Fernando Latapí was the author of over three hundred papers along his career. Leprosy became his passion for 45 years, and the source behind his major medical contributions. He published a great deal of writings in medical magazines and journals. One of Latapí's passions was teaching, something he did for many years. He taught his students about health service, interaction with patients, kindness as well as academic content. He stated that someone giving a class or talking to a patient should guarantee that the listener laughed, or cried because it indicated trust in the doctor.
He made contributions to medicine such as being the first one to employ successfully sulphones for treatment of mycetomas and the proposal of the term "pintides" for the secondary lesions of pinta. He also discovered a previously unknown disease in 1956, calling it "dyschromia en confetti" which is caused by hydroquinones. Dr. Latapí also established terms such as "early" and "late" syphilis and corticoderma. He modified the Morgan scheme in syphilis and rediscovered necrotizing erythema that is also known as Lucio phenomenon. There is even a "Latapi Lepromatosis" which is a form of diffuse nonnodular lepromatous leprosy [49,50].

Figure 24. Fernando Latapi.

AGUSTIN CHEVEZ ZAMORA
Mexican patologist.

IGNACIO ALVARADO
He was a member of the Mexican Academy of Medicine, he worked in yellow fever and he was a coworker with Rafael Lucio in the description of diffuse leprosy.

LUDWIGS SIGN
Swelling in the submental area, the tongue is displaced upwards and that may cause the inability to close the mouth. Cellulitis of the deep cervical fascia. Also known as Ludwig's Angina [51].

WILHELM FRIEDRICH VON LUDWIG
German surgeon, 1790-1865 (Fig. 25). Ludwig showed promise in medicine at an early age, and at 14, he went to Neuenburg to continue his classical studies while beginning to study medicine under a surgeon. Ludwig received a certificate of proficiency in 1807, whereupon he went on to study surgery, medicine, and obstetrics at the University of Tübingen. His performance was so exemplary that he was awarded a gold medal by King Frederick I in 1809—before graduating—for the advancement of surgery. In July 1811, Ludwig received his doctorate.
Unfortunately, before he could commence his study tour, Napoleon attempted to conquer Russia, and previously exempt students were called to service. Ludwig served initially as the doctor for 3rd Infantry at the Schorndorf garrison, and subsequently as director for the Württemberg field hospital at Smolensk in 1812.
He contracted typhus and was captured by the Russians; after recovering from typhus, he served as a Russian noblewoman's personal physician. Once he was freed from Russian capture in 1814, Ludwig returned home and directed a typhus hospital in Hohenheim, where he completed his military service in 1815. Shortly after leaving the military, Ludwig was honored with title of full professor of surgery and obstetrics at Tübingen in 1815. Before fulfilling it, however, he commenced his initially planned study tour that had been put off in light of the war. Upon returning to Tübingen in 1816, Ludwig, having experienced the equipment available at other facilities in Germany, immediately supplemented Tübingen clinic's own supplies and reference literature with his own salary.
Ludwig was appointed as one of King Wilhelm I's personal physicians.
When Ludwig went to Stuttgart to serve the king, he was quickly recognized as a great diagnostician, and he was soon promoted to be the royal family's chief physician.
He remained in Stuttgart for most of the remainder of his life; between 1835 and 1846, he served as director of the medical college, president of the Württemberg Medical Association, and chairman of the first Stuttgart scientific congress's medical section.
Ludwig published his now-famous paper on Ludwig's angina with no title in 1836. A colleague dubbed the condition „Angina Ludovici" (Ludwig's angina) a year later.
Beginning only in his seventies, the physician suffered several health problems, including a bladder stone removed during 1865 in two separate sessions a few months apart. Somewhat ironically, he died December 1865 a week after the onset of an unspecified neck inflammation, which was probably not the condition that bears his name [52].

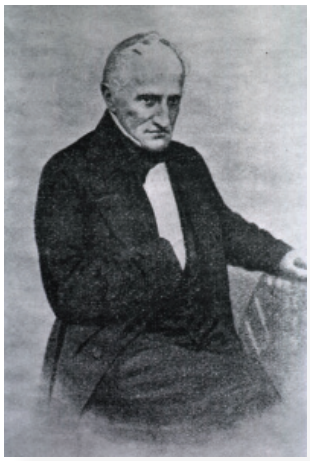

Figure 25. Wilhelm Friedrich von Ludwig.

LUSITANUS'S SIGN

Chromidrosis, perspiration resembling the color of sooty water [53].

ABRAHAM ZACUTUS LUSITANUS

Portuguese-Dutch physician and medical historian, 1557-1642 (Fig. 26). Born in Lisbon into an illustrious Marrano family and a descendant of Abraham ben Samuel Zacuto. Zacutus became an important figure among Jewish physicians and had a large practice. His non-Jewish name was Manuel Alvares de Tavara. In 1625 he moved to Amsterdam, where he openly returned to Judaism, was circumcised, adopted the name Abraham, and began to use the name Zacuth in his writings. He engaged in fruitful scientific activity, and published many medical books. His main strength is revealed in his accurate clinical descriptions of plague, diphtheria, exanthematous diseases, and malignant tumors; he was one of the first to describe blackwater fever. A first work was published in 1629 in Amsterdam under the title De Medicorum principum historia [54].

