Volume 11, Number 4 October 2020
p. 335- 437
Issue online since Thursday October 29, 2020

ISSN: 2081-9390
DOI: 10.7241/ourd

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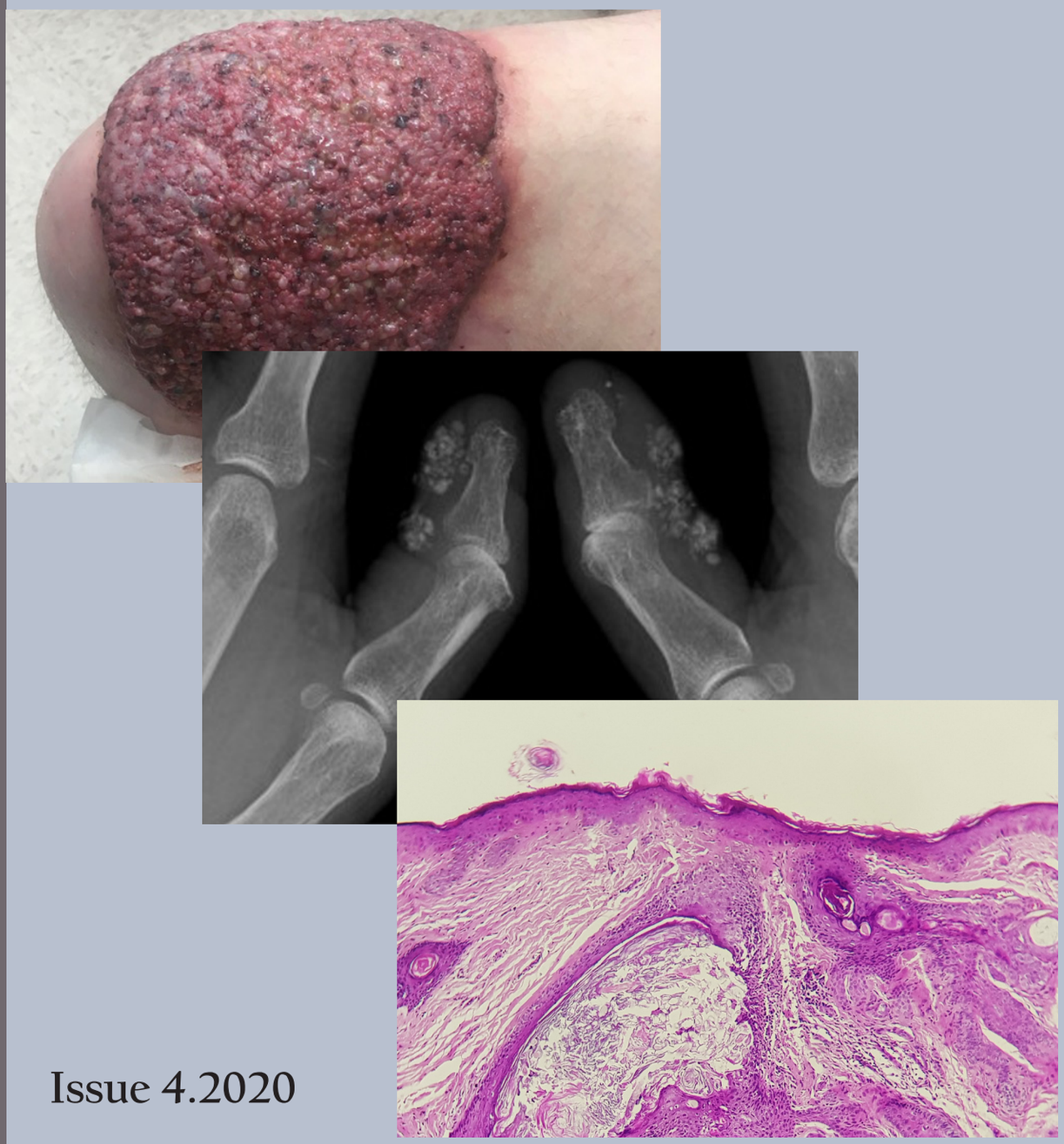

Issue 4.2020

Editorial Pages

e-ISSN: 2081-9390
DOI: 10.7241/ourd

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Original Article

An XPC and XPA genetic study on xeroderma pigmentosum patients in a Moroccan population

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ABSTRACT

Background: Xeroderma pigmentosum (XP) is a rare hereditary disease characterized by hypersensitivity to UV radiation due to alterations in the nucleotide excision repair (NER) pathway. The XPA and XPC gene mutations are most common in North African countries. Our goal was to perform a molecular study on patients with XP followed in our northeastern Moroccan region to determine their genetic profile. **Materials and methods:** We explored the nonsense (c.682C> T, p.Arg228X) mutation at the XPA gene and a two-base pair deletion (c.1643_1644delTG or p.Val548Ala fsX25) at the XPC gene level with the molecular PCR sequencing technique. Subsequently, the relationship between the mutations found and the symptomatic and progressive features was analyzed. **Results:** In the course of our work, the alterations of the two XPA and XPC genes responsible for xeroderma pigmentosum in a sample of 24 index cases belonging to 22 unrelated families were characterized, revealing 14 cases of XPC and 6 cases of XPA. The study on the correlation between genotypes and phenotypes in our study showed that neurological involvement was significant in XPA patients and that these XPA patients develop malignant skin tumors earlier than XPC patients. **Conclusions:** In our XP population, the alterations of the XPA and XPC genes responsible for xeroderma pigmentosum in a sample of 24 index cases belonging to 22 unrelated families were characterized, revealing 14 cases of XPC and 6 cases of XPA. Neurological involvement was significant in XPA patients and these XPA patients were found to develop malignant skin tumors earlier than XPC patients.

Key words: Xeroderma pigmentosum; XPA gene; XPC gene; Morocco

INTRODUCTION

Xeroderma pigmentosum (XP) is a rare genetic disease with autosomal recessive inheritance first described in 1870 by Hungarian dermatologist Moritz Kaposi, who coined the term *xeroderma*, Latin for "dry or parched skin." The term *pigmentosum* underlines the pigmentary disturbances in patients suffering from this disease [1,2]. Its autosomal recessive transmission explains its relative frequency in countries where consanguinity is high and the size of families is considerable, for instance, in Morocco [3]. In 1968, Cleaver demonstrated a deficiency of UV repair of deoxyribonucleic acid (DNA) in XP cells [4], which produces hypersensitivity to ultraviolet rays and, consequently, a high risk of developing signs of "Heloderma" and poikiloderma associated with xerosis and skin fragility, sometimes evolving to infected and trailing ulcerations, as well as cutaneous malignant tumors and oculars at an early age [5]. Indeed, it has been shown that the clinical heterogeneity of this disease is linked to the existence of alteration in the genes belonging to the various classical complementation groups—XP-A to XP-G—which are distinguished by certain symptomatic and evolutionary peculiarities. The product of each of these genes plays a specific role in the nucleotide excision resynthesis (NER) DNA repair pathway. The human XPA and XPC gene mutations are most common in Maghreb countries [3,6,7].

How to cite this article: Bay Bay H, Rasso A, Aqil N, Bouguenouch L, Ouldim K, Elloudi S, Douhi Z, Mernissi FZ. An XPC and XPA genetic study on xeroderma pigmentosum patients in a Moroccan population. Our Dermatol Online. 2020;11(4):335-339.

Submission: 16.02.2020; **Acceptance:** 28.04.2020

DOI: 10.7241/ourd.20204.1

The Goal of the Study

In this work, we performed a molecular study of the XPA and XPC genes on XP patients followed in our region to determine their genetic profile. Subsequently, the relationship between the mutations found and the symptomatic and progressive features was analyzed.

MATERIALS AND METHODS

This was a cross-sectional, prospective, descriptive, and analytical study conducted from June 2017 through January 2018 at the Dermatology Department of Hassan II University Hospital in Fez, which drains patients from the northeastern region of Morocco.

All patients followed for xeroderma pigmentosum (XP) were included in the collaboration with the Genetics Department. We described the epidemiological and clinical features of these patients, then explored the two most common mutations in North African countries with the molecular PCR sequencing technique. We, first, explored the XPC gene mutation at exon 9 (c.1643_1644delTG or p.Val548Ala fsX25) in all patients, followed by the XPA gene at exon 6 (c. 682C> T, p.Arg228X) for those in whom the first XPC mutation was negative.

These XP patients were examined in a day hospital. Sampling was performed in two 5-mL EDTA (ethylenediaminetetraacetic acid) tubes, each of blood, which, then, were sent to the Genetics Department for DNA extraction and PCR sequencing. The tubes were stored at -20°C for later use. The results of molecular sequencing were obtained after two weeks on average.

After obtaining the sequence of exon 9 of the XPC gene and that of exon 6 of the XPA gene, a bioinformatic analysis of the sequences was performed—in particular, identification of the similarities between the query sequence and the sequence from the database by the Blast software. Subsequently, the relationship between the mutations found and the symptomatic and progressive features of the patients was analyzed.

Ethics Statement

Ethics approval was obtained from the ethics committees of the University Hospital Center Hassan II in Fez, Morocco. All patients, or their parents, were informed of the conditions related to the study and gave their informed consent for the study and for publication.

RESULTS

We collected a sample of 24 patients from 22 unrelated families, two of whom had two children with AIDS. The average age was 15 years with extremes ranging from 2 to 63 years. The majority of patients (n = 20) were under 25 years of age. The patients studied had a sex ratio (M/F) of 0.6, with 9 (37.5%) males and 15 females (62.5%). The patients came from different parts of Morocco, mainly from the northwest, with a predominance of the Fez region (n = 14). The majority of the patients were of rural origin (n = 16). 62.5% (n = 15) of the patients had first-degree consanguinity, 16.7% (n = 4) had second-degree consanguinity, while 20.8% (n = 5) had no consanguinity.

All our patients had a dark phototype, with 79.2% (n = 19) phototype IV, 16.7% (n = 4) phototype III, and 4.2% (n = 1) phototype V. The mean age of onset of early symptoms of the disease was 42 months, with extremes ranging from one month up to 20 years. Photophobia and cutaneous photosensitivity were consistent signs in all our XP patients. Dermatological examinations found a poikiloderma appearance in all patients. The majority of the patients had benign skin tumors (n = 19); these tumors were made of nevi (Fig. 1), warts, seborrheic keratoses, pyogenic granulomas, keratoacanthomas, and ruby angiomas. The patients had precancerous pigmented and unpigmented actinic keratose lesions (Fig. 2), as well as various malignant skin tumors, such as basal cell carcinomas (BCC), squamous cell carcinomas (EC) (Fig. 3), and melanomas. No cases of sarcoma or lymphoma were noted. Ocular involvement of allergic or bacterial conjunctivitis was noted in 8 patients (33%).

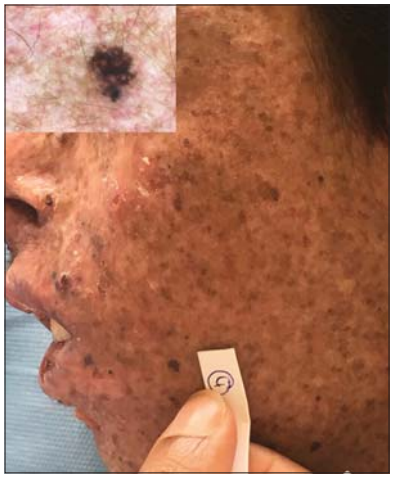

Figure 1: Junctional naevus in a patient with XP.

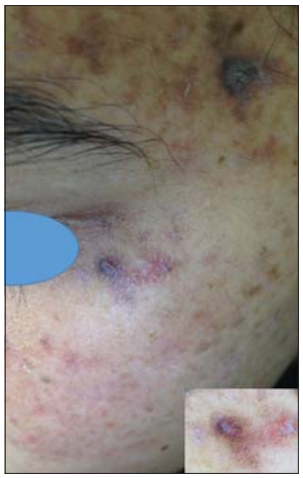

Figure 2: Actinic keratosis in a patient with XP.

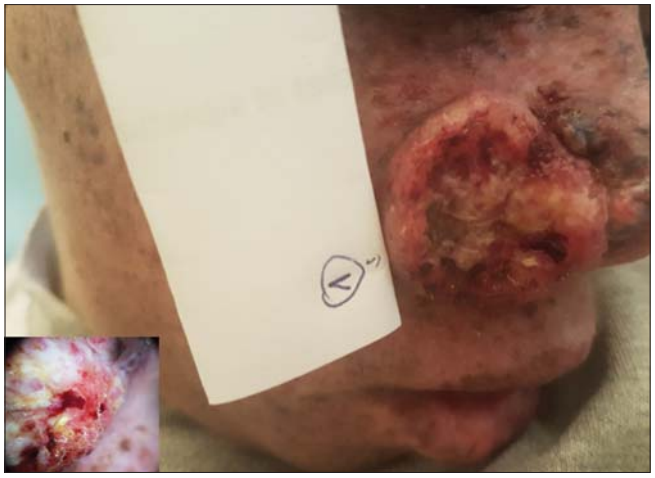

Figure 3: Squamous cell carcinoma in a patient with XP.

Three patients developed ocular tumors of squamous cell carcinoma, responsible, in two of them, for bilateral blindness and, in one patient, for unilateral enucleation. Two patients had failure to thrive; one had rickets; and one had high blood pressure. A molecular study of the XPC gene revealed that the mutation was found in 14 patients with common deletion of the T and G nucleotides affecting exon 9 of the XPC gene (c.1643_1644delTG or p.Val548Ala fsX25), 12 in the homozygous state and 2 in the heterozygous state.

A molecular study on XP brothers from two families revealed the presence of deletion of exon 9 of the XPC gene.

As for the analysis of the XPA gene performed on the 10 patients in whom the XPC gene analysis did not reveal pathogenic abnormalities, six patients had a nonsense mutation (c.682C> T, p.Arg228X) serving at the level of the XPA gene and 4 patients had no abnormality (c.682C> T, p.Arg228X). The results indicated that neurological involvement was significant in XPA patients. (P = 0.023). The same genetic group showed earlier malignant skin tumors (of less than 6 years) with the occurrence of acute reaction after exposure to the sun, when compared to patients with XPC (P = 0.000).

DISCUSSION

Xeroderma pigmentosum (XP) is a rare autosomal recessive genetic disorder that affects the Moroccan population with a relatively high incidence rate when compared with Europe. We were able to characterize 24 XP patients—the largest group analyzed in Morocco to date. The sex ratio of our patients was 0.6, with a predominance of women; this is consistent with the results of a 2010 study by Soufir et al. [3]. Inbreeding was found in 79.2% of cases. The average age of onset was 42 months in the Soufir study, as in ours [3]. The diagnosis of the disease was reached later, at an average age of 9.5 years.

Clinical manifestations were photophobia, photosensitivity, pruritus, poikiloderma, and xerosis in all patients, in agreement with the results reported in the literature [3,4]. These XP patients had benign cutaneous tumors: nevi, warts, seborrheic keratoses, botriomyomas, keratoacanthomas, and ruby angiomas, with variable frequency. Malignant skin tumors appeared in 79% of the XP patients, with CBC in 70.8% of cases, EC in 37.5% of cases, and melanoma in 12.5% of cases. This high frequency of cutaneous tumors might be explained by the delay of the diagnosis of the disease and, therefore, the delay in initiating photoprotective measures. Soufir et al., in 2010, and Senhaji et al., in 2012, observed the same results [3,6]. In our study, the average age of development of the first skin cancer was 9.3 years; all patients who had developed skin cancer developed at least one cancer other than a melanoma (CBC and/or CE) in areas exposed to the sun. In 2000, Chavanne et al. reported that the average age of development of the first skin cancer was 11.7 years in 7 XPC patients from southern Europe [8]. In 2012, Schafer et al. reported a mean premature age of 7.1 years in 16 XPC patients from Germany [9]. The low frequency of neurological involvement in our series was similar to that reported in the Soufir study [3].

In the literature, ocular involvement in XP is variable and depends on the complementation group; this

includes photophobia, conjunctivitis, keratitis, entropion, ectropion, and ocular tumors.

The XPC and XPA groups have a higher risk of developing this type of damage than the XPE group. In our study, the results matched those found in the literature without any difference in the severity of ocular involvement, whatever the genetic group [10]. PCR sequencing revealed that the nonsense mutation (c.682C> T, p.Arg228X) at the XPA gene level was present in 25% (n = 6) of our XP patients. Common deletion of the nucleotides T and G affecting exon 9 of the XPC gene (c.1643_1644delTG or p.Val548Ala fsX25) was found in 58% (n = 14) of the patients, 12 in the homozygous state and 2 in the heterozygous state. In these two heterozygous patients, another mutation ought to be sought to consider compound heterozygosity.

A molecular study by Soufir et al. of 66 unrelated families in the Maghreb region showed that 85% of the patients had XPC gene mutations; among them, 87% shared the founding mutation (approx. 1643 1644delTG). 12% of the XP patients had mutations in the XPA gene, with a mutation frequency (c.682C> T) of approximately 87.5% [3]. In an Algerian series, the XPA mutation (c.682C> T) was present in 2 of 19 patients (10.5%) and the XPC mutation (1643 1644delTG) was present in 17 of 19 patients (89.5%) in the homozygous state [11]. In a study conducted in Casablanca, the XPC mutation (c 1643 1644delTG) was estimated to account for more than 76% of cases of XP in Moroccan patients [12]. Another study conducted at the same institution involving XP patients with neurological involvement revealed the presence of the nonsense mutation (c.682C> T) in the homozygous state at the level of the XPA gene in 78 patients [3].

The frequency of XPA mutation was previously described in North Africa, but it is more common in Japan [3]. The common homozygous XPC mutation (c.1643_1644delTG) has been described in North Africa, mainly in patients from Tunisia, and three patients from Italy, Egypt, and Africa, respectively [7,8]. Two compound heterozygous patients (XP132BE and XP30BE) were from the United States and Honduras. In our study, there was no significant difference between XPA and XPC patients in the age of onset of the disease. In contrast to the literature describing an earlier age of onset of XPA [10,13].

The prevalence of malignant skin tumors is higher in XPC patients than in XPA patients, which might be explained by the early onset of XPA, leading to early photoprotection, thus preventing the occurrence of skin tumors [14,15]. This difference was absent in our study, which may have been due to the delay in the consultation of parents because of the lack of knowledge on this pathology.

CONCLUSION

In our work, the alterations of the XPA and XPC genes responsible for xeroderma pigmentosum in a sample of 24 index cases belonging to 22 unrelated families were characterized, revealing 14 cases of XPC and 6 cases of XPA. Our study on the correlation between genotypes and phenotypes revealed that neurological involvement was significant in XPA patients and that these XPA patients developed malignant skin tumors earlier than XPC patients, which requires earlier implementation of photoprotective strategies to prevent such damage.

Acknowledgments

We are indebted to all patients who participated in this study and gave their consent. We thank all volunteer investigators and the medical staff of the Department of Dermatology and Genetics.

Statement of Human and Animal Rights

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

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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

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Original Article

MYZAP a newly protein expressed in the skin is autoantigen for patients with endemic pemphigus foliaceus in El Bagre, Colombia

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ABSTRACT

Background: We detected autoantibodies against a new complex cell junction, the area composita of the heart [an intricate cell junction that includes the protein Myocardial Zonula Adherens Protein (MYZAP, AKA MYOZAP)] in patients affected by a new variant of endemic pemphigus foliaceus in El Bagre, Colombia, South America (El Bagre-EPF). **Methods:** We aimed to study if MYZAP was expressed in the skin, and, if so, its relationship with El Bagre-EPF autoantigens. We utilized a case-control study, testing 43 patients and 43 controls from the endemic area matched by demographics, age, gender, living place, and work activities using multiple immunological methods. **Results:** MYZAP is expressed in the human skin (epidermis and dermis), as well in the skin appendages, their neurovascular supply structures, and neural receptors (in all of these sites, mostly in the cells junctions). MYZAP present in the cell membranes, and is also located in intracytoplasmic and nuclear regions. All El Bagre-EPF patient autoantibodies perfectly colocalized with MYZAP (a commercial antibody from Progen Biotechnik, Heidelberg, Germany) in the skin ($p < 0.01$). **Conclusion:** We describe for the first time in the medical literature the expression of a new protein MYZAP in several structures in the skin, colocalizing with El Bagre-EPF autoantigens and suggesting that further studies could focus on the putative roles of this molecule in the skin.

Key words: Endemic pemphigus foliaceus in El Bagre, MYZAP, skin, cells junctions

Abbreviations: Endemic pemphigus foliaceus (EPF), endemic pemphigus foliaceus in El Bagre (El Bagre-EPF), fogo selvagem (FS), hematoxylin and eosin (H&E), immunofluorescence (DIF), immunohistochemistry (IHC), confocal microscopy (CFM), basement membrane zone (BMZ), intercellular stain between keratinocytes (ICS), The intercalated disc (ID), adherens junctions (AJ), desmoglein 1 (Dsg1), Myocardial Zonula Adherens Protein (MYZAP), (glutamate ionotropic receptor N-methyl-D-aspartate receptor type subunits (GRINL1A), adherens junctions (AJs), the intercalated disk (ID), serum response factor (SRF), The ionotropic glutamate N-methyl D-aspartate (NMDA), fluorescein isothiocyanate (FITC).

INTRODUCTION

Endemic pemphigus foliaceus (EPF) provides a superb model to study autoimmune diseases, given its geographic and family clustering, immune response, patient genetics and putative triggering factor(s) [1-9]. EPF is seen in South America, Central America, as well as in Tunisia, Africa [6] and it has a genetic component, as well as putative triggering factors [1-10]. El Bagre-EPF is an autoimmune disease that has several clinical forms including a form frustre (localized to the skin, mostly of the face and upper chest), and a spectrum

How to cite this article: Abreu Velez AM, Upegui-Zapata YA, Valencia-Yepes CA, Upegui-Quiceno E, Yi H, Howard MS. MYZAP a newly protein expressed in the skin is autoantigen for patients with endemic pemphigus foliaceus in El Bagre, Colombia. Our Dermatol Online. 2020;11(4):340-345.

Submission: 02.07.2020; **Acceptance:** 07.07.2020

DOI: 10.7241/ourd.20204.2

of more extensive involvement including presentations resembling Senear-Usher syndrome and a systemic form affecting multiple organs [11-15].

Our recent studies indicated colocalization of the El Bagre-EPF autoantibodies with the Myocardial Zonula Adherens Protein (MYZAP) (AKA MYOZAP), in the area composita of the heart, in its conductive system, and in vessels [11]. Given the fact that El Bagre-EPF patients have autoantibodies to MYZAP in the cardiovascular system, we aimed to search for the expression of MYZAP in the skin and, if present, for any relationship with El Bagre-EPF autoantibodies.

MATERIALS AND METHODS

Patients

A human quality assurance review board approved the studies at the Hospital Nuestra Señora del Carmen in El Bagre. All participants signed informed consent forms. We tested 43 patients with El Bagre-EPF and 43 healthy controls from the endemic area, matched by age, gender, demographics (including history of malaria, gastrointestinal infections or sexually transmitted diseases, dengue, tuberculosis; cohabitation with domestic animals; exposure to wild animals, living and working activities, distance to rivers; tobacco, marijuana or liquor habits; exposure to agricultural and jungle vegetation; exposure to rodents, mosquitoes, and snakes and other jungle animals during rest or work hours; basic diet, and employment activities). The patients were evaluated clinically, and biopsy samples were assessed by hematoxylin and eosin (H&E) staining, by direct immunofluorescence (DIF), immunohistochemistry (IHC), confocal microscopy (CFM), ELISA, immunoblotting (IB) and immunoprecipitation (IP), and indirect inmunoelectron microscopy (IEM) as previously described [3-5,8-10]. For DIF, biopsies were taken from perilesional skin on the chest; control biopsies were also obtained from the chest. For the IIF, the skin samples were obtained from cadaver donors with a proper Institutional Review board permit.

Patients were included only after these tests were performed and if they fulfilled the following full diagnostic criteria for El Bagre-EPF: (i) the patient presented the clinical and epidemiological features described for this disease; (ii) they lived in the endemic area; (iii) their serum displayed intercellular staining between epidermal keratinocytes by DIF and to the basement membrane zone of the skin, using fluorescein isothiocyanate (FITC)-conjugated monoclonal antibodies to human total IgG or to IgG4, as previously described; [3-5] (iv) their serum was positive by IB for reactivity against desmoglein 1 (Dsg1) and plakin molecules, as previously described [4,5], (v) their serum immunoprecipitated a Concanavalin A affinity-purified antigen bovine tryptic 45 kDa fragment of desmoglein 1 (Dsg1) [8]; and (vi) the patient serum yielded a positive result using an ELISA when screening for autoantibodies to pemphigus foliaceus (PF) antigens [9].

DIF and IIF Studies

Our studies were performed as previously described [3-5,7-10]. The slides were counterstained with 4,6-diamidino-2-phenylindole (Pierce, Rockford, IL, USA). We also used antibodies to a mouse monoclonal antibody for myocardium-enriched zonula occludens-1-associated protein (Myozap; Progen Biotechnik, Heidelberg, Germany, Cat no. 651169). For the secondary antibody to MYZAP, we utilized Texas red-conjugated goat anti-mouse IgG (Thermo Fisher Scientific, Waltham, MA). All samples were consistently run with positive and negative controls. We classified our findings as negative (-), weakly positive (+/-), positive (++) and strongly positive (+++) [3-5].

Confocal Microscopy (CFM)

Colocalization of the patient's autoantibodies with commercial antibodies was confirmed using CFM. Our CFM studies were performed as previously described [11-15]. In brief, we utilized standard 20X and 40X objective lenses; each photoframe included an area of approximately 440 x 330 μm. Images were obtained using EZ-1 image analysis software (Nikon, Tokyo, Japan). For colocalization experiments with serum autoantibodies, we used the previously described antibodies to MYZAP [16].

Indirect immunoelectron microscopy (IEM)

Our technique was performed as previously described [11]. Postembedding immunogold labeling was performed on samples, and human skin was used as an antigen. The tissue was fixed in 4% glutaraldehyde with 0.2% paraformaldehyde, and embedded in Lowicryl® resin. Sections of 70 nm thickness were cut and blocked; the grids were then washed, and the primary antibody was incubated, washed, and a secondary antibody solution, specifically 10 nm Gold-conjugated protein A PBS-BSAC

(Aurion, EMS™) was applied [11-15]. The samples were then double-stained with uranyl acetate and lead citrate, and observed under a Hitachi H7500 transmission electron microscope. Immunogold particle images displaying any pattern of positivity were then converted to TIF format as previously described [11-15].

Statistical Analysis

We used Fisher's exact test to compare two nominal variables (e.g. positive and negative) of the antibody response. We also compared the differences when evaluating: (i) positivity of the El Bagre EPF autoantibodies between patient cases and controls; and (ii) patient antibody results versus the commercial antibodies to MYZAP. A $p < 0.01$ with 98% confidence or more was considered statistically significant. We used GraphPad QuickCalcs software from GraphPad Software (La Jolla, CA, USA).

RESULTS

DIF, IIF, CFM and IEM studies showed that MYZAP is expressed in human skin epidermis, dermis, and the basement membrane zone (BMZ); this was noted in all the El Bagre EPF patient cases and all the controls, indicating that MYZAP is widely expressed in the skin and is a constitutive protein ($p< 0.01$). Using DIF and CFM, the MYZAP commercial antibody perfectly colocalized with the autoantibodies from patients affected by El Bagre-EPF in the skin in 98% of the cases ($p< 0.01$) (Table 1). There was no positive colocalization with MYZAP in any of the matched control individuals.

In El Bagre-EPF patients autoantibodies and their colocalization with MYZAP were clearly appreciated using DIF and CFM, and both techniques revealed that cell junctions were positive in 98% of the cases ($p< 0.01$). The cells junctions were positive in the epidermis, and the BMZ as well as in all skin appendices and their neurovascular supplies. At higher magnifications, the MYZAP locations were observed at the plasma membranes (including both cell and nuclear). MYZAP was also in observed intracytoplasmic and intra-nuclear locations in the epidermal cells in 98% of the cases ($p< 0.01$). In the dermis, the mesenchymal endothelial cell junctions were also positive for MYZAP, colocalizing with the El Bagre-EPF autoantibodies ($p < 0.01$). Of interest, the neurovascular bundles in both the upper and lower dermis were strongly positive for MYZAP as well as all free and encapsulated skin neural receptors; these sites also demonstrated colocalization with El Bagre-EPF autoantibodies (Figs. 1 and 2).

Using the indirect immunoelectron microscopy, MYZAP was mostly located at the cell junctions of the epidermis (Fig. 1).

Table 1 shows detailed results of DIF on chest skin from El Bagre-EPF patients. As shown, in the autoimmune response was polyclonal.

DISCUSSION

In this study, we demonstrated for the first time the presence of the protein MYZAP in the skin (and confirmed MYZAP as a new El Bagre-EPF autoantigen). MYZAP was originally titled MYOZAP (Myocardium-enriched Zo-1-interacting Protein), and designated as a novel intercalated disc protein (ID) [16]. In this study we demonstrate that MYZAP is expressed in the skin at multiple sites, mostly at cell junctions.

MYZAP has been shown to be strongly expressed in human heart, lung and skeletal muscle; in cardiac

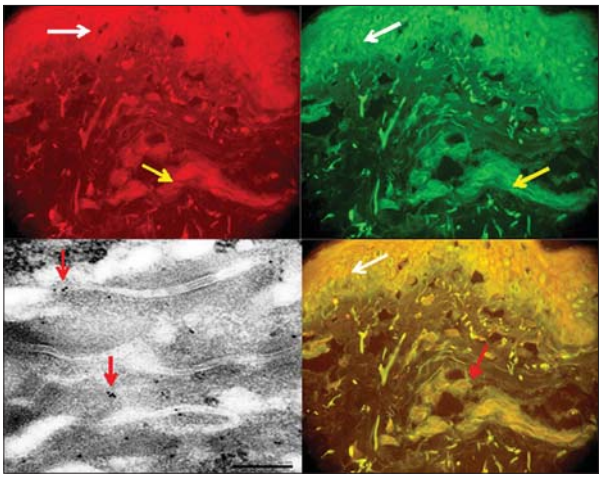

Figure 1: Confocal microscopy data is presented in the upper left, upper right and lower right images). Upper left, red being expressed in the entire skin including the epidermis (white arrow) (with strongest expression in the corneal and granulosum layers; 200X). MYZAP is also expressed in the basement membrane zone, and in the dermis including both the superficial and deep neurovascular plexuses (yellow arrow). The upper right panel shows the positivity of the El Bagre-EPF autoantibodies using anti-IgG FITC conjugated showing in green the stain in the epidermis (white arrow), and in the vessels (yellow arrow) (200X). The lower right figure shows a confocal image of both MYZAP and El Bagre-EPF autoantibodies perfectly colocalizing in the epidermis (white arrow), as well as in the dermis (red arrow) (200X). The lower left panel using IEM data demonstrating positive staining for MYZAP in skin epidermal cell junctions IEM photographs of patient skin, showing MIZAP antibodies labelled with 10 nm Gold-conjugated protein A antibodies (tiny black dots). The antibodies are located in the epidermal cells junctions (red arrows), (100kV).

Table 1: DIF data documenting expression and positivity of El Bagre-EPF patient autoantibodies in chest skin, and respective colocalizations with MYZAP

Autoantibodies, Marker	Number of positive cases in the skin and its appendices	Positive skin structures, including cell junctions	Strength of staining	Colocalization with MYZAP
IgG	42/43	Intracytoplasmic and pericytoplasmic staining on keratinocyte cell junctions as well as BMZ cell junctions (uneven pattern). Superficial and deep dermal neurovascular bundles. Dermal mesenchymal-endothelial cell junctions. All the neurovascular supplies of all skin appendices, and neural receptors. Eccrine and sebaceous glands including their ducts/isthmus, and their cell junctions. Arrector pili muscles.	(+++)	100%
Fibrinogen	42/43	Similar pattern to IgG	(+++)	100%
IgM	40/43	Similar pattern to IgG	(+++)	100%
Albumin	40/43	Similar pattern to IgG	(+++)	100%
C3c	38/43	Similar pattern to IgG	(+++)	100%
C1q	32/43	Similar pattern to IgG	(++)	100%
IgA	3/43	Positive to some cell junctions below the BMZ	(+)	0%
IgD	29/43	Similar pattern to IgG	(++)	100%
IgE	10/43	Positivity on some individual cells migrating from the upper dermal vessels	(+)	0%
Lambda	42/43	Similar pattern to IgG	(+++)	100%
Kappa	42/43	Similar pattern to IgG	(+++)	100%

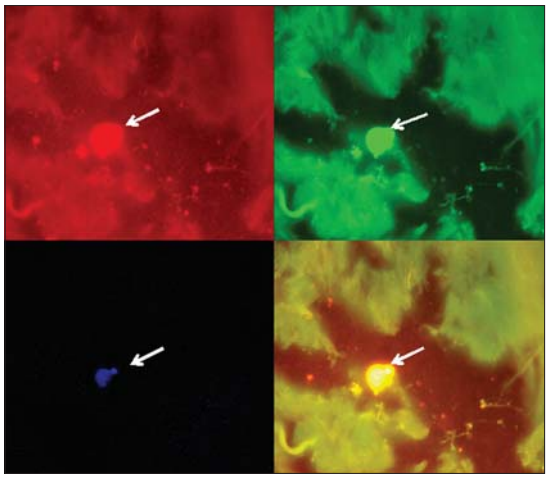

Figure 2: A confocal image shows a four panel figures. In the upper left panel we observe the positivity of a nucleated neural dermal receptor stained with DAPI (white arrow) (400X). In the upper right figure we observed a positive stain against a skin dermal receptor showing the positivity of the El Bagre-EPF autoantibodies using anti-IgG FITC conjugated in green the stain (white arrow), (400X). In the left lower panel we show a positive stain using the Myzap Texas red conjugated antibody against a dermal neural receptor (white arrow) (400X). In the lower right panel we show colocalization of DAPI, the patient's autoantibodies and MYZAP being positive to the dermal neural receptor (white arrow), (400X).

tissue, it localizes to the ID and directly binds to desmoplakin (another El Bagre-EPF autoantigen). It has been shown that in the heart that MYZAP bind to myosin phosphatase-RhoA interacting protein, a negative regulator of Rho activity with additional intracellular signal transduction functions [17].

It is important to note that the skin and the heart share numerous molecules; these are often altered in cardiocutaneous syndromes [18]. Of interest, many molecules expressed in the heart are also El Bagre-EPF antigens including desmoplakins 1 and 2, p0071 and ARVCF [13-15].

In vivo, knockout studies of the MYZAP protein in zebrafish lead to contractile dysfunction and cardiomyopathy. MYZAP is a 54-kD protein, not a member of any of the recognized cytoskeletal and junctional protein multigene families; it is a component of the plaques of the composite junctions in the ID connecting the cardiomyocytes of mammalian hearts [17]. MYZAP has one conserved domain; specifically, metal ion transporter CorA-like (MIT CorA-like), a divalent cation transporter in superfamily cl00459 at the genetic location 267 → 358 (See supplemental Table 1) [18,19] .

MYZAP has been also identified as a novel major component of adhering junctions in endothelia of the blood and the lymphatic vascular systems [20]. El Bagre-EPF autoantibodies also recognize these structures. More specifically, MYZAP is a primary constituent of the cytoplasmic plaques in the adherens junctions (AJ); it links endothelial cells of the mammalian blood and lymph vascular systems, including the desmoplakin-containing complexus adhaerentes of the virgultar cells of the lymph node sinus [17]. We previously demonstrated that in the heart (including its conducting system), neurovascular system and the optic nerve envelope, MYZAP colocalizes with El Bagre-EPF autoantibodies [13,14]. We also previously documented that MYZAP is expressed in the kidney (also colocalizing with El Bagre-EPF autoantibodies) [15].

Other monikers for MYZAP include glutamate ionotropic receptor N-methyl-D-aspartate receptor type subunits (GRINL1A), Upstream Protein, Gup, Myocardium-Enriched ZO1-Associated Protein, and Myocardial Intercalated Disc Protein [21]. MYZAP in the heart directly binds to and/or colocalizes with other key ID components including β-catenin, N-cadherin, plakophilin-2, desmoplakin and zonula occludens, and also binds to Dysbindin [17].

The MYZAP gene has been reported to be part of the ionotropic glutamate N-methyl D-aspartate receptor [21]. This is a glutamate receptor and ion channel (via gated ions) protein found in nerve cells; it is activated when glutamate and glycine bind to it. When activated, it allows positively charged ions to flow through the cell membrane [21].

Recently, genome-wide association studies of atrial fibrillation using non-coding, low-frequency coding and splice variant MYZAP genes were associated with disease risk through unknown mechanisms [22]. Based on this study and our previous studies showing that MYZAP is part of the heart conducting system, and given that El Bagre-EPF patients suffer cardiac rhythmic problems, MYZAP is likely of great importance to normal heart rhythm. Normal cardiac rhythm is modulated via the neural system and electrical impulses; we wonder if this molecule and its cell junction partners may play a similar synaptic role in the skin and other organs. Further studies could focus on complex putative roles beyond the cell junctions, as previously documented for selected retinal gap junctions [23].

We also suggest that this new El Bagre-EPF autoantigen may provide a conceptual framework to understand the breakdown of self-tolerance, if indeed such modifications are present in this autoimmune disease.

In conclusion, we describe for the first time the presence of MYZAP in the skin with multiple localizations, and further colocalizing with El Bagre-EPF patient autoantibodies. Further studies are needed to study potential utility in monitoring disease development and treatment, via roles in etiology and pathophysiology. Based on the location of this protein in our study, the function of MYZAP in the skin seems to be related to cell junctions. However, as with MYZAP in the heart, the functions of the molecule in the skin need to be further elucidated.

ACKNOWLEDGEMENT

To the patients and El Bagre community.

Statement of Ethics

Our patient gave informed consent. Although Institutional Review Board (IRB) approval for a case report is not needed, the US Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule restricts how protected health information (individually identifiable health information) on any patient may be made. Compliance with patient privacy, institutional rules, and federal regulations were followed. No photos or illustrations that contain identifiable features are included in the case report, and the case(s) described in the report are not so unique or unusual that it might be possible for others to identify the patients.

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

Our Dermatology Online

Original Article

Evaluating the extent of agreement between the EARP (Early Arthritis for Psoriatic Patients) and PEST (Psoriasis Epidemiology Screening Tool) questionnaires in screening for psoriatic arthropathy in patients with psoriasis in a tertiary-care dermatology outpatient department

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ABSTRACT

Background: The prevalence of psoriatic arthropathy (PsA) among psoriatic patients ranges from 5% to 42%, with some cases of rapidly progressive disabling arthropathy. If detected early, PsA can be considerably improved by timely therapeutic intervention. Various screening tools have been developed to screen psoriatic patients for arthritis, but there is a paucity of literature on the agreement between the two. **Aim:** Evaluating the extent of agreement between the EARP (Early Arthritis for Psoriatic Patients) and PEST (Psoriasis Epidemiology Screening Tool) questionnaires in screening psoriatic patients for psoriatic arthropathy in a tertiary-care dermatology outpatient department (OPD). **Materials and Methods:** 100 prospective psoriatic patients with no prior diagnosis of PsA reporting to our dermatology OPD were administered EARP and PEST questionnaires. The extent of agreement between the two questionnaires was calculated by Cohen's kappa coefficient. Those positive for PsA by one or both of the questionnaires were evaluated using the CASPAR criteria. **Results:** 43 patients were positive for PsA by EARP, whereas 13 patients were positive by PEST; and all of these 13 patients were EARP positive as well. All the patients who were either EARP or PEST positive continued to meet the CASPAR criteria, showing a positive predictive value of 100% for both questionnaires. The extent of agreement between EARP and PEST was found to be low (0.312). **Conclusion:** EARP is a better screening tool for PsA than PEST, as the latter failed to screen positively a significant number of psoriatic patients for psoriatic arthropathy. The extent of agreement between the two questionnaires can, thus, be considered poor.

Key words: Psoriasis; Psoriatic arthropathy; EARP; PEST; CASPAR

INTRODUCTION

Psoriasis is a common chronic relapsing inflammatory disease with dermatological as well as systemic manifestations. The estimated worldwide prevalence of psoriasis ranges from 0.51% to 11.43%, while the prevalence in India varies from 0.44% to 2.8% [1,2]. Psoriasis is currently considered a multisystem disorder

How to cite this article: Singh S, Sood A, Sinha P, Joshi R, Patrikar S, Das P. Evaluating the extent of agreement between the EARP (Early Arthritis for Psoriatic Patients) and PEST (Psoriasis Epidemiology Screening Tool) questionnaires in screening for psoriatic arthropathy in patients with psoriasis in a tertiary-care dermatology outpatient department. Our Dermatol Online. 2020;11(4):346-350.

Submission: 05.01.2020; **Acceptance:** 06.03.2020

DOI: 10.7241/ourd.20204.3

with chronic inflammation linked with psoriatic arthropathy, obesity, hypertension, dyslipidemia, and insulin resistance [3]. Psoriatic arthropathy can be acutely disabling, leading to a poor quality of life (QoL).

There is now enough evidence to believe that early diagnosis of PsA may prevent disabling arthropathy [4]. Since, in most patients with psoriasis, skin lesions precede those of joint involvement, dermatologists are at an advantageous position to screen patients for PsA [5]. In the past few years, numerous screening tools for PsA detection have been devised: Toronto Psoriatic Arthritis Screening Questionnaire-II (TOPAS-II), Psoriatic Arthritis Screening and Evaluation (PASE), Psoriasis Epidemiology Screening Test (PEST), and Early Arthritis for Psoriasis Patients (EARP) [6]. Among the above four, EARP and PEST are simple, self-administered, and easy-to-use questionnaires that can be used in busy dermatology OPDs to screen patients for PsA (Tables 1 and 2). We tested the extent of agreement between these two questionnaires in a tertiary-care dermatology center in western India and their positive predictive values.

MATERIALS AND METHODS

Study Design

The following cross-sectional study was conducted in one of the tertiary care dermatology OPDs in western India from September 2018 to March 2019. Ethical approval was obtained from an institutional ethical committee. 100 patients were selected from the dermatology OPD over a period of 6 months according to the inclusion and exclusion criteria of the study.

Table 1: EARP questionnaire (scores of 3 or above are positive).

Question	Yes	No
Do your joints hurt?	1	0
Have you taken anti-inflammatory more than twice a week for joint pain in the last 03 months?	1	0
Do you wake up at night because of low back pain?	1	0
Do you feel stiffness in your hands for more than 30 minutes in the morning?	1	0
Do your wrists and fingers hurt?	1	0
Do your wrists and fingers swell?	1	0
Does one finger hurt and swell for more than 03 days?	1	0
Does your Achilles tendon swell?	1	0
Do your feet or ankles hurt?	1	0
Do your elbow or hips hurt?	1	0

Table 2: PEST questionnaire (scores of 3 or above are positive).

Question	Yes	No
Have you ever had a swollen joint (or joints)?	1	0
Has a doctor ever told you that you have arthritis?	1	0
Do your finger nails or toe nails have holes or pits?	1	0
Have you had pain in your heel?	1	0
Have you had a finger or toe that was completely swollen and painful for no apparent reason?	1	0

Inclusion Criteria

All diagnosed cases of psoriasis visiting the dermatology OPD were included in the study.

Exclusion Criteria

All previously diagnosed cases of psoriatic arthropathy, rheumatoid arthritis, gout, and other rheumatic diseases were excluded from the study.

Methodology

The participants were provided with an informed assent sheet highlighting the purpose, methodology, risks, benefits, and confidentiality of the study as well as the right to refuse participation. All patients willing to participate and having met the inclusion and exclusion criteria and filled a written informed consent were enrolled in the study. The enrolled patients were asked to fill EARP and PEST questionnaires along with a predesigned basic disease data sheet. Parents were asked to consent and fill the questionnaires on behalf of patients younger than 18. Patients scoring positive in either the EARP or PEST questionnaire or both underwent radiography, and were tested for RA factor in order to meet the CASPAR criterion of psoriatic arthropathy (Table 3).

Statistical Analysis

Data analysis was performed using the software SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp. The extent of agreement between the results of the two questionnaires was calculated by Cohen's kappa coefficient.

Ethics Statement

Ethical approval was obtained from an institutional ethical committee.

RESULTS

Of the 100 patients enrolled in our study, 76 were males and 24 were females. The mean age was 47 years,

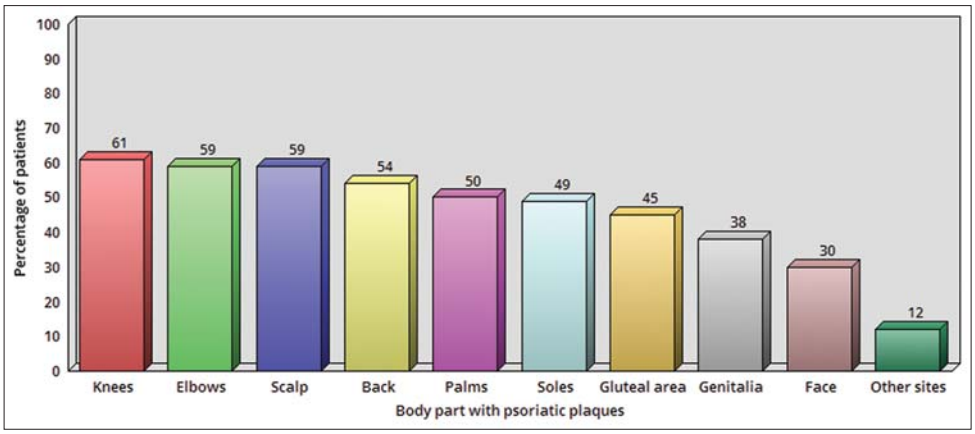

Figure 1: Distribution of patients according to the part of the body affected by psoriatic lesions.