Galeazzi and Zacutus Lusitanus said the perspiration resembled sooty water and they gave the name of chromchidrosis.

Figure 26. Abraham Zacutus Lusitanus.

LUTZ SIGN

Clinical signs to elicit characteristics of blisters are a crucial part of the examination of patients with vesiculobullous disorders. It is therefore essential for dermatologists to be familiar with, or rather be expert at eliciting these signs, which include Nikolskiy sign, bulla spread sign, Sheklakov sign/false-Nikolskiy sign, and pseudo-Nikolskiy sign/epidermal peeling sign.

In the traditional „bulla spread" sign or Lutz sign, the margin of an intact bulla is first marked by a pen. Slow, careful and unidirectional pressure applied by a finger to the bulla causes peripheral extension of the bulla beyond the marked margin. The bulla thus extended has an irregular angulated border in pemphigus vulgaris, while a regular rounded border is observed in bullous pemphigoid or other subepidermal blistering disorders [55].

Lutz sign may also be elicited on a burst blister if a substantial portion of the roof is intact. The Asboe-Hansen sign is a variation of the bulla spread sign [56].

This sign is positive in all varieties of pemphigus and many cases of subepidermal blisters, including bullous pemphigoid, dermatitis herpetiformis, epidermolysis bullosa acquisita, cicatricial pemphigoid, dystrophic epidermolysis bullosa, Stevens-Johnson syndrome and toxic epidermal necrolysis. Due to fragility of the roof of the blister it is usually negative in Hailey-Hailey disease and staphylococcal scalded skin syndrome [55].

WILHELM LUTZ

Swiss dermatologist, 1888-1958 (Fig. 27). He studied in Basel, then for a brief period in Vienna, and received his doctorate at his alma mater in 1912. He spent his internship and period as assistant in Basel at the pathological institute under Ernst Hedinger (1873-1924), at the dermatological clinics in Bern under Josef Jadassohn (1863-1936), and in Basel under Bruno Bloch (1873-1933) and Felix Lewandowsky (1879-1921). He received the venia legendi for dermatology and venereology in Basel in 1916, being appointed full professor in 1922 [57,58].

In 1922, in the pages of the Berlin „Archiv für Dermatologie und Syphilis" Felix Lewandowsky and Wilhelm Lutz presented the first complete description of epidermodysplasia verruciformis (Lewandowsky'ego-Lutz dysplasia, called Lewandowsky-Lutz dysplasia, EV) [57].

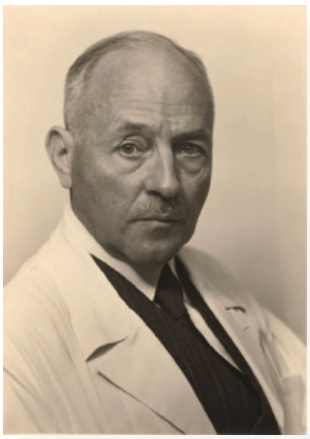

Figure 27. Wilhelm Lutz.

Acknowledgement

Dr. PRK Bhargav MS, MCh, FAIS - Department of Endocrine and Metabolic Surgery, Mamata Medical College and Superspeciality Hospital, Khammam - 507 002, Andhra Pradesh, India.
Seth J. Orlow MD PhD - Chairman, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY, USA.
Marcia E. Herman-Giddens, PA, DrPH - Adjunct Professor, Department of Maternal and Child Health University of North Carolina, School of Public Health, Chapel Hill, NC, USA.
Dr Frederick O. Akinbo - University of Benin, School of Basic Medical Sciences, Department of Medical Laboratory Science, Benin City, Nigeria.
Dr Le Le Win - Department of Medical Research, Lower Myanmar, Yangon, Myanmar.
Dr Kristine Lillebø - Department of Microbiology, Haukeland University Hospital, Bergen, Norway.
Dr. Dieudonne Sankara - Department of Control of Neglected Tropical Diseases, World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland.

From Figures:
Figure 4. Takao Toyokawa MD PhD - Division of General Internal Medicine and Infectious Diseases, Okinawa Prefectural Southern Medical Center and Children's Medical Center, Okinawa, Japan.
Figure 11. Dr. D. N. Guha Mazumder - Director DNGM Research Foundation and Prof. & Head, Dept. of Medicine & Gastroenterology, (Retd.), Institute of Post Graduate Medical Education & Research (IPGME&R), Kolkata. Address : Kolkata -700 053, India.

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2.2014 (11.April.2014)