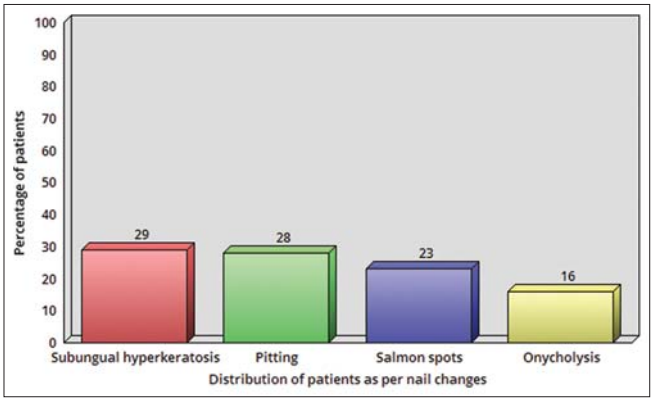

Figure 2: Distribution of patients according to nail changes.

ranging between 9 and 79 years. The patients had been suffering from psoriasis for an average duration of 7 years, with a minimum and maximum duration of 40 days and 31 years, respectively.

The distribution of patients according to the sites affected by psoriatic lesions is depicted in Fig. 1. 40% of the patients were found to have changes in nail structure and architecture, which are associated with psoriasis. The distribution of patients according to the type of nail involvement is shown in Fig. 2. 45% of the patients reported to suffer from some type of joint pain. The distribution of patients according to the different joints involved is shown in Fig. 3. Joint pain had a progressive course in 22% of the patients. 40% of the patients had stiffness of the joints at some point of time during the day. Among them, 34% complained of joint stiffness in early morning hours; 12% while asleep; and 8% and 2% complained of most joint stiffness during afternoon and evening hours, respectively. In an analysis of the EARP and PEST questionnaires, 43 out of the 100 enrolled patients scored positive for EARP (≥3), while 13 patients scored positive for PEST (≥3); all of these 13 patients were EARP positive as well. All those

Table 3: The Classification Criteria for Psoriatic Arthritis (CASPAR) for diagnosis of psoriatic arthropathy.

Criteria	Point value
Current psoriasis	2
Personal history of psoriasis	1
Family history of psoriasis	1
Typical psoriatic nail dystrophy (onycholysis, pitting, hyperkeratosis)	1
Negative rheumatoid factor	1
Current dactylitis or history of dactylitis (recorded by rheumatologist)	1
Hand or foot plain radiography: evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (excluding osteophytes)	1

who were either EARP or PEST positive continued to meet the CASPAR criteria, which is the gold standard for diagnosis of PsA, showing a positive predictive value of 100%. The extent of agreement between EARP and PEST, as calculated by Cohen's kappa coefficient, was 0.312. In our study, EARP was superior to PEST, as PEST failed to screen positively a significant number of psoriatic patients for psoriatic arthropathy.

DISCUSSION

Psoriasis is one of the most common diseases examined in dermatology OPDs. Chronic systemic inflammation associated with psoriasis results in its association with metabolic syndrome, in complications, and in psoriatic arthropathy. The prevalence of inflammatory arthritis in the general population is 2–3%, whereas the prevalence in psoriasis is 6–42% [7]. The prevalence of psoriasis in the world population is estimated at 2–3%. Depending on genetic susceptibility and the geographic region, the prevalence of PsA ranges from 5% to 42% [8]. In a multiethnic retrospective study conducted at a rheumatology and dermatology referral center in Singapore, PsA was found to be significantly more

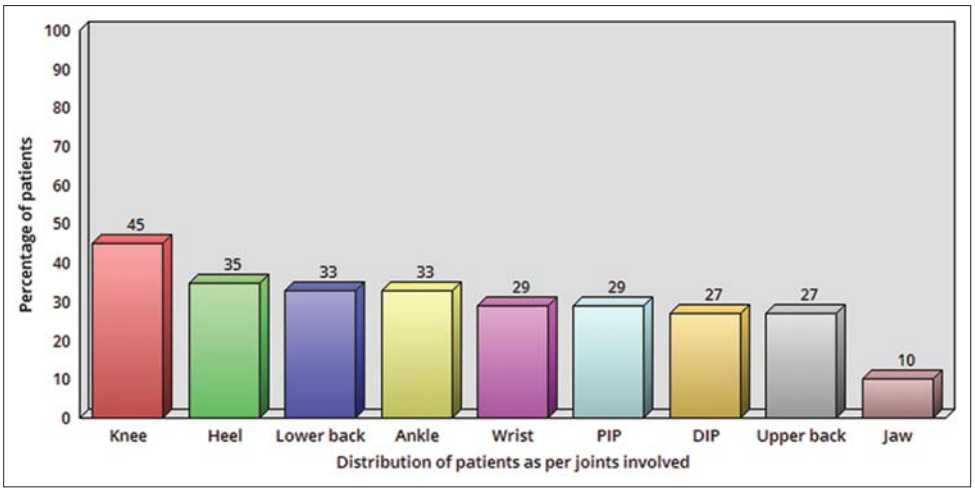

Figure 3: Distribution of patients according to joint involvement.

common among the Indian population as compared to people of other ethnicities ($p < 0.000001$) [9].

The spectrum of disease activity of PsA ranges from a benign course with mild symptoms to a rapidly destructive course resulting in permanent disability and a poor QoL [10]. In 75% of the patients, psoriatic skin lesions preceded joint symptoms, proving the appropriateness of diagnosing PsA in dermatology OPDs [8]. Presently, the gold standard for diagnosing PsA is the CASPAR criteria, which have a sensitivity of 91.4% and a specificity of 98.7% [11]. The CASPAR criteria were designed to be used by physicians and investigators, and requires serological testing of RA factor and bone radiography to have all its criteria met. A busy dermatology OPD may preclude dermatologists from asking each and every psoriatic patient about joint symptoms. Moreover, patients may not associate joint symptoms with psoriasis and may be less likely to report joint pain to a dermatologist, instead receiving drugs and alternative medicine for undiagnosed PsA from other sources, leading to a delayed diagnosis and the negative consequences of PsA. EARP and PEST are simple, objective, and self-administered screening tools that can help with screening psoriatic patients for PsA in dermatology OPDs. However, there have only been a few studies comparing the whole variety of these tools. We tested these screening tools in our dermatology OPD for their extent of agreement and positive predictive values. In our study, 76% of the subjects were males, as compared to 85% in Prasad et al. [12], 63% in Kumar et al. [13], and 51% in Karreman et al. [5]. The mean age of the patients in our study was 47 years, as compared to 33.1 years in Kumar et al. [13] and 55.7 years in Karreman et al. [5]. The average duration of psoriasis in our study was found to be less (7 years) than in other studies: 9.88 years in Kumar et al. [13] and 20.7 years in Karreman et al. [5]. Joint involvement in our study was classified according to Moll and Wright's criteria: polyarthritis (32%), spondyloarthropathy (31%), asymmetric oligoarthritis (28%), predominant distal interphalangeal (DIP) joint involvement (24%), and arthritis mutilans (1%). Kumar et al. reported that the most common pattern of PsA is polyarthritis (58%), followed by spondyloarthropathy (49%), asymmetric oligoarthritis (21%), predominant DIP arthritis (3%), and arthritis mutilans (1%) [13]. Nail involvement is an often-overlooked manifestation of psoriasis and affects approximately 10–78% of psoriatic patients, with 5–10% suffering from isolated nail psoriasis [14]. Our study showed that 40% of the psoriasis patients had nail structure and architecture changes: subungual hyperkeratosis (29%), pitting (28%), salmon spots (23%), and onycholysis (16%). Prasad et al. [12] reported that the most common nail change is pitting, followed by subungual hyperkeratosis; while Kumar et al. [13] found pitting to be the most common, followed by onycholysis and subungual hyperkeratosis. In our study, 41.8% of the patients with psoriatic arthropathy had nail changes. The reported frequency of nail involvement in patients with PsA is 87% according to Kumar et al. [13] and 63% according to Scher et al. [15]. Our study showed that EARP was superior to PEST, as PEST failed to screen positively a significant number of psoriatic patients for psoriatic arthropathy.

Our study was limited to the small sample of 100 patients. Moreover, we were not able determine the true and false negatives of the two questionnaires, since we did not further evaluate the subjects who were screened

negative by the questionnaires, in order to reduce the risk of unnecessary X-ray exposure. Due to a lack of data on the true and false negatives, it was impossible to calculate the sensitivity and specificity of the two questionnaires in our study.

CONCLUSION

Our study yielded findings commensurate with previous studies, showing that EARP is a more sensitive screening tool for PsA than PEST. However, the poor agreement between the two questionnaires underlines the need for the development of more effective PsA screening tools.

ACKNOWLEDGEMENTS

- Major Arunjeet Bhan, Assistant Director of Health, I Corps Headquarters, Indian Army
- Anirban Nandy, Data Scientist, Pune, India
- Statement of Human and Animal Rights

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

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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

Our Dermatology Online

Original Article

Evaluation of the response of pyogenic granuloma to 0.5% topical timolol solution

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ABSTRACT

Background: Pyogenic granuloma (PG) is a benign reactive vascular proliferation of the skin or mucous membranes that is classically treated surgically. Numerous case reports and case series have described successful treatment of PG and other vascular tumors with β-blockers. **Aim:** The aim is to evaluate the benefit of 0.5% topical timolol in the treatment of PG and the possible factors that may affect its response to treatment. **Materials and Methods:** This is a single-arm, open-label, prospective, interventional, therapeutic trial, conducted at the Center of Dermatology and Venereology in Baghdad Medical City, Baghdad, Iraq, from December 2017 through September 2019. Patients diagnosed clinically with PG were treated topically with 0.5% timolol maleate ophthalmic solution twice daily under occlusion and monitored every two weeks for response. Clinical response was evaluated based on the difference in the size of lesions after treatment, and was classified into complete response, partial response, and no response. **Results:** Thirty patients were enrolled in the study. The female-to-male ratio was 1.7:1 and the adult-to-child ratio was 2:1. The overall duration of treatment with topical timolol ranged from three days to twelve weeks with a mean and SD of 4.5 ± 2.9 weeks. At the end of the study, there was a statistically significant reduction in mean tumor size ($p < 0.05$). Eleven patients (36.7%) achieved complete resolution with an average duration of five weeks of treatment; seven patients (23.3%) achieved partial resolution (overall response was 60%); while twelve patients (40%) displayed no response to treatment. **Conclusion:** 0.5% topical timolol maleate is a safe alternative treatment option for PG regardless of the patient's sex and age, the size of the tumor, and the duration of the disease.

Key words: Pyogenic Granuloma; Beta-blockers; Topical Timolol solution

INTRODUCTION

Pyogenic granuloma (PG), also known as lobular capillary hemangioma, is a benign vascular tumor that appears on the skin and mucous membranes. PG can occur spontaneously, in sites of injury, or within capillary malformations [1]. It is usually painless unless associated with a secondary infection. Its aesthetically displeasing appearance and its tendency to produce recurrent profuse bleeding upon minor traumas often bring these lesions into notice [2].

Generally, PG lesions do not show a tendency for spontaneous resolution while recurrence is commonly seen after incomplete removal [2]. Exceptions include drug-induced PG, scalded PG, and granuloma gravidarum, which have been reported to resolve spontaneously after the resolution of the inciting factor [3-5].

Treatment modalities are mainly interventional and include curettage and cautery, surgical excision, chemical cauterization, laser removal, and sclerotherapy. Usually, these modalities require anesthesia and are complicated by intraoperative bleeding, postoperative pain, and scarring, as well as by a high recurrence rate (7.7% to 43.5%) [2,6,7].

In avoidance of these issues, topical treatment with imiquimod [8] and different β-blockers have been tried with variable success in different reports. Oral

How to cite this article: Al-Turfy IA, Najim SF. Evaluation of the response of pyogenic granuloma to 0.5% topical timolol solution. Our Dermatol Online. 2020;11(4):351-356.

Submission: 14.03.2020; **Acceptance:** 15.05.2020

DOI: 10.7241/ourd.20204.4

propranolol was reported to be effective in the treatment of recurrent PG, multifocal congenital PG, and scalded PG [4,9,10]. Topical propranolol was also used in 1% and 4% concentrations and was proved to be effective in most cases [11-13].

Malik and Murphy (2014) successfully treated a teenager a PG on the finger with 0.5% timolol ophthalmic gel [14]. Wine Lee et al. (2014) reached similar results with topical 0.5–2% timolol applied 2–3 times daily for 12–24 weeks or until the resolution of lesions [9]. Khorsand et al. (2015) reported successful treatment of a 5-month-old child with a PG on the cheek with a 0.5% topical timolol gel for 24 weeks, without recurrence [15]. Gupta et al. (2016) reported a case series of ten patients with PG treated with 0.5% timolol maleate ophthalmic solution applied four times a day with variable responses but no reported side effects [16]. Yet, few clinical trials have evaluated the degree of effectiveness of topical β-blockers in the treatment of PG in different age groups and the factors that may affect the response of PG to topical β-blockers.

MATERIALS AND METHODS

This study is a single-arm, open-label, prospective, interventional, therapeutic trial, conducted at the Center of Dermatology and Venereology in Baghdad Medical City, Baghdad, Iraq, from December 2017 through September 2019. Ethical approval was granted by the Scientific Council of Dermatology and Venereology of the Iraqi Board for Medical Specializations.

Thirty patients clinically diagnosed with a pyogenic granuloma of any size or duration, regardless of age and sex, participated in the study.

Exclusion Criteria

Excluded from the study were:

- patients who had been using medications known to induce pyogenic granuloma (e.g. oral contraceptives, retinoids, and indinavir) were excluded from the study to avoid misleading results;
- pregnant women;
- lesions preceded by scald injury;
- lesions with diagnostic uncertainty;
- patients with a contraindication to β-blocker medications (asthma, severe chronic obstructive pulmonary disease, bradycardia, heart block, cardiac failure, and hypersensitivity to β-blockers).

Information regarding the nature of the disease, treatment options, the nature of the study, and the medication used was conveyed to each patient and an informed consent was taken from each patient or, in the case of children, their relative.

The medical history taken included the duration of PG, precipitating factors, symptoms, previous therapeutic interventions, recurrence after a previous intervention, underlying medical illness, and current medications. The sites and sizes of lesions were recorded. The diameter of the largest lesion was measured with a tape measure on presentation and on each subsequent visit.

Patients were given timolol maleate ophthalmic solution in a 0.5% concentration (Apimol 0.5%, Amman Pharmaceutical Industries Co., Jordan) and were instructed to apply one to three drops—with a drop containing 0.25 mg of timolol maleate—spread it on the surface of the PG twice daily, cover the lesion with a bandage to facilitate absorption and avoid trauma as much as possible. Patients were instructed to return every two weeks for assessment.

The intended treatment duration was until the resolution of the PG. If no response was observed after four weeks of treatment or a worsening, such as an increase in size or bleeding, occurred despite treatment, topical timolol was discontinued and patients were referred for surgical intervention.

On follow-up visits, the patients were asked about bleeding, pain, and any other side effects observed. Measurements and color changes were noted as guides of early response, and photographs of lesions were taken at baseline and on each follow-up visit to facilitate comparison, maintaining the same distance, position, and lighting.

Clinical response to the topical timolol therapy was evaluated depending on the difference in size between the first and last visit and identified accordingly as complete response, partial response, or no response.

- No response: no change in size or an increase in size despite continuous treatment.
- Partial response: a decrease in size in response to therapy, but no complete clearance.
- Complete response: complete resolution of lesions. Patients with complete resolution were followed up for a minimum of four weeks up to a maximum of twelve weeks.

Data organization and statistics were performed using Microsoft Office 2013 Excel. A statistically significant result was at a p of less than 0.05.

RESULTS

Thirty patients participated in the study, 19 (63.3%) females and 11 (36.7%) males, giving a female-to-male ratio of 1.7:1. Their age ranged from 6 to 55 years with a mean and SD of 28.5 ± 16.2 years. Ten (33.3%) patients were children (<18 years old) and 20 (66.7%) were adults (≥18 years old).

Patient characteristics regarding precipitating factors, presenting symptoms, and previous interventions are elucidated in Table 1.

The duration of the disease ranged from one week to two years with a median duration of four weeks before presentation.

Nineteen lesions (63.3%) were located on the head and neck area, ten lesions (33.3%) on the extremities—mostly on one of the fingers—and one (3.3%) on the trunk.

The total duration of treatment with topical timolol ranged from three days to twelve weeks with a mean and SD of 4.5 ± 2.9 weeks.

Table 2 shows the sizes of lesions at presentation and following the 0.5% topical timolol therapy. There was a statistically significant decrease in size after treatment with timolol solution (p = 0.004).

Eighteen patients (60%) displayed a measurable clinical response within three days to four weeks of treatment with 0.5% timolol, among which eleven (36.7% of all patients) achieved complete resolution (Figs. 1 and 2) with an average duration of five weeks of treatment, ranging from three days to twelve weeks, and showed no recurrence after a minimum of four weeks of follow-up. The earliest response was observed in a nine-year-old boy with a PG on the face that disappeared completely three days after starting treatment (Fig. 1). The other seven patients (23.3% of all patients) achieved only partial resolution (Fig. 3). Surgical removal was offered to these patients.

Twelve patients (40%) showed no response to treatment, among which seven achieved no change in size after four weeks of continuous application of 0.5% topical timolol twice daily. The remaining five patients experienced an increase in lesion size despite the application of topical timolol twice daily. Electrocautery was performed for these patients.

No local or systemic side effects were recorded in this trial apart from mild itching reported by one patient.

There was no statistically significant correlation between a patient's sex or age and the response to treatment, as shown in Tables 3 and 4, respectively. Similarly, there was no statistically significant correlation between the

Table 1: Distribution of patients according to precipitating factors, associated symptoms, and a history of previous interventions.

Characteristic	Number (%)
Precipitating factors	
Trauma	7 (23.3%)
HSV	2 (6.7%)
Folliculitis	2 (6.7%)
Chronic paronychia	1 (3.3%)
Unknown cause	18 (60%)
Associated Symptoms	
Bleeding	18 (60%)
Pain	2 (6.7%)
None	10 (33.3%)
Previous intervention	
Yes	7 (23.3%)
No	23 (76.7%)

Table 2: The size of PG before and after treatment with topical timolol.

Size(mm)	Minimum	Maximum	Mean	SD[a]	P value[b]
Before treatment (n=30)	4	23	9	4.2	0.004*
After treatment (n=30)	0	20	5.5	5.9	

[a] Standard deviation [b] Calculated by Paired t-test *Statistically significant

Table 3: The clinical response of PG to topical timolol according to sex.

Response	Gender	
	Male n=11	Female n=19
Complete response Number (%)	3 (27.3%)	8 (42.1%)
Partial response Number (%)	3 (27.3%)	4 (21.1%)
No response Number (%)	5 (45.4%)	7 (36.8%)
Mean response ± SD	44.5% ± 46.7%	53.7% ± 46.6%

*P value= 0.6 *Calculated by student's t–test

Table 4: The clinical response of PG to topical timolol according to the patient's age.

Response	Age (year)	
	<18 (n=10)	≥18 (n=20)
Complete response number (%)	4 (40%)	7 (35%)
Partial response number (%)	3 (30%)	4 (20%)
No response number (%)	3 (30%)	9 (45%)
Mean response±SD	59%±45.8%	46%±46.7%

*P-value= 0.5 *Calculated by student's t-test

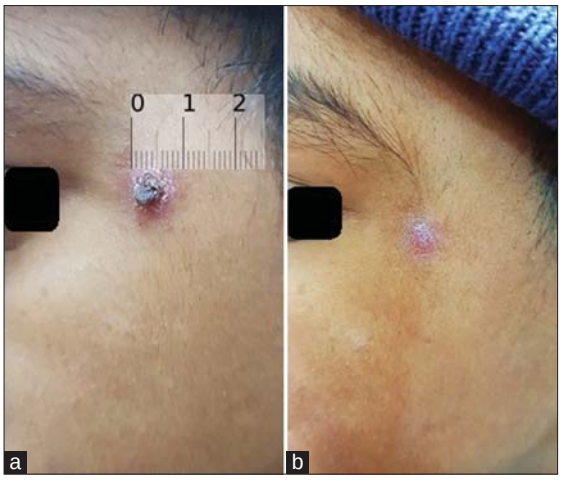

Figure 1: A nine-year-old boy with a PG on the face (a) before treatment and (b) with complete resolution after three days of treatment with topical timolol.

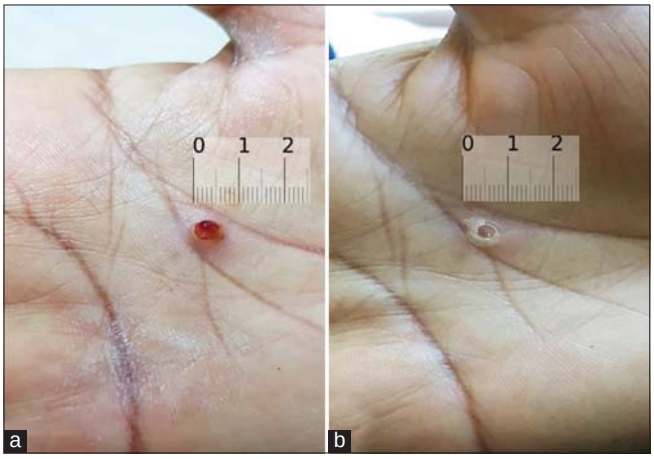

Figure 2: A fifty-five-year-old female with a PG on the palm (a) before treatment and (b) with complete resolution after three weeks of treatment with 0.5% topical timolol.

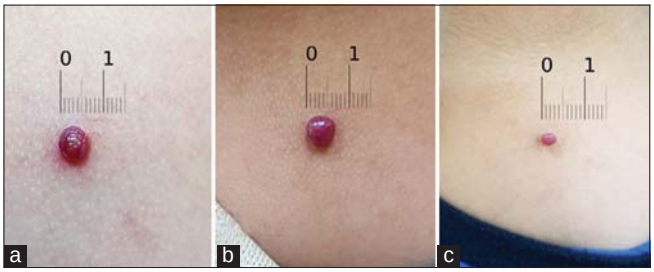

Figure 3: A six-year-old with a PG on the neck (a) before treatment, (b) after two weeks of treatment, and (c) after ten weeks of treatment, with the lesion showing a partial response.

response to treatment with the duration of a lesion (Fig. 4) or its size (Fig. 5) at presentation.

DISCUSSION

A significant number of case reports and case series have reported the use of the topical β-blockers

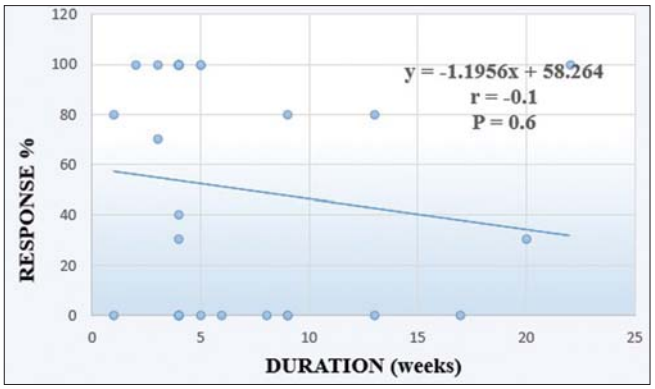

Figure 4: A scatter plot showing the relationship between the duration of PG and the response to treatment (r – correlation coefficient).

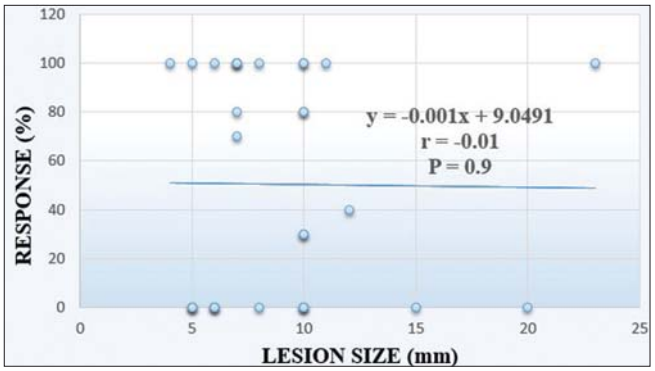

Figure 5: A scatter plot showing the relationship between the size of a PG lesion and the response to treatment (r – correlation coefficient).

propranolol and timolol for the treatment of PG, but few studies have evaluated the effectiveness of these topical preparations or compared the effectiveness of different preparations and their concentrations.

In this study, the response of PG to topical timolol, a nonselective β-blocker, was evaluated in different age groups.

A topical ophthalmic 0.5% timolol preparation was chosen due to its high potency, which is about eight to ten times greater than that of propranolol [17], as well as its low side-effect profile [18-20], easy availability, and insignificant cost.

Thirty patients participated in the study. Sixty percent of them responded to topical timolol. The first response was three days after starting treatment. A complete response was seen in 36.7% of patients, a partial response in 23.3%, and no response in 40%. The mean size of PG decreased significantly after the timolol treatment.

This variation in the response of PG to topical timolol may be explained by the weak expression of

β-adrenergic receptors on the surface of PG, as reported by Chisholm et al. (2012) in 50% of lesions, in contrast to the uniform strong expression of β-receptors on the surface of infantile hemangioma [21].

Chisholm, however, considered only two PG lesions, hence it seems that more research is necessary to confirm these results.

Since topical timolol is applied by the patient at home, varying degrees of compliance and adherence to treatment might be another factor explaining the variability in response.

The clinical responses in our study were comparable to those reported by Gupta et al. (2016), who found complete resolution in 40% of patients (compared to 36.67% in our study), partial resolution in 30% (compared to 23.33% in our study) and no response in 30% (compared to 40% in our study) after the application of ophthalmic 0.5% timolol maleate solution four times daily. In a study by Gupta et al. (2016), the time needed for a complete response was three to twenty-four days [16], whereas, in our study, it ranged between three days and twelve weeks. The difference in the time needed to achieve a complete response may be explained by the application topical timolol four times a day in the study by Gupta et al.

Gupta et al. could not draw a conclusion about the relationship between the response to treatment and the duration of a lesion due to a small sample size. Our study concluded that there was no statistically significant correlation between the duration of a lesion before treatment and its response to treatment.

A great number of researchers have reported higher success rates with topical propranolol than with topical timolol: Neri et al. (2018) used 1% propranolol ointment under occlusion to treat pediatric PG. Twenty-two patients received treatment, of which 59% achieved complete resolution in a mean of 9.5 weeks (compared to 36.6% of those with a mean of five weeks in our study), 18% had partial resolution after 1% propranolol ointment (compared to 23.3% in our study), and 23% showed no response to treatment (compared to 40% in our study) [11].

A higher concentration of propranolol was evaluated by Mashiah et al. (2019) in a retrospective study. Eighteen pediatric patients treated with a 4% propranolol gel twice daily without occlusion were enrolled. Eleven lesions (61.1%) resolved completely by the end of the treatment (compared to 36.6% of those treated with timolol in our study); two lesions (11.1%) almost resolved; and five (27.7%) underwent curettage [12].

The better response of PG to propranolol may be explained by the difference in age in the study population, as both of the propranolol studies were restricted to a pediatric-age group, whereas our study included different age groups. It must be noted that, in our study, the response rate in children was higher than in adults, but there was no statistically significant relationship between the age of the patient and the response to treatment.

The higher response rate in children may be due to the increased absorption through the thinner skin in children and, perhaps, also due to the higher commitment of parents to treat their children.

CONCLUSION

0.5% topical timolol is a safe alternative treatment for PG particularly if the surgical approach is difficult or contraindicated or not preferred by the patient, as in small children, elderly patients with comorbid illnesses, in cosmetically-sensitive areas such as the face, nails, and lips, and in PGs that recurred after a previous surgical intervention. However, it is not recommended to continue treatment with topical timolol if no response is achieved after four weeks.

Patients of all ages and sexes are candidates for this modality of treatment, regardless of the size or duration of their PG.

Further studies using a combination of oral and topical β-blockers, especially for large, unresponsive lesions are recommended in search of more complete and definitive results.

Statement of Human and Animal Rights

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

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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

Our Dermatology Online

Brief Report

Knowledge, attitude, and behavior in the prescription of topical steroid for dermatological disorders among medical practitioners

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ABSTRACT

Background: The misuse and abuse of topical corticosteroids have increased manifold and the occurrence of adverse effects has, simultaneously, shown an upward trend. This has further been aggravated by the irrational prescribing behavior on the part of non-dermatologists. **Aim:** This study aimed to evaluate the knowledge, attitude, and behavior of medical practitioners in prescribing topical corticosteroids. **Material and Methods:** This was a cross-sectional, questionnaire-based study conducted at a tertiary center in northern India among 110 medical practitioners. Results: All of the medical practitioners had been routinely prescribing topical corticosteroids without a clear indication, being completely unaware of possible side effects. This study revealed gaps in knowledge and unhealthy attitudes toward the ethical aspects of the rational use of steroids. **Conclusion:** Our study revealed huge gaps in the knowledge and awareness about the potencies, side effects, and rational use of steroids. This further highlights the need to involve dermatologists in contributing and providing medical knowledge.

Key words: Knowledge; Medical practitioners; Topical steroids; Side effects

INTRODUCTION

Ever since the discovery of hydrocortisone, also known as Compound F, in 1952, topical corticosteroids have come a long way and established their indispensable role in the medical field. The armamentarium has expanded with the discoveries of novel drugs, ranging from low-potency to high-potency corticosteroids [1]. They are highly efficacious owing to their anti-inflammatory, immunosuppressive, and antiproliferative effects and have become the mainstay of therapy in a wide array of dermatological conditions [2]. However, various side effects and complications have emerged due to the rampant unethical use and abuse of topical corticosteroids. The various factors contributing to their misuse include the dearth of stringent laws regarding their sale, ignorance among patients, and even medical practitioners regarding their proper dosage, indications, and side effects, imprecise prescription, lack of coordination between dermatologists and other medical practitioners, and their difficult accessibility to dermatologists. The situation is further compounded by incorrect information provided by manufacturers. The repercussions can be seen in the form of various complications, such as the rising menace of resistant and recalcitrant dermatophyte infections, Topical Steroid Damaged/Dependent Face (TSDF), cutaneous atrophy, and hypertrichosis [3]. The following study was, thus, conducted to investigate the knowledge about and the attitude toward topical corticosteroid prescription by various specialists and medical practitioners for various dermatological disorders, as well as their behavior in patient counseling.

MATERIAL AND METHODS

This was a cross-sectional, questionnaire-based study conducted at a tertiary center in northern India among

How to cite this article: Abrol S, Sharma R. Knowledge, attitude, and behavior in the prescription of topical steroid for dermatological disorders among medical practitioners. Our Dermatol Online. 2020;11(4):357-359.

Submission: 01.03.2020; **Acceptance:** 25.05.2020

DOI: 10.7241/ourd.20204.5

various medical practitioners to assess the knowledge, attitude, and steroid prescribing behavior of medical professionals in various dermatological disorders.

All medical graduates with an M.B.B.S degree, a postgraduate degree, or a diploma in various specialties were included in the study and a written informed consent was taken from each of them. A total of 110 participants were willing to participate in a survey in questionnaire form. The questionnaire was self-designed in view of lack of any such questionnaire available (Table 1). Following the distribution of the questionnaires and their completion, feedback was taken on whether the study helped in creating more awareness regarding the menace of topical corticosteroid abuse.

Statistical analysis was performed using the software Epi Info. Wherever necessary, Fischer's exact test was used to compare variables. A p value below 0.5 was interpreted as statistically significant.

RESULTS

A total of 110 medical professionals participated in the study, among which 64 (58.1%) were M.B.B.S graduates, and the other 46 (41.8%) were either postgraduates or diploma holders. Table 2 shows the distribution of their medical specialties. All of the participants had, in their practice, prescribed topical steroids to patients with various dermatological indications. Only 21 (19%) were most often sure about the dermatological diagnosis, whereas the other 89 (80.9%) were most often unsure. The most common indication for which 55 (50%) of the practitioners prescribed topical steroid was tinea, followed by general-purpose/fairness creams (37%/33.6%). Out of the 110 practitioners, 32 (29%) prescribed steroids even in an uncertain diagnosis. Various indications for topical steroid application are listed in Table 3. The most commonly used topical steroid was betamethasone, which was used by 32 (29%) of the medical practitioners in their routine practice, followed by mixed-combination creams used by 29 (26.3%); the rest is listed in Table 4. Only 27 (24.5%) were aware of the potencies of steroids. Out of the 110 medical practitioners, only 7 (6.3%) and 24 (21.8%) were aware of the various side effects of topical steroids. Unfortunately, only 11 (10%) referred a patient suffering from a dermatological disease to a dermatologist at the first visit, and a meager 27 (24.5%) did so following the absence of improvement of a skin disease, its worsening, or development of side effects.

Table 1: Study questionnaire.

1	Speciality	
2	Do you prescribe topical steroids	Yes/No
3	Indication for prescribing topical steroids	
4	Were you sure of the dermatological diagnosis	Yes/No
5	Which topical steroid do you most commonly prescribe	
6	Are you aware of the various potencies of topical steroid	Yes/No
7	Do you know about the various side effects of topical steroid	Yes/No
8	Do you refer the patient to a dermatologist before prescribing topical steroid for a dermatological disorder	Yes/No
9	Was the patient referred to a dermatologist on development of various complications or worsening of the skin condition after the topical steroid prescription	Yes/No

Table 2: Distribution of medical specialties.

1	MBBS(MEDICAL OFFICERS)	34
	MBBS(JUNIOR RESIDENTS)	30
	DERMATOLOGISTS	3
	PHYSICIANS	7
	GYNAECOLOGISTS	6
	PAEDIATRICIANS	3
	SURGEONS	5
	ENT SPECIALISTS	6
	OPHTHALMOLOGISTS	3
	ORTHOPAEDICIANS	3
	PSM	3
	PHARMACOLOGISTS	3
	MICROBIOLOGISTS	2
	PATHOLOGISTS	2

DISCUSSION

Since their discovery, the use of topical steroids has revolutionized the treatment of various dermatoses, which can be attributed to their immediate relief from the various modes of action, such as immunosuppression, antiproliferation, antiangiogenic, and anti-inflammatory effects [4]. Over the years,

Table 3: Distribution of indications for the use of topical steroids.

1	TINEA	55
2	GENERAL PURPOSE/ FAIRNESS CREAMS	37
3	UNSURE DIAGNOSIS	32
4	MELASMA	31
5	ACNE	25
6	ECZEMA	20
7	PSORIASIS	19
8	LICHEN PLANUS	12
9	MISCELLANEOUS(KELOIDS, INSECT BITES etc)	10

Table 4: Most commonly used steroids.

1	BETAMETHSAONE	32
2	MIXED COMBINATION	29
3	CLOBETASOL	17
4	MOMETASONE	15
5	BECLOMETHASONE	10
6	OTHERS	7

they have become the epitome of treatment of all dermatological manifestations and the magic wand in the hands of practitioners [5].

However, the rapid onset and the immediate relief perceived by patients have led to their rampant misuse by patients and even non-dermatologists and practicing physicians, leading to a wide array of side effects, such as tinea incognito, erythema, and TSDF. The problem is further compounded by the dearth of stringent laws relating to their sale, and the easy availability of over-the-counter drugs for fairness and general cosmetic creams [6]. Some of the side effects are permanent and irreversible, having huge psychological morbidity upon the patients. The rising resistance of dermatophytes to antifungals is one such dreaded complication due to the inadvertent prescription of steroids by non-dermatologists reported by various studies [7].

Our study focused on medical practitioners and aimed to assess their knowledge and attitude toward steroid prescription, finding an alarming rate of topical steroid prescriptions by various medical practitioners. In 80.9% of these cases, prescriptions were made without a proper diagnosis. The most common indication was tinea treated with general-purpose creams. However, other studies reported acne as the most common indication [1,8]. Only 6.3% of the medical practitioners were aware of the side effects and a meager 10% referred their patient to a dermatologist for proper diagnosis. A study from Saudi Arabia drew similar conclusions, whereby the knowledge of topical steroid use in general practitioners was inadequate [9]. These findings have a greater significance in present-day scenarios. Similar alarming results were reported in another study [10].

Our study showed a clear lapse in the knowledge about topical steroids and the prescription behavior of medical practitioners, thus reaffirming the need to address this issue through a concerted and thorough approach. Similar findings have been reported by various other studies [11,12].

CONCLUSION

This survey clearly illustrates the knowledge gaps prevalent among various non-dermatologists and medical practitioners regarding the potency, usage, and side effects of topical steroids. This assumes great significance against the backdrop of the rising menace of antifungal resistant dermatophyte infections and TSDF. Thus, serious efforts at all levels are imperative to bridge these gaps, while advocating the correct and rational use of topical steroids by various medical practitioners needs to be encouraged.

Statement of Human and Animal Rights

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

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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

Our Dermatology Online

Brief Report

Erythema induratum of Bazin: A study of 34 cases in an endemic country

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ABSTRACT

Background: Cutaneous tuberculosis represents 1–2% of cases of tuberculosis. The purpose of this work is to reevaluate the epidemiological and clinical profile and the therapeutic and evolutionary paraclinical understanding of this entity in Fes, Morocco. **Materials and Methods:** The following was a descriptive and retrospective study conducted from January 2006 through April 2018 at the Dermatology Department of Hassan II CHU in Fes, Morocco, and Diagnostic Centers for Tuberculosis and Respiratory Diseases. **Results:** We identified 34 cases of an average age of 48 years and a sex ratio of 0.03. Chronic nodular hypodermitis of the lower limbs leaving pigmented scars was found in 100% of cases and fistulized in 52.9%. IDR was phlyctenular in 47% of cases. Cutaneous histology revealed an inflammatory granuloma with vasculitis in 32.35% of cases. All the patients received antibacterial treatment for six months. Recidivism was found in 20.5% of cases. Treatment with dapsone was prescribed for these patients with good evolution. **Conclusion:** Confronted with chronic nodular hypodermitis of the legs, the clinician must consider the origin of tuberculosis, keeping in mind epidemiological, clinical, histological, and immunological findings.

Key words: Bazin's indurated erythema; Tuberculous; Epidemiological profile; Clinical profile; Therapeutic

INTRODUCTION

Cutaneous tuberculosis is still common in Morocco, representing 1–2% of cases of tuberculosis and 0.1–1% of skin diseases [1]. Erythema induratum of Bazin (BEI) is a nodular vasculitis but still poses a problem as to its tuberculous origin. Its management remains poorly understood [2]. The purpose of this work is to reevaluate the epidemiological and clinical profile and the therapeutic and evolutionary paraclinical understanding of this entity in the region of Fes, Morocco.

MATERIAL AND METHODS

This is a prospective and retrospective study conducted at the Dermatology Department of Hassan II CHU in Fes, Morocco, and Diagnostic Centers for Tuberculosis and Respiratory Diseases (DCTRD) on cases of cutaneous tuberculosis hospitalized from January 2006 through April 2018. Selected files were analyzed according to a grid with epidemiological, clinical, paraclinical, and therapeutic data.

RESULTS

We identified thirty-four cases of IBS. The average age was 48 years, with extremes ranging from 21 to 70 years. The sex ratio was 0.03, with a high female predominance of 30 females per male. The majority of the patients came from rural areas and were of low socioeconomic status.

Tuberculous contagion was present in the patients' history. One patient had a history of pulmonary tuberculosis but no family history. No cases of HIV infection were identified. The average duration of evolution was two years.

How to cite this article: Assenhaji Louizi I, Baybay H, Zinoune S, Douhi Z, Elloudi S, Mernissi FZ. Erythema induratum of Bazin: A study of 34 cases in an endemic country. Our Dermatol Online. 2020;11(4):360-362.

Submission: 21.12.2019; **Acceptance:** 23.02.2020

DOI: 10.7241/ourd.20204.6

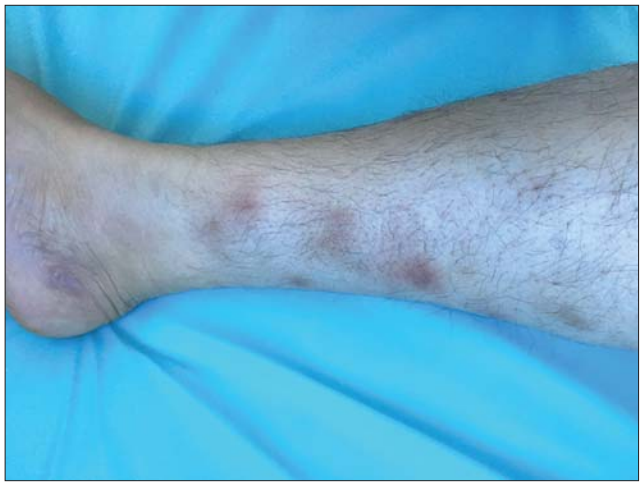

Figure 1: Chronic nodular hypodermitis of the lower limbs.

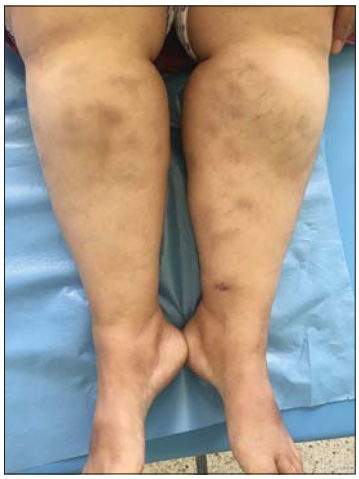

Figure 2: Pigmented scars after BEI lesions on the lower limbs.

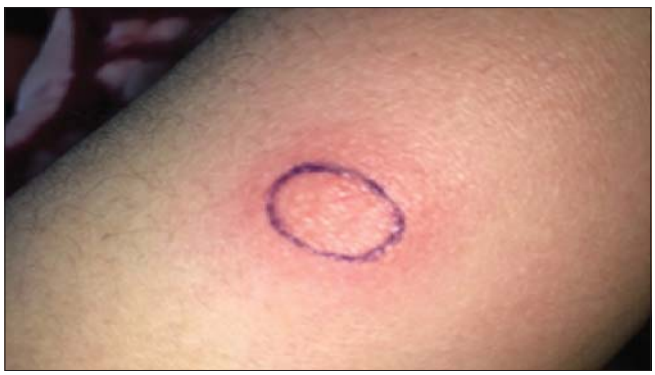

Figure 3: The phlyctenular reaction of intradermal tuberculin.

Clinically, all patients had chronic nodular hypodermitis of the lower limbs, fistulized in eighteen cases (Fig. 1), leaving pigmented scars in all patients (Fig. 2).

The intradermal tuberculin reaction was phlyctenular in sixteen patients (Fig. 3). Cutaneous histology revealed an inflammatory granuloma of the lipophagic type associated with vasculitis in eleven cases.

A search for Koch's bacillus in skin lesions by PCR (polymerase chain reaction) was not conducted

All patients received antibacterial treatment for six months, with complete healing in 29 patients and recidivism in seven. Treatment with dapsone was prescribed for these patients with good evolution and without recurrence after six months.

DISCUSSION

Cutaneous tuberculosis has a protean clinical presentation, representing 1% of cases of extrapulmonary tuberculosis in endemic areas [3].

Erythema induratum of Bazin (BEI) was first described by Ernest Bazin in 1861 and, thereafter, in 1900, BEI was considered a manifestation of tuberculin hypersensitivity [1]. Currently, the term nodular vasculitis (NV) is often synonymous. The number of cases of BEI reported is on the decrease in most developed countries while the incidence of tuberculosis is decreasing [1].

The pathogenesis of BEI remains poorly understood and its link to tuberculosis remains controversial. Most authors consider BEI a multifactorial disorder with multiple different causes, tuberculosis essentially being a hypersensitive immune response to M. tuberculosis [4,5].

EIB is a recurrent chronic eruption occurring in young and middle-aged females in good health and with no systemic signs. EIB manifests itself by the presence of purple nodules or deep plaques on the posterior and anterolateral legs, feet, thighs, and arms, with the face rarely affected [1]. The lesions are not warm and not especially painful and tend to ulcerate centrally. Most of the lesions resolve spontaneously within several months, leaving postinflammatory hyperpigmentation and pigmented scars, which were found in all our patients [1].

Histologically, the epidermis may be intact or ulcerated. Lobular panniculitis with granulomatous inflammation with focal necrosis, sometimes with tuberculoid granulomas, and with central caseous necrosis [1] and a superficial or deep, perivascular or periadnexal, inflammatory lymphohistiocytic infiltrate is often present. Vasculitis of small and medium-sized vessels

with fibrinoid necrosis and purpura may appear [1]. Special stains demonstrate no presence of acid-fast bacilli, but detection of M. tuberculosis by PCR suggests the presence of tuberculous DNA in the lesions [6].

However, because assessments conducted often do not provide sufficient evidence for the origin of tuberculous cutaneous lesions, it is necessary to employ the notions of endemic countries, recent tuberculosis contagion, positivity of IDR to tuberculin, and association with extracutaneous tuberculosis [7].

The management of BEI is poorly documented [8], but involves standard WHO anti-TB drugs (four-drug therapy, then dual therapy for six months), Generally, cutaneous TB must be treated with the same regimen as systemic TB, and there is no role for single anti-TB drugs [1]. However, with the high risk of recidivism and in the case of the failure of antibacterial treatment, dapsone may be a good therapeutic alternative, as in our study [7].

CONCLUSION

Confronted with chronic nodular hypodermitis of the legs, the clinician must consider the origin of tuberculosis, keeping in mind epidemiological, clinical, histological, and immunological findings, especially after good evolution with anti-tuberculosis drugs. Nevertheless, a study with larger sampling is desirable.

Statement of Human and Animal Rights

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

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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

Our Dermatology Online

Brief Report

Efficacy of topical 85% formic acid solution in the treatment of warts

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ABSTRACT

Background: Warts represent a common skin disorder that may cause pain and cosmetic deformities. Although their spontaneous clearance can occur at any time, the high rate of transmission makes their treatment absolutely necessary. **Materials and Methods:** 139 patients diagnosed with warts participated in our study, which involved dipping a cotton bud in an 85% formic acid solution and applying it to the warts for 3 seconds once weekly. A dermatologist examined the patients in a well-lighted room at baseline and after 4, 6, and 10 weeks of treatment. **Results:** After completing the treatment, 79 out of the 139 patients (56.8%) showed complete remission of warts, 20 (28.8%) were partially cured, and 40 (14.4%) showed no change. Formic acid caused a first-degree chemical burn in 5 patients in the sixth week of treatment, resulting in a ten-day intermission until its next application. Only 15 patients (10.8%) complained about a burning sensation, which appeared after 6 applications in 8 patients and after 10 applications in the other 7 patients. Among the patients cured completely, 52 (65.8%) needed 10 weeks of treatment, 19 (24.05%) needed 6 weeks, and 8 (10.15%) achieved complete remission after 4 weeks. **Conclusions:** Our study demonstrated that formic acid is a safe and economic therapeutic option for the treatment of warts that produces favorable results with few adverse effects.

Key words: Warts, Formic acid, Efficacy

INTRODUCTION

Warts are defined as benign tumors caused by the infection of keratinocytes with the human papillomavirus (HPV) and appearing as well-defined hyperkeratotic protrusions. Warts may take different morphological forms depending on the type of virus, their location, the immunological status of the patient, and the environmental factors. The types of warts observed include common, plantar, plane, filiform, and anogenital [1]. Various studies have discovered that a significant portion of school-age children and young adults are infected with HPV. Impairment of epithelial barrier function—mainly by trauma—and consequent inoculation of the virus, leads to the formation of warts, easily spread by autoinoculation and direct and indirect contact [2].

The high risk of contagion and the high rate of recurrence prompt patients to search for effective therapy as soon as possible. An overview of the available literature demonstrates that, although several treatments have been tested, none of them offers complete and safe disappearance of warts without side effects [2]. Formic acid is a topical agent that has been used with positive results. The following is a study that aimed to estimate the efficacy of topical 85% formic acid in the treatment of warts and to propose such treatment as a novel therapeutic option.

MATERIALS AND METHODS

The study involved 139 patients who referred to the outpatient clinic of Andreas Syggros University Hospital

How to cite this article: Gerodimou M, Gerochristou M, Emmanouil G, Douvali T, Mazioti M. Efficacy of topical 85% formic acid solution in the treatment of warts. Our Dermatol Online. 2020;11(4):363-366.

Submission: 17.05.2020; **Acceptance:** 06.08.2020

DOI: 10.7241/ourd.20204.7

of Cutaneous and Venereal Diseases, Athens, Greece, and who were diagnosed with warts. Eligible patients were above 18 years old and had shown warts under no previous treatment for the last 6 months. The exclusion criteria included pregnancy, malignancy, diabetes mellitus, concomitant wounds and ulcers, and recent surgery. All participants gave written informed consent and received detailed instructions, according to which they had to dip a cotton bud in an 85% formic acid solution and apply it to their warts for 3 seconds once weekly. Patients were advised to put Vaseline around the warts before the application of formic acid in order to prevent irritation of the healthy skin. A dermatologist examined the patients in a well-lighted room at baseline and after 4, 6, and 10 weeks of treatment. A positive response to treatment was defined as the disappearance of warts, a partial response as a reduction in the total number of warts, and no response as no change in wart formations.

Statistical analysis was performed using the software SPSS Statistics, version 20.0, with the formula *mean ± standard error of the mean (SEM)*. *p* values below 0.05 were considered statistically significant.

RESULTS

After completing the treatment, 79 out of the 139 patients (56.8%) showed complete remission of warts, 20 (28.8%) were partially cured, and 40 (14.4%) showed no change.

Among the patients cured completely, 52 (65.8%) needed 10 weeks of treatment, 19 (24.05%) needed 6 weeks, and 8 (10.15%) achieved complete remission after 4 weeks. As for the patients who showed a partial response, the number of warts remained stable during the first four weeks of therapy, whereas it was reduced between the sixth and tenth weeks.

Formic acid caused a first-degree chemical burn in 5 patients in the sixth week of treatment, resulting in a ten-day intermission until its next application. Only 15 patients (10.8%) complained about a burning sensation that appeared after 6 applications in 8 patients and after 10 applications in the other 7 patients.

The mean age was 34.42 ± 16.48 years. Females comprised 57.7% of the patients. The mean number of warts at baseline was 3.5 ± 6.1.

95 patients (68.3%) had palmar warts, 35 (25.2%) had plantar warts, 8 (5.8%) had palmoplantar warts, and one (0.7%) had a common wart on the scalp. Among the females, 80% had palmar warts, 18.8% had plantar warts, and 1.2% had palmoplantar warts. Among the males, palmar warts were noted in 52.7% of them, plantar warts in 33.9%, and palmoplantar warts in 11.9%. The only patient with a wart on the scalp was male.

A Pearson's chi-squared test demonstrated that the sex-to-wart-location relationship was statistically significant ($p = 0.002$), but revealed no significant relationship between the complete disappearance of warts and their location ($p = 0.822$).

DISCUSSION

Warts represent a common skin disorder that may cause mild or even severe pain and cosmetic deformities. Although their spontaneous clearance can occur at any time, from a few months to years, the high rate of transmission makes their treatment absolutely necessary. The number, size, and location of warts and the age, compliance, and immunological status of the patient are the main factors that determine the choice of treatment [1].

First-line therapy involves the topical use of caustic acids to cause the destruction of the infected area of the epidermis. Salicylic acid in a concentration of 12–26%, possibly with the addition of lactic acid, is commonly used because of its keratolytic effect, which leads to the reduction of warts and the stimulation of the inflammatory response. Monochloroacetic and trichloroacetic acids and cantharidin are other highly irritant chemicals that can be used. The successful outcome of therapy with these chemicals requires their accurate application, that is, avoiding the healthy skin. Otherwise, chemical burns and pain are likely to occur [2].

Second-line treatments comprise cryotherapy, lasers, hyperthermia, photodynamic therapy, and surgical excision. Cryotherapy is commonly used and gives good results, but may easily cause frostbite injuries and pain [3]. Laser treatment is effective but its high cost, the risk of posttreatment scarring, the relatively long healing time, and the presence of infection particles in laser fumes are significant disadvantages [4]. Finally, several investigators have used topical or intralesional imiquimod, podophyllin, and podophyllotoxin, but their efficacy in the complete elimination of warts has not yet been proven [5].

Formic acid is a natural chemical found in ants, also produced industrially and used as a food additive. Formic acid applied to human tissue in high concentrations provokes denaturalization and coagulative necrosis, leading the virally infected cells to death. Clinically, formic acid application makes warts more whitish and causes the desquamation of their superficial layer [4].

The high success rate of wart treatment has been mentioned after topical puncture with 85% formic acid in a period of 1 to 3 months [6,7]. Tippanawar et al. have also reported that 82% of patients treated with 80% formic acid intralesionally achieved complete disappearance of warts after 10 applications [4]. Handjani et al. compared the efficacy of a topical 85% formic acid preparation with a combined topical solution of salicylic and lactic acid, and proved it to be an effective cure for warts after the use of formic acid, especially for warts located on the hands [8]. The results of our study are in accordance with the clinical trials set forth above. The efficiency of our therapy reached 56.8% in a period of 10 weeks, indicating that the topical application of 85% formic acid is an effective treatment for warts. Fig.1 shows the clinical result of formic acid application on a palmar wart after 10 weeks of treatment.

Apart from its efficacy, the use of formic acid is an inexpensive option with no equipment requirements. In addition, the risk of posttreatment scarring and nail dystrophy is low, and patients can return to their occupations immediately; no local anesthesia is required, which makes it well tolerated by children [4,6-8]. As in all therapies, treatment with formic acid, a chemical acid, poses some adverse effects. A burning sensation, pain, and post-inflammatory hyperpigmentation may occur. Their incidence depends mainly on the concentration of formic acid and the duration and frequency of therapy. Balagué et al. were the first to mention a third-degree chemical burn in a patient after the application of a formic acid ointment continuously for six hours with an occlusive dressing. Although most of the adverse effects of formic acid are topical, blindness after eye contact is mentioned in the literature. Furthermore, continuous use of formic acid can lead to systemic absorption, causing acidosis, memory loss, confusion, and kidney and liver damage [7]. In our study, only 15 patients (10.8%) complained about a burning sensation, which occurred after 6 applications in 8 patients and after 10 applications in the other 7 patients. Furthermore, formic acid caused a first-degree chemical burn in 5 patients in the sixth week of treatment, resulting in a ten-day intermission until its next application.

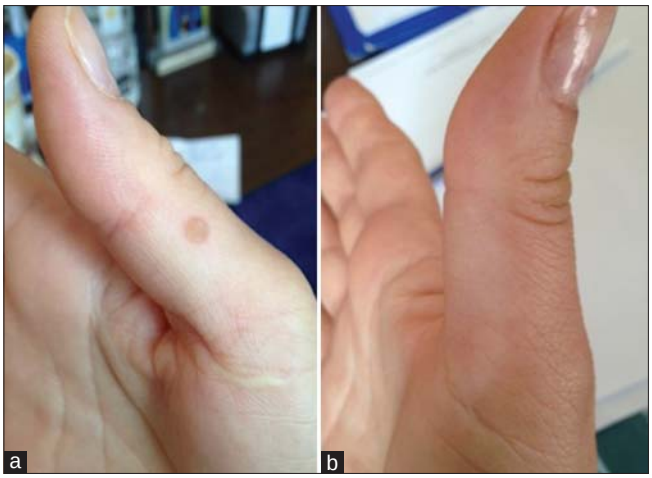

Figure 1: (a) A palmar wart at baseline. (b) The same palmar wart after 10 applications of topical 85% formic acid solution.

CONCLUSIONS

Our study demonstrated that formic acid is a safe and economic therapeutic option for warts that gives good results with few adverse effects. Because it was not double-blind, the study showed some inevitable limitations. However, it highlights the necessity of conducting future large-scale studies in order to substantiate the effectiveness and benefits of these various treatments.

Statement of Human and Animal Rights

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

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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

Our Dermatology Online

Case Report

Lichen planus pemphigoides: Lesional immunopathologic features

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ABSTRACT

Lichen planus pemphigoides (LPP) is a rare autoimmune bullous dermatosis. The disease features combined features of bullous pemphigoid and lichen planus. Here we describe a case with histological and immunopathological features of LPP in a 59 year old male. Skin biopsies were taken for hematoxylin and eosin (H&E) as well for direct immunofluorescence (DIF) and for immunohistochemistry (IHC) stains. The H&E staining displayed a subepidermal blister, with a dense lymphohistiocytic infiltrate located along the basement membrane zone of the skin (BMZ). The DIF was positive at the BMZ for IgG, C3c, C1q, fibrinogen and albumin. The same markers were positive in a linear dermal band. Cytoid bodies were positive with IgG. The IHC staining demonstrated very positive staining over the entire BMZ with metallothionein, as well as C5b-9/MAC staining. The inflammatory infiltrate was positive for HLA-DPDQDR antigen. Our findings demonstrate that in this case HLA-DPDQDR antigen may play an important role presenting the antigens, and the roles of C5b-9/MAC and metallothionein need further investigation.

Key words: Lichen planus pemphigoides; Cytoid bodies; Basement membrane zone; Metallothionein

Abbreviations: Lichen planus pemphigoides (LPP), hematoxylin and eosin (H&E), immunohistochemistry (IHC), direct immunofluorescence (DIF), basement membrane zone (BMZ), 4',6-diamidino-2-phenylindole (DAPI).

INTRODUCTION

Lichen planus pemphigoides (LPP) is a rare, autoimmune bullous dermatosis first described by Dr. Moritz Kaposi, and demonstrating combined features of lichen planus and bullous pemphigoid [1]. The clinical presentation of LPP may simulate bullous pemphigoid, making the diagnosis problematic. Clinically, LPP is characterized by a sudden onset of tense, dome-shaped bullae preceding, during, or after an eruption of lichen planus [1]. The blisters may arise on uninvolved skin or on pre-existing lichen planus lesions [2]. In LPP the lesions most usually involve the distal extremities, but they may occur in a generalized form. Oral and conjunctival mucosal involvement has been reported [3]. LPP more commonly affects males, usually in the fourth or fifth decade of life. LPP has been also associated with prescription and over the counter medications, including herbal supplements, angiotensin-converting- enzyme inhibitors, PUVA (including narrow band therapy), weight reduction products and simvastatin among others [4-6]. A detailed clinical, histopathological, and immunological evaluation is essential for the diagnosis of LPP. The basement membrane zone (BMZ) is considered one of the most affected structures in LPP. It is important to ask patients about any systemic disorders as well as current mediations. The etiology is fundamentally idiopathic; however, there are numerous case reports of drug-induced LPP.

Statement of Ethics

Our patient gave informed consent. Although Institutional Review Board (IRB) approval for a case report is not needed, the US Health Insurance

How to cite this article: Abreu Velez AM, Jackson BL, Howard MS. Lichen planus pemphigoides: Lesional immunopathologic features. Our Dermatol Online. 2020;11(4):367-370.

Submission: 13.04.2020; **Acceptance:** 01.10.2020

DOI: 10.7241/ourd.20204.8

Portability and Accountability Act of 1996 (HIPAA) Privacy Rule restricts how protected health information (individually identifiable health information) on any patient may be made. Compliance with patient privacy, institutional rules, and federal regulations were followed. No photos or illustrations that contain identifiable features are included in the case report, and the case(s) described in the report are not so unique or unusual that it might be possible for others to identify the patients.

A 59 old male consulted the dermatologist for the presence of persistent patches with pruritic, pink to violaceous, flat-topped, polygonal papules on the volar wrists, extensor elbows, and bilateral lower legs of 6 months duration. Some areas showed hyperpigmentation and scaling. The patient further develops some microvesicles. Systemically he had no significant medial history and was not taking medications. Skin biopsies were taken for hematoxylin and eosin (H&E) as well for direct immunofluorescence (DIF) and for immunohistochemistry (IHC) staining. These were performing as previously described [7-9]. Workup revealed lichen planus pemphigoides (LPP). The histopathology and direct immunofluorescence were compatible with LPP. The patient was prescribed with Clobetasol propionate™ cream 0.05% for the trunk, extremities, and nails and momethasone furoate cream 0.1% for the face with improvement; anti-histamine was added for the itching.

Skin biopsies were taken for hematoxylin and eosin(H&E) staining, direct immunofluorescence (DIF) and for immunohistochemistry (IHC) stains, which were performed as previously described [8-11]. For DIF, we classified our findings as previously categorized [8-11], i.e. negative (-), weakly positive (+), positive (+++) and strongly positive (++++).

IHC stains were performed utilizing a Leica Bond MAX IHC automatized platform (Buffalo Grove, Illinois, USA) using Novolink™ detection with Compact Polymer™ technology. Specifically, for primary staining we utilized a Bond Max platform autostainer with bond polymer refined Red detection DS9390, an alkaline phosphatase linker polymer and fast red chromogen (red staining). For our secondary staining, we utilized bond polymer refined detection DS9800, a horseradish peroxidase linker polymer and DAB chromogen (brown staining). The staining was performed as previously described. Positive and negative controls were consistently performed. We used mouse anti-human monoclonal Dako (Carpinteria, California, USA) antibodies to HLA-DPDQDR antigen (clone CR3/43), complement/C5b-9/MAC (clone aE11) and metallothionein (clone E9).

Examination of the H&E tissue sections demonstrated a dense lymphohistiocytic infiltrate located along the dermal/epidermal junction. In addition, occasional Civatte body necrotic keratinocytes were present within these areas (Fig. 1). A subepidermal blister was seen. The results of the DIF are shown in Table 1 and are also shown in Figure 1.

The IHC showed strong positive staining along the entire BMZ with metallothionein, being stronger in

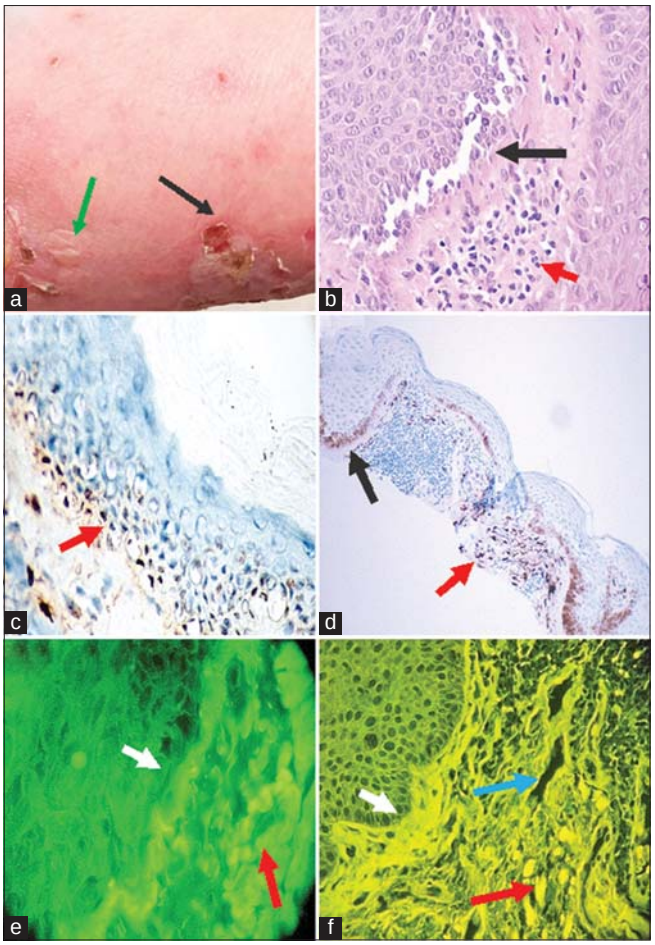

Figure 1: (a-b) H&E staining at 200 and 400X respectively, showing some basal layer involvement with some basement membrane zone separation(black arrows) and an inflammatory infiltrate in the upper dermis (red arrows). c. IHC positive staining at the BMZ using C5b-9/MAC (dark staining, red arrow; 400X). d. IHC showing positive staining with metallothionein at the BMZ (black arrow), but also in the upper dermal inflammatory infiltrate (red arrow; 100X). e. DIF positive staining at the BMZ (white arrow), as well as against the upper dermal inflammatory cells using FITC conjugated anti-human IgG (red arrow). f. DIF positive staining for IgG at the BMZ (white arrow), against upper dermal blood vessels (blue arrow) and involvement of individual cells including the presence of cytoid bodies(red arrow; 400X).

Table 1: DIF Results

Catalog no., antibody, dilution	Results
F0202-2.Polyclonal rabbit anti-human IgG FITC, 1:20 dil, Agilent Dako.	Positive linear deposits at the BMZ junction (+++), and also positive clumps in the superficial dermis, resembling those seen in lichen planus (+++.)
F0203-2. Polyclonal rabbit anti-human IgM FITC, 1:20 dil, Agilent Dako.	Negative
F0204-2.Polyclonal rabbit anti-human IgA FITC, 1:20 dil, Agilent Dako.	Negative
F020102-2.Polyclonal rabbit anti-human C3 FITC, 1:20 dil, Agilent Dako.	Positive granular deposits at the BMZ junction) (+).
F0111-02. Polyclonal rabbit anti-human Fibrinogen FITC, 1:40 dil, Agilent Dako.	Positive linear stain deposit at the BMZ (++).
D2030-02. Anti-human IgD FITC, dil 1:25, Southern Biotech.	Positive linear deposits at the BMZ junction (++), and also positive clumps in the upper superficial dermis, resembling those seen in lichen planus (++).
F0117-2.Polyclonal rabbit anti-human Albumin FITC 1:40 dil, Agilent Dako	Positive linear deposits at the BMZ (+++), and also positive clumps in the superficial dermis, resembling those seen in lichen planus (+++).
SKU 104202 Anti-human IgE, FITC 1:25 dil, Low F/P - 2-4.9, from Kent Laboratories.	Negative
F0254-2. Polyclonal rabbit anti-human C1-q FITC, 1:20 dil, Agilent Dako.	Negative
Negative control	Negative

some areas of the BMZ and also strong positivity with C5b-9/MAC. We also observed positive staining in the dermal infiltrate with HLA-DPDQDR antigen.

DISCUSSION

It has been previously described that patients with classic lichen planus who later experience subepidermal blisters on the trunk and extremities are clinical features consistent with lichen planus pemphigoides [1-3]. Usually the histopathology of LPP is categorized by typical findings of a lichenoid tissue reaction with subepidermal bullae and linear deposits of IgG and C3 along the basement membrane zone on DIF of peri-bullous skin. Immunofluorescence of perilesional skin shows usually linear deposits of C3 along the dermoepidermal junction or BMZ [3]. The patient IgG autoantibodies have been shown to be directed to the 180 kD bullous pemphigoid antigen (BPAG2, Type XVII collagen) using immunoblotting. Interestingly, we also detected positive patchy staining with metallothionein and C5b-9/MAC at the basement membrane zone of the skin. Our findings attest to the similarity of immunopathology in these two subepidermal blistering skin diseases. The pathogenesis of LPP is partly explained. Some authors hypothesize that a primary inflammatory process by lichen planus causes the release and exposure of other molecules that were not initially recognized as antigens by the immune system, possibly leading to epitope spreading and/or to a secondary autoimmune response against the BMZ. These circulating autoantibodies may then induce a secondary, subepidermal bullous dermatosis. Further, previous authors described the presence of LPP in a patient whom later presented with herpes gestationis [10]. In this case, the distension of the abdominal surface may have exposed new antigens.

LPP has been also associated with chronic hepatitis B virus infection, as documented in lichen planus [11].

We searched for studies that investigated mononuclear cells in an LPP infiltrate, and found very few studies. Here we include the best study and their results: mean percentage of positively stained dermal-infiltrating cells were shown to be a mix of CD8 and CD20, followed by minor percentages of CD3, CD4 and FOXP [12]. These authors noted that the cell infiltrate were a combination of cells previously documented in lesional areas of bullous pemphigoid and lichen planus, indicating that LPP is a unique nosologic entity.

Our DIF findings also show a clear mix of the pertinent disease features, with cytoid bodies of lichen planus, the BMZ involvement and the dermal band staining; our findings are similar to those described by others [13], with the addition of the strong immunofluorescence features in the dermal band and cytoid bodies.

In our case, we also note the lesional presence of C5b-9/MAC at the BMZ in this case of lichen planus pemphigoides. The presence of complement C5b-9/MAC has also been recently detected in patients affected by endemic pemphigus foliaceus in El Bagre, Colombia, South America in skin biopsies correlating with disease severity and previously established serologies [14]. It would be of interest to study for the presence of C5b-9/MAC in a larger series of patients affected by this disease. Recently, several groups have shown the presence of metallothionein expression in lichen planus epithelial and inflammatory cells. These authors suggested an extensive anti-apoptotic response in the keratotic form of the disease [15]. Thus, the roles of C5-b9/MAC and metallothionein in LPP warrant further studies.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Source of Support: Nil, **Conflict of Interest:** Georgia Dermatopathology Associates (GDA).

Our Dermatology Online

Case Report

Facial actinic lichen nitidus in a geriatric Tunisian female

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ABSTRACT

Actinic lichen nitidus (ALN) is an unusual variant of lichen nitidus (LN) appearing only on photo-exposed areas. It is usually seen in deeply pigmented adult and pediatric patients with a history of significant sun exposure during the summer months. We report an atypical case of facial ALN in a geriatric Tunisian female with a one-year history of facial pruritic lesions marked during the summer months. A histologic examination was suggestive of lichen nitidus, and the diagnosis of ALN was reached. ALN is a photoinduced lichenoid eruption that shows the classical histologic features of lichen nitidus with a degree of clinical similarity. Only five cases of exclusively facial lesions have been reported. This type of dermatosis occurs commonly in pediatric patients and young adults. ALN affects preferentially individuals of darker skin tones. Only one case of ALN in a patient of a lower Fitzpatrick skin phototype, as our case, had previously been reported.

Key words: Lichenoid Eruptions; Lichen nitidus

INTRODUCTION

Lichen nitidus (LN) is an inflammatory skin disorder most commonly occurring in children. Its etiology remains unknown [1]. Actinic lichen nitidus (ALN) is an unusual variant of LN that appears only on photo-exposed areas [2]. It is usually seen in deeply pigmented adult and pediatric patients with a history of significant sun exposure during the summer months [2-4]. It was previously reported as a summertime actinic lichenoid eruption and lichen nitidus actinicus [4]. This entity appears to be an underrecognized disease in the north of Africa [4]. We report an atypical case of facial ALN in a geriatric Tunisian female.

CASE REPORT

A 62-year-old Tunisian female presented herself at our Dermatology Department with a one-year history of facial pruritic lesions marked during the summer months. A physical examination revealed numerous symmetrically distributed, flesh-colored, shiny papules associated with brownish erythematous plaques on the forehead, cheeks, nose, and chin, sparing the frontal hairline, vertical forehead folds, nasolabial folds, upper eyelids, and the area of the upper lip shaded by the nose. The patient's Fitzpatrick phototype was III (Fig. 1). The rest of the examination—mainly of the hair, nails, and mucosas—were normal. A histological examination revealed a dense granulomatous lichenoid infiltrate filling the papillary dermis and being bordered by elongated epidermal rete ridges in a "ball-in-a-claw" pattern. The epidermis was slightly thinned with an orthokeratotic stratum corneum and focal parakeratosis (Fig. 2). This aspect was suggestive of LN. The patient was treated with topical corticosteroids and photoprotection with partial remission.

DISCUSSION

ALN is a photoinduced lichenoid eruption that shows the classical histologic features of lichen nitidus with a degree of clinical similarity. It appears only on photo-exposed areas [2]. It was first reported in India in 1978 by Bedi, who described 25 patients with hypopigmented

How to cite this article: Ameur K, Soua Y, Njim L, Belhadjali H, Youssef M, Zili J. Facial actinic lichen nitidus in a geriatric Tunisian female. Our Dermatol Online. 2020;11(4):371-372.

Submission: 10.12.2019; **Acceptance:** 11.02.2020

DOI: 10.7241/ourd.20204.9

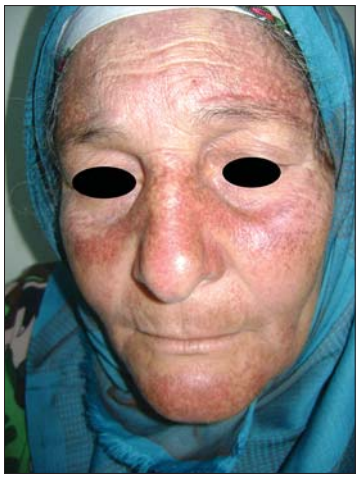

Figure 1: Multiple shiny flesh-colored papules associated with brownish erythematous plaques distributed on the face.

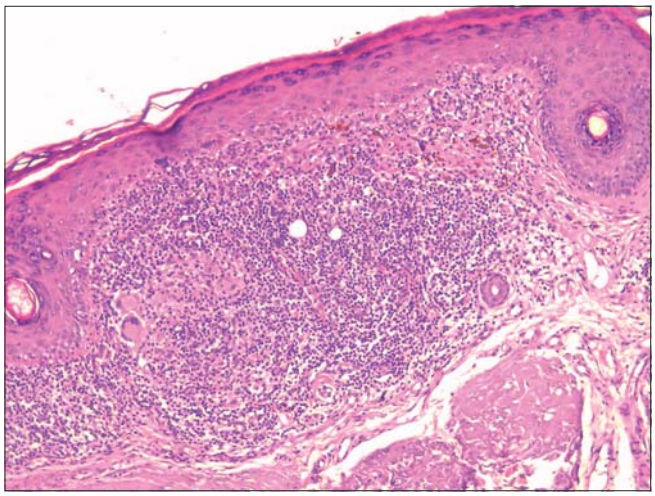

Figure 2: A dense granulomatous lichenoid infiltrate embraced by rete ridges under a thinned epidermis (H&E, 200×).

pinpoint papules in sun-exposed areas and named the entity a summertime actinic lichenoid eruption [5]. The term of ALN was proposed in 1991 by Kanwar et al., who described six children with this clinical presentation [6].

Since then, short series of patients with the same clinical presentation have been reported [2,3]. This dermatosis occurs commonly in pediatric patients and young adults. Most of the reported cases of ALN have described lesions on the forehead, dorsum of the hands, and the V area of the neck [7]. Only five cases of exclusively facial lesions have been reported [4,7].

ALN affects preferentially individuals of darker skin tones (Fitzpatrick skin types IV and V) from Africa, America, the Middle East, and India [2]. The only case of ALN in a patient of a lower Fitzpatrick skin phototype, as our case, was reported by Solano-Lopez in a Caucasian European patient [2]. The differential diagnosis includes actinic folliculitis, sarcoidosis, and mucinosis. The diagnosis of ALN is confirmed by a histopathological examination, which reveals the characteristic aspects of LN [3]: a dense, well-circumscribed, subepidermal infiltrate, sharply limited to one or two adjacent dermal papillae in a "ball-in-a-claw" pattern. Giant cells are sometimes present. A true granuloma may occasionally be found, although caseation is never present [5,6]. The treatment of ALN is based on local corticosteroids and photoprotection. One patient has been successfully treated with hydroxychloroquine [4].

CONCLUSION

This case highlights the existence of this entity in individuals of lower Fitzpatrick skin phototypes.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

Linear scleroderma following an intralesional steroid: Was it coincidental?

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ABSTRACT

A 23-year-old female presented herself with a gradual hardening of the skin over the left arm and forearm present for eight months prior. The hardening appeared one month following an intralesional steroid in the left epicondyle area administered for pain and swelling at the site, which were present for three months and associated with painful swelling over the left hand. An examination revealed a depigmented patch over the left lateral epicondyle along with shiny, yellowish, indurated, and hypopigmented to skin-colored plaque extending from the midarm to the wrist over the posterolateral aspect of the upper left extremity. A histopathological examination revealed features suggestive of scleroderma. The patient was diagnosed with linear scleroderma and treated with methotrexate and hydroxychloroquine with significant improvement after six weeks.

Key words: Steroid; Scleroderma; Hypopigmentation

INTRODUCTION

Corticosteroids are the mainstay of the treatment of scleroderma. Out of the many side effects of intralesional steroids—including hypopigmentation, skin atrophy, hypertrichosis, and telangiectasia—skin sclerosis and scleroderma have not yet been reported. Herein, we report a case of linear scleroderma, which appeared one month following an intralesional injection of a corticosteroid. Whether it was because of the steroid itself or because of its indirect inducement remains unknown.

CASE REPORT

A 23-year-old female presented herself with a gradual hardening of the skin over the left arm and forearm present for eight months prior. The hardening appeared one month following an intralesional steroid—40 mg triamcinolone acetonide—in the left epicondyle area administered for pain and swelling at the site, which had been present for three months since the injection. This was associated with a painful swelling of the left hand along with the weakness of the left hand, mainly the left ring finger. There was no history of Raynaud's phenomenon or other systemic symptoms. An examination revealed a depigmented patch 3 × 2.5 cm in size over the left lateral epicondyle, adjacent to several scaly papules coalescing into a plaque, along with a shiny, yellowish, indurated, and hypopigmented to skin-colored plaque extending from the midarm to the wrist over the posterolateral aspect of the upper left extremity. A tender swelling 5 × 7.5 cm in size was present over the dorsum of the left hand with normal overlying skin but with weakness in the extension of the middle and ring fingers (Figs. 1 – 3). A systemic examination was normal. A histopathological examination revealed a marked increase in collagen with a paucity of adnexal structures in the dermis and dermal collagen intersecting into the subcutaneous fat, which are features suggestive of scleroderma (Fig. 4). An immunofluorescence assay for antinuclear antibody (ANA) was positive (1+), with cytoplasmic patterns with a titer of 1:80. The level of serum vitamin D was

How to cite this article: Bachaspatimayum R, Vikram Singh S. Linear scleroderma following an intralesional steroid: Was it coincidental? Our Dermatol Online. 2020;11(4):373-375.

Submission: 12.06.2020; **Acceptance:** 17.08.2020

DOI: 10.7241/ourd.20204.10

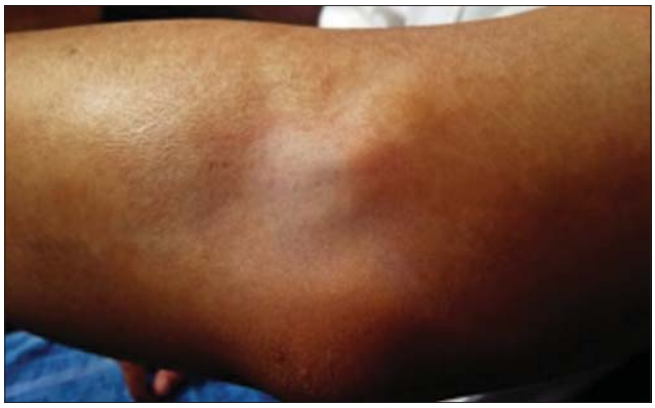

Figure 1: A depigmented irregular patch 3 × 2.5 cm in size over the left lateral epicondyle.

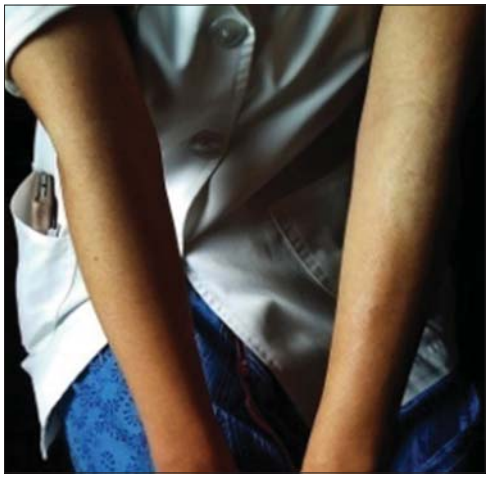

Figure 2: A shiny, yellowish, indurated, and hypopigmented to skin-colored plaque extending from the midarm to the wrist over the posterolateral aspect of the upper left limb.

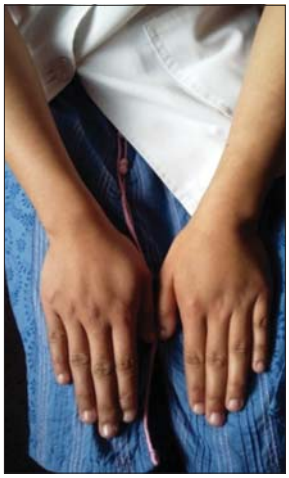

Figure 3: A tender swelling 5 × 7.5 cm in size over the dorsum of the left hand with normal overlying skin.

insufficient (26 ng/mL). Other routine investigations—including anti-dsDNA (anti-double stranded DNA) antibodies, anti-centromere antibodies, and an X-ray

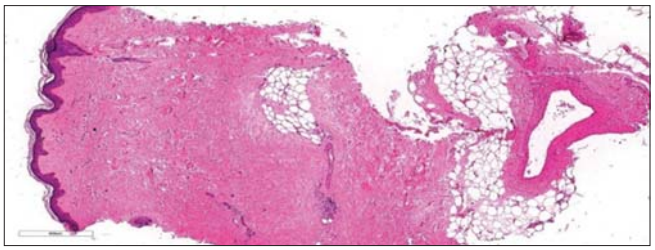

Figure 4: A histopathological examination showing a marked increase in collagen with a paucity of adnexal structures in the dermis and dermal collagen intersecting into the subcutaneous fat, revealing features suggestive of scleroderma (H&E, 10×).

Figure 5: The last follow-up (one year after) with significant softening of the induration and repigmentation of the depigmented areas of the plaque.

of the left hand in an anteroposterior and lateral view—were normal. The patient was diagnosed with linear scleroderma and treated with oral methotrexate 15 mg/week, hydroxychloroquine 200 mg BD, and 0.1% topical tacrolimus BD with significant improvement by week four (skin softening and repigmentation of the depigmented and hypopigmented areas) with regular monitoring of the hematocrit and liver function. However, the brownish discoloration without skin tightening began to expand over the left shoulder by the second month and stopped after three weeks. The patient is still on regular follow-ups with no significant adverse effects. Fig. 5 shows the clinical photograph after one year of treatment when significant softening of the induration was found along with repigmentation of the depigmented areas of the plaque.

DISCUSSION

A systematic review of literature by Brinks et al. [1] lists the dermal adverse events of local corticosteroid injections to include irritation, changes

in skin color, skin and perilymph atrophy, soft tissue calcification, skin defects, hypopigmentation, sterile abscesses, ecchymosis, and allergic rash, and the infectious adverse events to include cellulitis, localized abscesses, septic bursitis, atypical mycobacterium infections, necrotizing fasciitis, and protothecosis. The local adverse events include local pain, tingling or numbness in the hands, local neural damage, and tendon rupture, and the systemic adverse events include allergic reactions, facial flushing, and disturbance of the menstrual pattern. Hypopigmentation and skin atrophy can occur following local steroid injections, although the mechanism by which hypopigmentation occurs is unclear [2]. Physical injury, including local injections, has also been described as a possible provoking factor of localized scleroderma [3]. Skin induration can also occur, besides systemic sclerosis, in localized forms of scleroderma as well as in conditions unrelated to scleroderma or systemic sclerosis, classified as scleroderma variants. These conditions are rarely associated with sclerodactyly or Raynaud's phenomenon, and autoantibody formation does not occur [4]. In our case, the assay for ANA, although positive, was insignificant. Thus, whether the onset of the disease after the steroid injection was coincidental or was provoked by trauma from the injection is yet to be elucidated, although the latter seems likely. In systemic sclerosis, microvascular injury is a very early event and the same changes may occur in morphea [5]. Mechanical injury may have caused vascular endothelial damage and neuronal injury, which could have contributed to the development of trauma-induced scleroderma [3]. In any case, we recommend further research in this pursuit.

CONSENT

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

Improvement of linear scleroderma of the limbs after treatment with long-pulsed 1064 nm Nd:YAG laser: A case report

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ABSTRACT

Linear scleroderma is a variant of localized scleroderma characterized by longitudinal bands of dense scleroatrophic skin sometimes causing deformities of the upper and lower extremities. Some case reports on small groups of patients suggest benefits of lasers in patients with localized scleroderma. We report a case of a twelve-year-old female with a two-year history of linear scleroderma on the right lower limb treated with 1064-nm long-pulsed Nd:YAG laser with successful results. Laser therapy may be a promising tool in the treatment of linear scleroderma.

Key words: Linear scleroderma Nd:YAG 1064 nm laser

INTRODUCTION

Linear scleroderma is a rare variant of localized scleroderma involving the superficial and deeper layers of the dermis usually beginning in childhood [1]. Fibrosis of the dermis and subcutaneous tissue leads to induration and shrinking of the skin. Depending on the extent of the lesions and the level of fibrosis, muscle and underlying bone may be affected and flexion contractures may occur. Changes in collagen tissue in these localized cases are very similar to cases of scleroderma but without visceral involvement.

No specific treatment is available for linear scleroderma.

CASE REPORT

A twelve-year-old female presented herself at our office with a two-year history of skin hardening on the right lower limb with pigmentary changes (Fig. 1). Complete blood count, the erythrocyte sedimentation rate, urinalysis, and liver and kidney function were normal. Antinuclear antibodies were negative. A physical examination revealed a firm diffuse sclerotic band with blotchy hyperpigmentation extending from the anterior aspect of the thigh to the lower part of the right leg.

A biopsy of the lesions showed a histological pattern of scleroderma with bundles of eosinophilic collagen throughout the reticular dermis and intimal thickening, narrowing, and obliteration of vessels (Fig. 2).

The patient and the patient's relatives were informed of the self-limiting character of the disease, but all insisted on treatment, considering the disfiguring aspect of the disease. Still, no treatment protocol for linear scleroderma exists. Several topical treatments, such as corticosteroids and pimecrolimus, were unsuccessful, with the plaque continuing to increase in area and becoming increasingly hardened. Taking into consideration the patient's young age, treatments based on methotrexate, systemic corticosteroids, and PUVA therapy were not recommended.

How to cite this article: Bimbi C, Koumoundourou D, Kyriakou G, Brzezinski P. Improvement of linear scleroderma of the limbs after treatment with long-pulsed 1064 nm Nd:YAG laser: A case report. Our Dermatol Online. 2020;11(4):376-378.

Submission: 27.12.2019; **Acceptance:** 27.04.2020

DOI: 10.7241/ourd.20204.11

Table 1: Comparison of two treatment methods

Treatment	Wavelength	Spot size	Pulse duration	Fluence	Cooling	Tx Interval
LimeLight	520 to 1100 nm	10x30 mm	B	8 to 11 J	5oC	MONTHLY
Genesis	1064 nm	5 mm	0,8 ms	14J	NO	MONTHLY

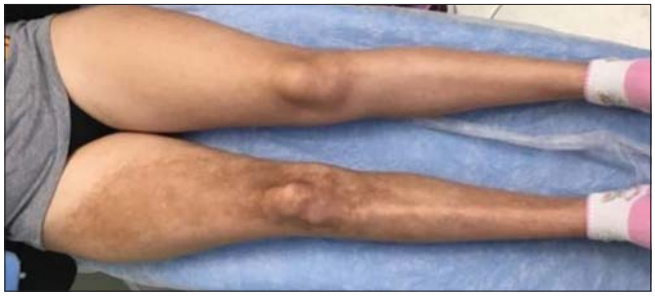

Figure 1: A wide, thick sclerotic band with blotchy hyperpigmentation extending from the anterior aspect of the thigh to the lower part of the right leg.

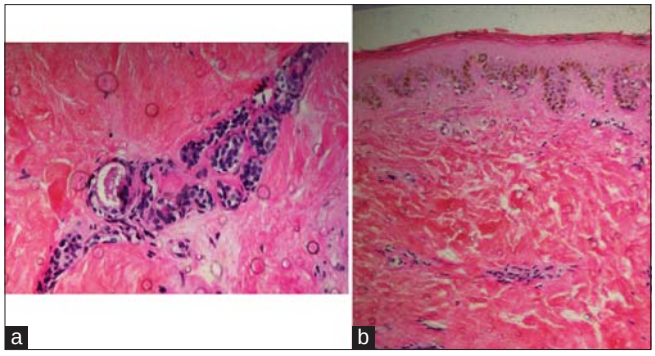

Figure 2: (a) A biopsy from the thigh showing thickened eosinophilic collagen bundles throughout the reticular dermis. (b) Lymphocyte infiltration around blood vessels and progressive vascular injury with persistent endothelial damage and narrowing and obliteration of vessels.

Sessions of 1064-nm YAG laser (Genesis) 14 J/cm2 with a 5-mm spot started with monthly intervals associated with pulsed light (LimeLight) 8–11 J/cm2, especially for hyperchromic parts (handpiece part of the Xeo Laser portable platform). Five laser sessions were performed (Table 1).

DISCUSSION

Although patients often receive good prognoses and spontaneous remission, linear morphea of the extremities may be accompanied by physical disability and limb length discrepancies when the underlying soft tissue and bone are involved. With the passage of time, the sclerotic bands may become thicker affecting the underlying tissues, specifically the fascia and musculature. In these cases, flexion contractures may occur resulting in the unaffected leg growing faster than the other. MRI of children with unilateral scleroderma

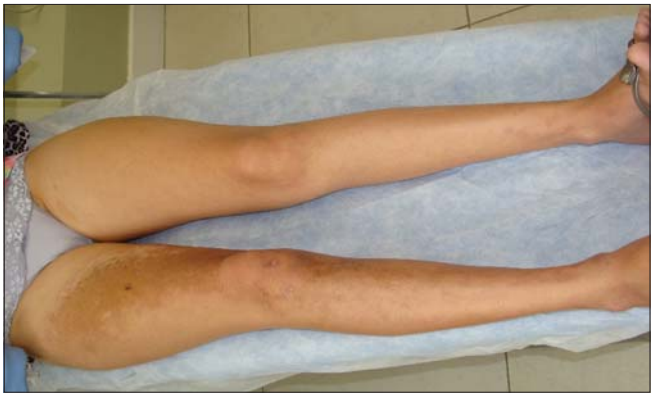

Figure 3: A follow-up five months later after five sessions, demonstrating softening of the plaques and improved mobility on the thigh to the lower part of the right leg area.

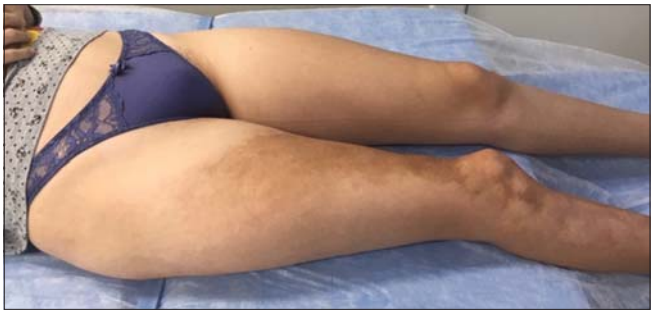

Figure 4: Six months after the last laser session showing the effects of the physical fitness exercises that were to normalize the muscles of the thigh and leg.

sometimes shows fascia thickening and deep tissue abnormalities in the extremities [2]. Any change in the size of the limbs may be permanent.

Presently, there is still no single, reliable, and effective treatment protocol for linear scleroderma. Given that physiotherapy may be effective in limiting disease progression and prevent the appearance of contractures, the young patient was advised to engage in physical fitness activity [3,4].

Although the use of laser is not yet enshrined in linear sclerosis, it has already been demonstrated to be very effective in organizing collagen tissue in scars, being also an effective modality in the treatment of morphea [5,6]. 1064-nm long-pulsed Nd:YAG laser suppresses collagen production and flattens keloids, as demonstrated by Abergel on cultures of keloid fibroblasts [7].

We started sessions of 1064-nm Nd:YAG laser 15 J/cm2 with a 5-mm spot. After a total of five treatments with this technique, the patient showed a good improvement (Figs. 3 and 4). The treated skin became more pliable, while the plaques softened and restored their mobility nearly to that of normal skin. Pulsed light was immensely effective and was also used especially in the treatment of the hyperchromic parts. Pigmented cells are denatured and epidermal melanin first darkens and, after three days, tends to diminish.

The patient has been followed up now for two years since the procedure. In this report, we investigate the benefits of 1064-nm Nd:YAG laser (Genesis, Cutera Inc.) applied in a noncontact mode on linear scleroderma resulting in visible clinical improvement.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

Linear lichen sclerosus of the face

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ABSTRACT

Lichen sclerosus (LS) is a chronic inflammatory disease of unknown origin that mostly affects women in their fifties and sixties and that commonly affects the anogenital region but may rarely present itself in extragenital areas. The most common locations of extragenital LS includes the neck, shoulder, and upper trunk. LS of the anogenital region is associated with an increased incidence of malignancies, which is not the case with extragenital LS. Herein, we report the case of a married 45-year-old female who presented herself to us with LS of the face of a linear pattern. Facial LS is quite rare and, even more so, in linear plaque patterns.

Key words: Extragenital; Facial; Follicular plugging; Lichen sclerosus; Linear

INTRODUCTION

Lichen sclerosus (LS) is a chronic inflammatory disease of unknown origin that mostly affects women in their fifties and sixties, although it may occur in men and children [1]. LS commonly affects the anogenital region, quite rarely presenting itself as an isolated extragenital lesion [2]. Extragenital lichen sclerosus (ELS) is most common on the neck, shoulders, and upper trunk. However, a linear distribution of ELS lesions is rare [3].

The etiology of LS remains unclear but strong evidence indicates that an autoimmune mechanism may play a significant role. LS is also characterized by genetic susceptibility [2]. LS of the anogenital region is associated with an increased incidence of malignancies, especially vulvar squamous cell carcinomas. The lifetime risk of developing this type of carcinoma is approx. 5%. However, no such risk is noted in ELS and LS in children [4].

The mainstay of treatment is still potent and ultrapotent topical corticosteroids. Other modalities include topical calcineurin inhibitors, topical and systemic retinoids, phototherapy, and photodynamic therapy [2].

Herein, we report a case of lichen sclerosus of the face that presented itself in a linear pattern, which has not been reported, to date, in Nepal.

CASE REPORT

A 45-year-old Nepali female presented herself with a single mildly pruritic linear plaque gradually increasing over the right temporal face for the last six months. The atrophic plaque extended from the right temple up to the angle of the mandible. Neither scaling nor surrounding hyperpigmentation was noted. There was no history of chronic illness.

On physical examination, a linear slightly atrophic plaque with prominent follicular plugging was noted along the right temporal-mandibular region. Cicatricial alopecia was also noted over the lesional skin of the temple (Fig. 1).

A histopathological examination of the skin from the center of the lesion revealed thinning of the epidermis with a lamellated keratin layer with areas of follicular plugging. The basement membrane was delicate. The dermis was relatively thickened. The focal areas

How to cite this article: Parajuli N, Poudel P, Tiwari S, Karki A. Linear lichen sclerosus of the face. Our Dermatol Online. 2020;11(4):379-381.
Submission: 08.02.2020; **Acceptance:** 16.04.2020
DOI: 10.7241/ourd.20204.12

in the lower dermis showed lymphocytic aggregates adjacent to hair follicles. Sparse hair follicles and a few horn cysts were seen in the upper dermis (Fig. 2). A diagnosis of lichen sclerosus was reached and the patient was started on a potent topical corticosteroid. A slight improvement was noted after two weeks. The patient was advised to attend regular follow-ups, but failed to do so.

DISCUSSION

While extragenital LS is not an uncommon entity, facial involvement is rare. There have been only a handful of cases of LS of the face mentioned in the literature [5-10]. Exclusive extragenital LS was reported to occur in up to 15% of patients [5].

The cause of LS is still largely unknown, but recent evidence points toward autoimmunity and genetic predisposition [2]. There is a slight increase in the risk of malignant transformation of genital LS, which is not the case with children as well as with ELS [4]. Although the exact prevalence of LS is unknown, it is more common in females, with a male-to-female ratio of 1:6, and may occur at any age [6]. Clinically, LS presents itself as macules, papules, or shiny white plaques with follicular corneal plugs [11]. The area may evolve into a dry, hypopigmented, or sclerotic, and later atrophic lesion. The resulting crinkling or cellophane paper-type appearance is pathognomonic of lichen sclerosus [2].

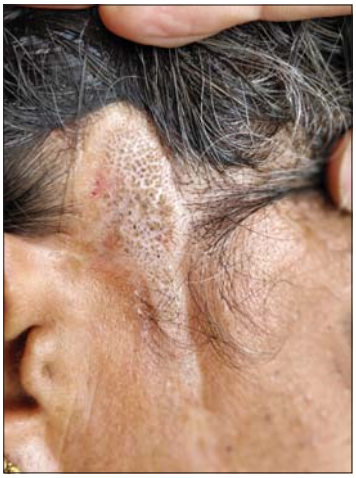

Figure 1: A linear plaque with prominent follicular plugging at the right temporal region of the face.

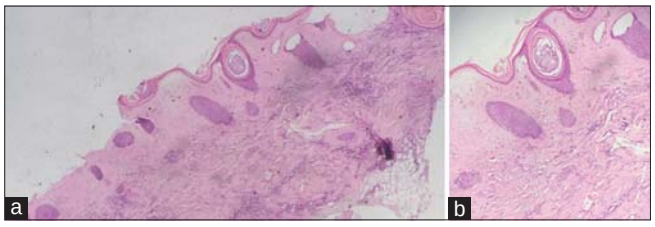

Figure 2: (a) A histopathological examination of the skin showing prominent lamellated keratin with areas of prominent follicular plugging (H&E, 40×). (b) A thinned epidermis with hyperkeratosis at higher magnification; the dermoepidermal junction showing sparse lymphocytic infiltration and a homogenized band of dense collagen in the upper dermis; focal areas in the lower dermis showing lymphocytic aggregates adjacent to hair follicles (H&E, 100×).

LS is mostly a clinical diagnosis. Because it may sometimes be confused with morphea, a histopathological examination is important to differentiate the two. LS has a characteristic histological pattern. The epidermal changes include hyperkeratosis, follicular occlusion, thinning of the epidermis, and vascular alterations in the basal layer. Subepidermal edema with homogenization of collagen, sclerosis, and dilation of small vessels with hemorrhage are also noted. A diffuse perivascular infiltrate of lymphocytes appearing under the edema may occur in the middle third of the dermis [12].

First-line treatment of LSA includes potent and ultra-potent topical corticosteroids. Second-line therapies include topical calcineurin inhibitors. Systemic agents include oral steroids, retinoids, and cyclosporine, and may be of some use [13].

CONCLUSION

This is the first case of linear ELS reported in Nepal. LS may be confused with morphea or discoid lupus due to the presence of follicular plugging and atrophy. A proper examination and a biopsy help to differentiate between these conditions.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

Isolated unilateral lichen sclerosus of the sole

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ABSTRACT

Extragenital involvement in lichen sclerosus is uncommon. Involvement of the palms and soles is very rare, with lichen sclerosus almost always showing elsewhere on the body. We describe the case of a female child with a linear hyperpigmented plaque on the right sole studded with keratotic papules. Dermoscopy showed scales and keratin plugs with surrounding pigmentation. Histopathology showed features of lichen sclerosus. This report describes a very rare occurrence of unilateral and isolated involvement of the sole with lichen sclerosus and its dermoscopic findings.

Key words: Lichen sclerosus; Lichen sclerosus et atrophicus; Dermoscopy; Follicular plugging

INTRODUCTION

Lichen sclerosus, also known as lichen sclerosus et atrophicus, is a chronic inflammatory disease that commonly affects the genitals. Extragenital involvement is seen in around 15–20% of cases [1]. Isolated involvement of the palms or soles is extremely rare. Herein, we report a case of isolated unilateral lichen sclerosus of the sole in a female with dermoscopic and histopathological findings of this rare presentation.

CASE REPORT

A ten-year-old female presented herself to us with asymptomatic discoloration on the right sole persistent for the last eight months. On examination, a linear atrophic hyperpigmented plaque 5 cm × 2 cm in size was present on the right sole, extending from the midfoot to the proximal part of the heel (Fig. 1). The plaque was studded with small keratotic papules. The rest of the cutaneous examination, including the genitals, was normal. Dermoscopy of the plaque showed scaling and keratin plugs surrounded by a rim of pigmentation and scales (Fig. 2). Histopathology of the area showed hyperkeratosis, flattened rete ridges, homogenous and hyalinized dermal collagen, adnexal plugging, and a mild chronic superficial inflammatory infiltrate (Fig. 3). Based on these findings, a diagnosis of lichen sclerosus of the sole was reached.

DISCUSSION

Lichen sclerosus (LS) is a benign chronic inflammatory disease of unknown etiology with a clear female preponderance [2]. Autoimmunity, trauma and chronic irritation, genetic factors, hormonal influences, and infections have been proposed as the pathogenesis of the disease [3]. LS commonly affects the genitals and manifests itself as severely pruritic porcelain-white plaques with erosions, fissures, and atrophy, often leading to deformity of the external genitalia. On the extragenital areas, it presents itself as asymptomatic shiny white macules or plaques with follicular plugs. The common extragenital sites are the upper trunk, neck, arms, legs, ears, and nose [2]. Involvement of the palmoplantar skin is extremely rare and has almost always been described with lichen sclerosus also present on other areas [1-5]. The volar lesions have been described as papules and plaques ranging from white to erythematous and sometimes having keratotic papules on them [4].

How to cite this article: Adil M, Amin SS, Siddiqui B, Aijaz M, Mohtashim M, Mudassir M. Isolated unilateral lichen sclerosus of the sole. Our Dermatol Online. 2020;11(4):382-384.

Submission: 22.01.2020; **Acceptance:** 28.03.2020

DOI: 10.7241/ourd.20204.13

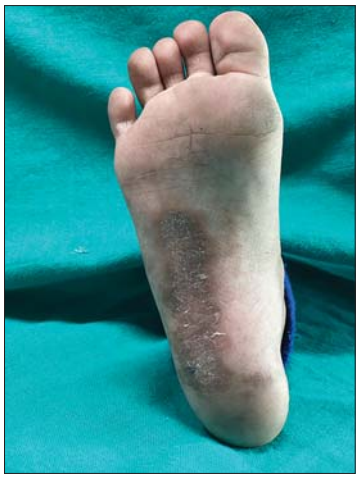

Figure 1: A linear atrophic plaque on the right sole.

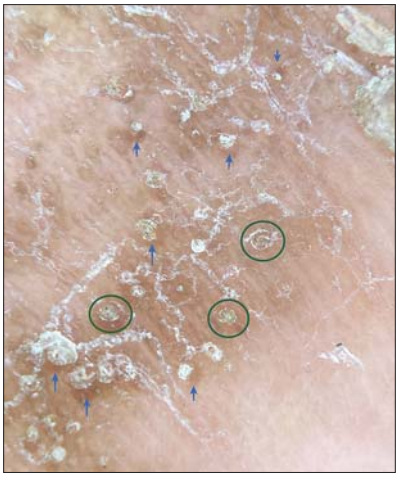

Figure 2: Polarized dermoscopy of the plaque showing scaling, adnexal plugs with pigment accentuation (blue arrow) and surrounding scales (green circles). (DermLite 4, 10×).

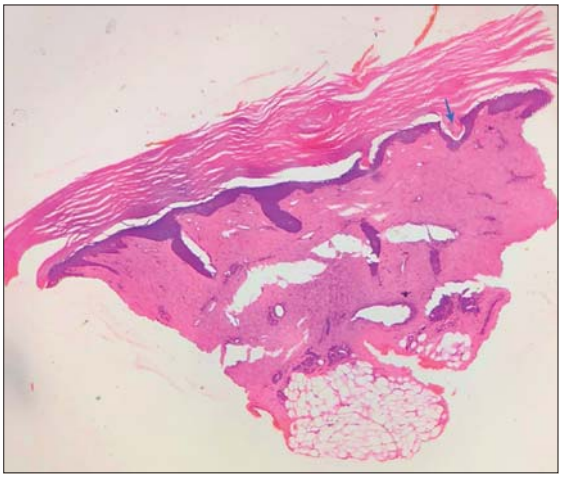

Figure 3: Hyperkeratosis and flattened rete ridges in the epidermis, homogenous and hyalinized dermal collagen with mild superficial chronic infiltrates in the dermis; adnexal plugging (blue arrow) seen at one end of the section (H&E, 40×).

Dermoscopy of extragenital lichen sclerosus reveals white structureless areas, comedo-like openings, comma vessels, hairpin-like vessels, and dotted vessels [6,7]. A dermoscopic examination of a palmoplantar location has probably never been done. While we found comedo-like openings, white structureless areas or vessels were not observed. This could have been due to the thickness of the volar skin. The presence of comedo-like openings is interesting as hair follicles are absent from the volar skin. However, keratotic papules on the palms in lichen sclerosus have been described [4]. We believe that these might be due to plugging of other skin adnexa.

Histopathology of lichen sclerosus shows hyperkeratosis, thinning of rete ridges, basal cell vacuolization, homogenous collagen, superficial perivascular infiltrate, and follicular plugging.

The differential diagnosis in our case included lichen sclerosus, morphea, lichen planus, and punctate palmoplantar keratoderma. Lichen planus is extremely itchy and shows colloid bodies and band-like infiltrates. Punctate palmoplantar keratoderma does not show epidermal atrophy, adnexal plugs, or an inflammatory infiltrate in the dermis. Morphea does not show adnexal plugging or basal cell degeneration. Although morphea and lichen sclerosus are considered two separate disease entities, some controversy still lingers around the two being different facets of the same disease, with coexistent lesions and one transitioning into the other [8].

The treatment of lichen sclerosus includes high-potency topical steroids, other immunomodulators, systemic retinoids, estrogen, and phototherapy, but the recurrence rate is high [9]. Surgical modalities may be needed in the case of stricture and deformity of the genitals.

We present a case of isolated unilateral lichen sclerosus of the sole and describe the dermoscopic findings of volar lichen sclerosus, which, to the best of our knowledge, has not been done before.

Consent

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

Lichen simplex chronicus positive for C5b-9/MAC, IgD and C3c as a result of recurrent bacterial hair follicular unit infection

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ABSTRACT

Lichen simplex chronicus (LSC) classically results from chronic scratching, and is often associated with an underlying skin condition. A 20-year-old female presented with recurrent inflammatory itchy papules and pustules, and thickened plaques for over six months duration on her arms. The patient had no clinical history of acne or rosacea. Skin biopsies demonstrated focal spongiosis and parakeratosis within the epidermis and histologic evidence of LSC. Gram positive bacteria were observed inside the sebaceous glands. DIF in the hair follicles was positive for IgD and C3c. IHC positivity with HLA-ABC and C5b-9/MAC was seen in the same areas. Our case illustrates how a chronic bacterial folliculitis may create an ongoing cycle of chronic inflammation and the case needs to be further investigate. In addition, it illustrates the importance of utilizing DIF and IHC in addition to H&E review in cases of LSC with obscure etiologies.

Key words: Hair follicle inflammation; lichen simplex chronicus; IgD; HLA-ABC; C5b-9; Gram positive

Abbreviations: Hematoxylin and eosin (H&E), immunohistochemistry (IHC), direct, immunofluorescence (DIF), basement membrane zone (BMZ), 4',6-diamidino-2-phenylindole (DAPI), Ulex europaeus agglutinin (Ulex), lichen simplex chronicus (LSC).

INTRODUCTION

Lichen simplex chronicus (LSC) may occur after chronic rubbing, eczema, lichen planus, stress, insect bites, dry skin, atopic dermatitis, neuropathies and amyloidosis, among many other conditions [1]. It is thus important to determine the etiology of each case of LSC.

CASE REPORT

A 20 year old female consulted a dermatologist, presenting with a greater than six month history of recurrent, erythematous papules and pustules on her arms with no clinical history of acne or rosacea. In addition, she presented with circumscribed pruritic plaques on the dorsal aspect of her arms. The patient described severe itching, and frustration because many previous physicians had believed that no underlying disease was present. Before her biopsies, ampicillin, Atarax® and mupirocin ointment had been prescribed with no improvement. She then decided to consult the dermatologist. Skin biopsies were obtained for hematoxylin and eosin(H&E) review, for immunohistochemistry (IHC) and for direct immunofluorescence (DIF) studies; these were performed as previously described [2]. No tissue culture was performed from the biopsies. After receiving the diagnosis, prednisone was given by for 3 weeks and did not help; fluocinonide ointment, 0.05% then provided improvement and relief for the patient.

How to cite this article: Abreu Velez AN, Jackson BL, Howard MS. Lichen simplex chronicus positive for c5b-9/MAC, IgD and C3c as a result of recurrent bacterial hair follicular unit infection. Our Dermatol Online. 2020;11(4):385-388.

Submission: 30.06.2020; **Acceptance:** 03.10.2020

DOI: 10.7241/ourd.20204.14

Skin biopsies were taken for hematoxylin and eosin (H&E) staining, direct immunofluorescence (DIF) and for immunohistochemistry (IHC); all were performed as previously described [2]. For DIF, we classified our findings as previously categorized [2], i.e., negative (-), weakly positive (+), positive (+++) and strongly positive (++++).

IHC stains were performed utilizing a Leica Bond MAX IHC automatized platform stainer (Buffalo Grove, Illinois, USA) using a Novolink™ detection with Compact Polymer™ technology. Specifically, for primary staining we utilized a bond polymer refined Red detection DS9390, an alkaline phosphatase linker polymer and fast red chromogen (red staining). For our secondary staining, we utilized bond polymer refined detection DS9800, a horseradish peroxidase linker polymer and DAB chromogen (brown staining). Positive and negative controls were consistently performed. We used anti-human monoclonal antibody to HLA-ABC antigen, clone W6/32, polyclonal rabbit anti-human IgD (code IR517), and C5B-9 (code M077) from Agilent-Dako (Carpinteria, California, USA).

Microscopic Description of the H&E tissue sections demonstrated focal spongiosis and parakeratosis within the epidermis. Evidence of LSC was present, with no ulceration. Within the dermis, a mild, superficial, perivascular infiltrate of lymphocytes and histiocytes with occasional eosinophils and mast cells was identified around blood vessels supplying the hair follicles (Fig. 1). A Gram stain confirmed the localized presence of Gram positive coccal bacteria in some BMZ and internal areas of the hair follicles and sebaceous glands.

DIF displayed the following results: IgG (++; dotted cell junctions in epidermal corneal keratinocytes), IgD and C3c (+++, scattered positivity within sebaceous gland lobules and hair follicle isthmus areas; colocalizing with both the Gram positive staining and the perifollicular infiltrate; +++); IgE (++), positive in the epidermal keratinocytes of the corneal layer, as well as inside the sebaceous glands. Opsonized bacteria were found inside the hair follicles, in areas positive for C3c and IgD (Fig. 1).

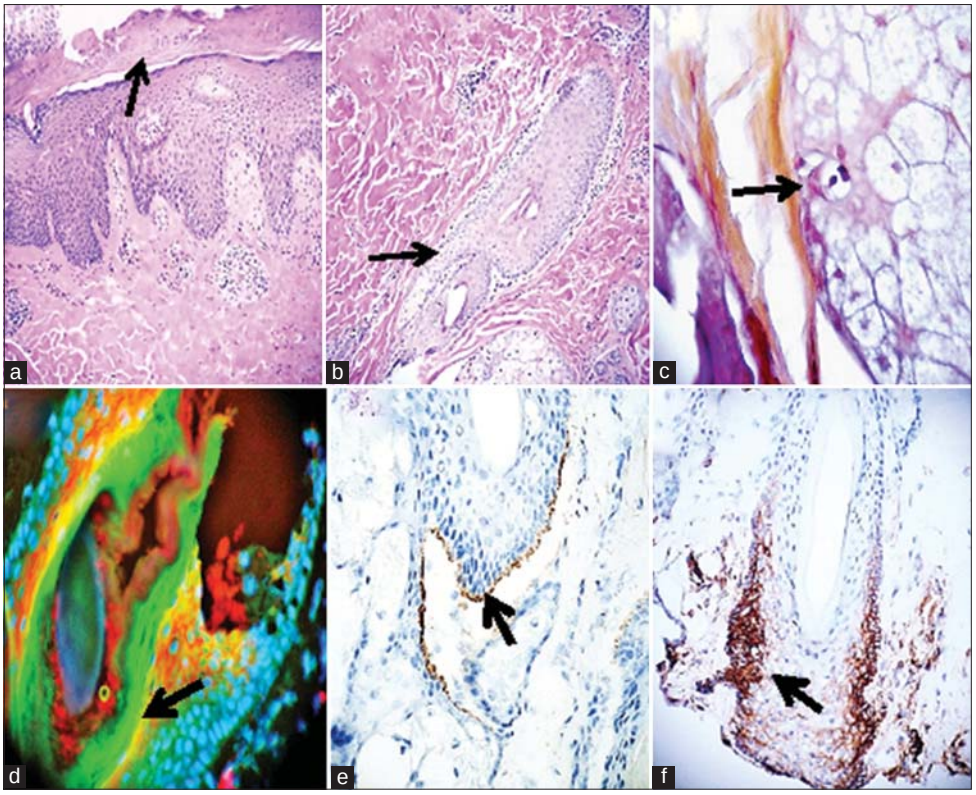

Figure 1: a and b. H & E staining. a) Evidence of LSC with hyperkeratosis of the epidermis (black arrow; 100X). b) Perifollicular inflammation (10X). c) Gram stain showing Gram positive bacteria (black arrow; blue staining; 400X). d) Positive DIF staining with FITC conjugated anti-human IgD antibody in the hair follicles near the bacteria (+++; green/yellow staining; black arrow). The red staining shows positive staining for *Ulex* and the blue staining represents counterstaining of cell nuclei with DAPI. e) IHC shows positive staining with C5b-9/MAC at the BMZ of the hair follicles (dark staining; black arrow). f) IHC staining, positive for HLA-ABC at the base of a hair follicle and its neurovascular supply vessels (brown staining; black arrow).

Complement C5b-9 was as well as HLA-ABC were positive in several spots in the basement membrane zone (BMZ) of the sebaceous glands as well as the BMZ of the hair follicles where the Gram-positive bacteria were seen (Fig. 1).

DISCUSSION

Lichen simplex chronicus (LSC) is a localized, well-circumscribed area of lichenification often resulting from repeated rubbing or scratching of the skin; it often results in tremendous patient discomfort and frustration. It occurs more in skin of patients affected by atopic, seborrheic and/or contact dermatitides, as well as psoriasis [1]. We present a case of chronic hair follicle inflammation induced by Gram positive bacteria. The infection resulted in strong reactivity via IgD and other immunoglobulins and complement that prolonged the subclinical inflammation. The hair follicles as well as the pilosebaceous units can be recurrently inflamed by infectious and parasitic entities. Not only in humans, but also in animals, often antimicrobial therapy is often given in superficial bacterial folliculitis but now knowing the underlying cause. One of the most common infections are seen due to *Demodex* mites, *Malassezia* spp [3-5]. Hookworms had been also associated with folliculitis [6]. Hair restoration using some synthetic fibers can also be cause of folliculitis [7].

We were able to confirm the small foci of Gram positive bacteria because the DIF and the IHC studies helped to localize them. IgD and C3c were the most consistently positive immune markers around the bacteria as well as in the perifollicular infiltrate. Of interest, both C5b-9/MAC and HLA-ABC were very positive in the area of the folliculitis and the inflammatory infiltrate. The terminal complement component [membrane attack complex (MAC)], A.K.A C5b-9. In some cases, it has been demonstrated that bacterial killing by complement requires direct anchoring of membrane attack complex precursor C5b-7. A significant effector role of the human complement system is to straight kill Gram-negative bacteria via Membrane Attack Complex (MAC) pores. MAC pores are assembled when surface-bound convertase enzymes convert C5 into C5b, which together with C6, C7, C8 and numerous copies of C9 forms a transmembrane pore that damages the bacterial cell envelope [8]. This may explain the reactivity that we observed using the IHC C5b-9/MAC stain.

In cases like ours and/or in any suspected recurrent folliculitis or pilosebaceous unit infection, advanced techniques may be helpful. These include 1) fluorescence in situ hybridization (FISH) using broad-range bacterial and fungal probes; 2) immunofluorescence microscopy, and 3) monoclonal antibodies directed towards Gram-positive bacteria and/or against *Staphylococcus spp*. and *Propionibacterium acnes* [3-4]. Most laboratories and/or medical practitioners lack these techniques; in our case, these tests were not performed. Of interest, when using DIF we were able to identify coccal bacteria labelling with IgD, C3c and, to a lesser degree IgE inside the sebaceous glands and hair follicular units.

CONCLUSION

In cases of recurrent lichen simplex chronicus of unknown etiology, it may be helpful to utilize direct immunofluorescence and immunohistochemistry in addition to a H&E histologic review. These combined methodologies can enhance confirmation of Gram stained bacterial infections.

STATEMENT OF ETHICS

Our patient gave informed consent. Although Institutional Review Board (IRB) approval for a case report is not needed, the US Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule restricts how protected health information (individually identifiable health information) on any patient may be used. Compliance with patient privacy, institutional rules, and federal regulations were followed. Specifically, no photos or illustrations that contain identifiable features are included in the case report, and the case described in the report is not so unique or unusual that it might be possible for others to identify the patient.

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

Our Dermatology Online

Case Report

Gingival mucormycosis: case report and literature review

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ABSTRACT

Mucormycosis is a rapidly progressive fungal infection characterized by endothelium invasion and the development of thrombi in blood vessels resulting in necrosis. Early diagnosis is crucial for effective treatment. Oral mucormycosis is an uncommon and possibly an underestimated disease. Herein, we present the case of a 31-year-old male previously diagnosed with refractory L2 acute lymphoblastic leukemia (ALL) who suffered gingival mucormycosis due to *Rhizopus arrhizus*. Empirical treatment with amphotericin B deoxycholate (ABD) was prescribed with clinical and mycological healing on day 17. Unfortunately, the patient had an unfavorable outcome because of the ALL and died 49 days after the admission due to multiple organ failure.

Key words: Mucormycosis; Hematological malignancies; Platelet count; *Rhizopus arrhizus*

INTRODUCTION

Mucormycosis is a fungal infection with a high mortality rate (>50%) caused by the *Mucorales* often occurring in immunosuppressed patients, as with diabetes mellitus, hematopoietic stem cell transplants, or associated hematological malignancy. Mucormycosis usually develops as an acute infection and presents itself in rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated clinical types. Oral mucormycosis is rarely seen in clinical practice and reported cases are scarce [1-3]. Herein, we present the case of a male patient with L2 acute lymphoblastic leukemia (ALL) with gingival mucormycosis, as well as a short review of the literature.

CASE REPORT

A 31-year-old male, previously diagnosed with L2 acute lymphoblastic leukemia (ALL) since 2016, was admitted to our hospital in April 2019 because of the fourth disease relapse. On admission, the patient had pancytopenia, severe leukopenia (2,100 cells/μL), thrombocytopenia (99,000 cells/μL), and anemia (8.8 g/dL). Treatment was started with a Hyper-CVAD regimen (hyperfractionated cyclophosphamide doses, vincristine, doxorubicin, and dexamethasone) but without clinical improvement. The leukopenia persisted through day 2 and a progressive decrease in platelet levels was observed (3,000 cells/μL). During the hospital stay, several necrotic ulcers developed at the first and second premolars of the right maxilla in the gingival region, as well as an edematous plaque over the hard palate (Fig. 1). A direct microscopic examination revealed broad, dichotomic, coenocytic, and hyaline hyphae. Sabouraud dextrose agar media yielded hairy, cottony, grayish-white colonies with broad non-septate hyphae, sporangiophores, rhizoids, sporangia, and sporangiospores visualized. The fungus was mycologically identified as *Rhizopus arrhizus* (formerly *R. oryzae*) and confirmed by molecular biology according to the following regions: ITS:

How to cite this article: Bonifaz A, Gabriela Fuentes-Nava A, Tirado-Sánchez A, Kassack JJ, Vega-Muñoz JD, Treviño-Rangel R, González GM. Gingival mucormycosis: case report and literature review. Our Dermatol Online. 2020;11(4):389-392.

Submission: 25.06.2020; **Acceptance:** 01.10.2020

DOI: 10.7241/ourd.20204.15

99/99.2 (NCBI), 95.67/100 (ISHAM-ITS), 96.64/100 (MycoBank); and D1/D2: 99/99.1 (NCBI), 95.26/99.53 (MycoBank). Hence, we reached a diagnosis of gingival (oral) mucormycosis caused by *Rhizopus arrhizus*. A biopsy was not taken due to severe thrombocytopenia (Fig. 2). A CT scan of the head failed to show evidence of bone involvement. Surgical debridement was not performed because of the patient's condition. Amphotericin B deoxycholate (ABD) was started at 1 mg/kg/day with clinical and mycological healing on day 17. Unfortunately, the patient's condition worsened with disseminated intravascular coagulation and the patient died on day 49.

DISCUSSION

Mucormycosis is an invasive fungal infection characterized by the rapid growth of filamentous fungi, leading to thrombosis and tissue necrosis [1,4]. *Rhizopus arrhizus* is the most common etiologic agent, followed by *Mucor circinelloides* and *Lichtheimia corymbifera*, which together account for around 70% of all infections [1,4-7]. In 2005, Roden et al. conducted a review of 929 cases [4]. The mean age was 38.8 years with a prevalence of males (65%). DM was the most common underlying condition. One hundred fifty-four patients presented with a malignant neoplasm, among which 147 (95%) were hematological.

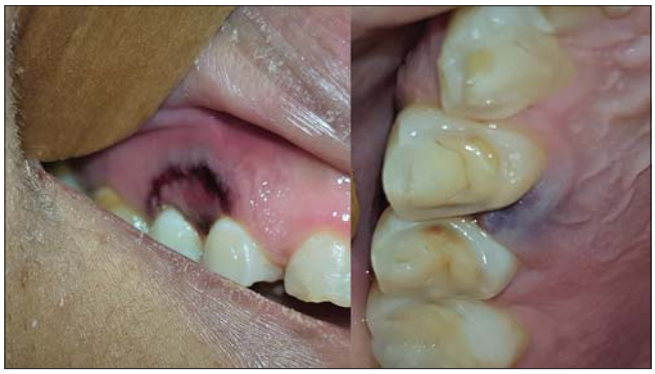

Figure 1: Gingival necrosis at the right maxilla and a violaceous and edematous plaque at the hard palate.

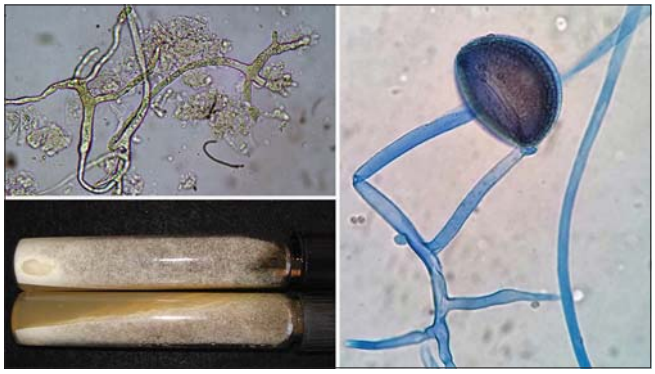

Figure 2: (a) Direct microscopic examination showing broad, dichotomic, non-septate, hyaline hyphae (KOH, 10×). (b) A cottony culture of *Rhizopus arrhizus* in Sabouraud dextrose agar. (c) Sporangium with sporangiospores and rhizoids typical of *Rhizopus* (cotton blue, 10×).

The *Mucorales* have the ability to cross physical barriers, finding innate immune cells: macrophages, neutrophils, and dendritic cells. Angioinvasion is a distinctive process in mucormycosis. Endothelium breakage causes thrombosis and tissue necrosis and allows for hematogenous dissemination. The *R. arrhizus* adheres directly to the endothelial cells and impels lesions through its internalization. The entrance to the endothelial cells is arbitrated by the endothelial cell surface receptor GRP78, which significantly increases acidosis and hyperglycemic conditions [5]. Patients with neutropenia have more extensive angioinvasion [8,9]. After crossing the endothelial tissue, *Mucorales* find platelets, recently identified as key effectors of the innate immune system, as they bear antimicrobial properties mediated by the release of platelet antimicrobial peptides such as platelet factor 4 (PF-4), as well as chemotactic properties mediated by the release of cytokines such as IL-1b. *In vitro* studies have shown that the platelets adhere to both spores and hyphae and significantly inhibit fungal germination and cause direct damage to hyphae [2,5].

Oral mucormycosis usually develops after the transpalatal extension of rhinocerebral infection. Cases located in the periodontal tissue (gingival and alveolar bone) are rare [8-10]. In general, we have had experience of palatal ulcer formation in up to a third of our patients, but gingival presetting is extraordinary and must be kept in mind in the oral forms of mucormycosis [10]. Table 1 shows a comparison of the characteristics of the reported cases, including this case.

In our search through the English-language literature, we found merely ten cases of periodontal mucormycosis: nine in patients with hematological malignancies and one in a diabetic patient. All patients underwent extension studies and the diagnosis of aspergillosis was ruled out. All cases, including this case, had active hematological malignancies. All patients had neutropenia (<500 cells/μL) and four patients with hematological malignancy had associated thrombocytopenia. Clinical manifestations were similar: the patients complained of gingival pain while

seven patients had a fever. Physical examinations revealed bluish, grayish, or whitish edematous plaques as well as necrotic changes. All patients received amphotericin B as a first-line treatment and three patients underwent surgical debridement. Seven of the eleven cases successfully completed the antifungal treatment and two patients died of pneumonia whereas our patient died from multiple organ failure. In one patient, the evolution was unknown [11]. The diabetic patient received treatment with amphotericin B and surgical debridement with favorable results [12]. Unlike rhinocerebral mucormycosis, the gingival type was observed without central nervous system involvement and with slower progression [1,8,13].

Mucormycosis is diagnosed by direct examination with Calcofluor, Fungifluor, or Blankofluor. Calcofluor analysis is not performed in daily practice due to the need for fluorescence microscopy [9]. Laboratory diagnosis is necessary, although bearing low sensitivity. The *Mucorales* grow rapidly to 37°C (98.6°F) in selective and nonselective media. The diameter of coenocytic (non-septate) or pauci-septate hyphae ranges from 6 to 25 μm. The branch angle is variable and includes bifurcations with an angle of ≥90° [8]. Histopathological examination makes it possible to distinguish between *Aspergillus* hyphae and *Mucorales* hyphae, defining the treatment. Mucormycosis is characterized by necrosis and vascular and perineural invasion [1]. No standardized tests are available for detecting *Mucorales*-specific antigens. The results of negative serum galactomannan and bronchoalveolar lavage tests support the diagnosis of mucormycosis [14]. (1,3)-β-D-glucan is a common part of the cell wall of a wide variety of fungi, but not the *Mucorales* [1].

Amphotericin B deoxycholate is one of the drugs approved for treating mucormycosis. However, given the associated toxicities, it is often replaced by lipid formulas. Early treatment with amphotericin B and the surgical debridement of the infected areas is the treatment of choice [1,14]. Posaconazole has shown significant clinical efficacy against the *Mucorales* [8,15]. Isavuconazole is a novel azole showing *in vitro* and *in vivo* activity against the *Mucorales* when compared with posaconazole [1,15]. On the other hand, fluconazole, voriconazole, echinocandins, and flucytosine show no *in vitro* activity against the *Mucorales* [1].

In hematologic patients, it is suggested to continue treatment until complete remission is achieved proved by imaging studies and reversing risk factors [1]. Alveolar osteonecrosis presents difficulty in surgical treatment since extensive debridement of the maxillary bones may trigger functional complications. In addition, the risks and benefits of surgical treatment should be carefully weighed in patients with neutropenia and thrombocytopenia [8]. During severe immunosuppression, primary prophylaxis with posaconazole has been recommended specifically for the prevention of mucormycosis, but a lack of controlled studies persists [1].

CONCLUSION

This was the case of a patient with L2 ALL displaying rare clinical primary gingival mucormycosis. The patient had an unfavorable outcome because, despite treatment, the ALL activity persisted, together with severe neutropenia and thrombocytopenia. The patient died due to multiple organ failure. In hematologic patients, prognosis usually depends on the response to treatment of hematologic neoplasia.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

A rare case of malignant pyoderma associated with ulcerative colitis both treated effectively with adalimumab

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ABSTRACT

Malignant pyoderma is considered to be an entity separate from pyoderma gangrenosum (PG). Scalp involvement in PG is rarely reported in patients with inflammatory bowel disease (IBD). An eighteen-year-old male with ulcerative colitis (UC) was admitted with occipital ulceration resistant to the usual antibiotic treatments. The patient later developed abdominal pain, bloody diarrhea, and fever. Histology was compatible with PG. Rectosigmoidoscopy revealed an acute UC flare-up. Given the absence of other infectious causes, a diagnosis of PG was retained. The patient was started on adalimumab at a dose of 80 mg. A positive response from the PG and the UC was observed after three weeks and complete healing of the ulcer after seven months. Our case shows the effectiveness of adalimumab in both diseases and suggests that the management of this type of pyoderma should be based on the control of the underlying IBD disease.

Key words: Pyoderma gangrenosum; Ulcerative Colitis; Adalimumab; Malignant Pyoderma; Scalp

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare inflammatory ulcerative dermatosis characterized by neutrophilic dysfunction, genetic influence, and a strong link with other underlying conditions, most notably, inflammatory bowel disease (IBD), arthritis, and hematological disorders. It currently remains a diagnosis of exclusion due to the lack of verified and accepted diagnostic criteria.

Malignant pyoderma (MP), which is now considered an entity separate from PG, is characterized by the lack of a considerable benefit from antibiotics along with predominant head and neck involvement, the absence of surrounding erythema, and the aggressive course of the disease.

Therapeutic strategies have been based especially on immunosuppressive therapy, such as corticosteroids, azathioprine, and cyclosporine. Lately, several retrospective reviews and studies have reported the efficacy of biotherapy, such as infliximab and adalimumab [1].

Adalimumab, which is a human monoclonal antibody to tumor necrosis factor-α, has proved to be successful in the treatment of PG associated with ulcerative colitis (UC). We report a rare case of MP with UC, both treated effectively with adalimumab.

CASE REPORT

An eighteen-year-old male with a four-month history of UC was admitted to our department with cranial ulceration, which had been evolving for two months and which had been resistant to the usual antibiotic therapy. The patient was previously prescribed oral prednisolone and Salazopyrin. Despite this,

How to cite this article: Belanouane S, Hali F, Baline K, Chiheb S, Marnissi F, Hliwa W. A rare case of malignant pyoderma associated with ulcerative colitis both treated effectively with adalimumab. Our Dermatol Online. 2020;11(4):393-396.

Submission: 10.09.2019; **Acceptance:** 15.11.2019

DOI: 10.7241/ourd.20204.16

the symptoms aggravated and the ulceration kept increasing in diameter. A physical examination revealed a large 8-cm occipital ulceration with indurated and undermined edges and a purulent base with slight bleeding from the ulcer bed (Fig. 1) extending from the right retroauricular region to the occipitoparietal area exposing the underlying tissue (Figs. 2a and 2b). Surprisingly, it was not sensitive on contact.

On palpation of the face and neck, no enlarged lymph nodes or other masses were found. Residual cribriform scars from previous ulcers were noted on the legs.

A biopsy including the border of the ulcer and the adjacent skin showed focal ulceration with mononuclear cell infiltration consisting predominantly of neutrophils with granulation tissue, which was in keeping with PG (Figs. 3a and 3b). Cultures were negative for bacterial, mycobacterial, and fungal infections. Wound swabs were positive for Pseudomonas aeruginosa, which was sensitive to the ceftazidime administered later. Viral swabs were negative.

Figure 1: The patient at the admission room.

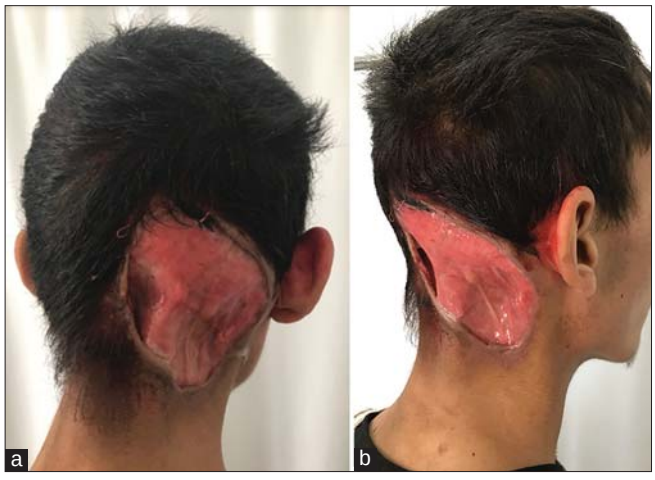

Figure 2: (a-b) The patient after carefully cleaning the wound, with the ulceration exposing the underlying tissues.

There was no presence of upper or lower airway symptoms. Other causes of ulcers were also excluded. Therefore—also, given the location of the PG and the absence of other infectious causes—the diagnosis of MP was retained. A radiological examination excluded osteolysis.

The PG was treated with both topical and oral steroids (prednisone at 1 mg/kg) as well as regular moist wound care.

On day two of admission, the patient developed ten episodes of bloody diarrhea associated with severe abdominal pain requiring urgent transfer to the Gastroenterology Department for control of the acute colitis crisis.

A second intestinal biopsy confirmed once more the diagnosis of UC and a rectosigmoidoscopy examination showed a macroscopic appearance compatible with a UC flare-up. A bolus of methylprednisolone was administered, which eventually effected partial remission. However, the PG kept increasing in diameter, reaching 11 cm in the longer axis within only eleven days.

Due to this clinical course, the patient was started on adalimumab administered subcutaneously at an induction dose of 80 mg every other week. Within 72 hours, an improvement was noted. The patient's pain improved drastically and the ulcer stopped progressing. A positive response of both the PG and the UC flare-up to the adalimumab was obtained in three weeks (Fig. 4). The steroids were then tapered off by 5 mg every three weeks and almost complete healing of the ulcer was observed in seven months (Fig. 5).

DISCUSSION

Malignant pyoderma (MP), which was described for the first time in 1968 as a new clinical entity by Perry et al., is now known as a variety of PG with an atypical location involving the head and neck [2].

Scalp involvement in PG is extremely rare. Approx. 50% of these patients have an underlying systemic disease, the most common being IBD, myeloproliferative disorders, and different forms of arthropathy [3].

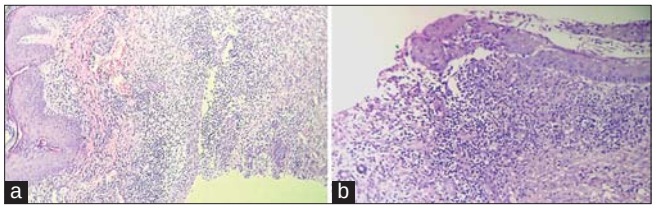

Figure 3: (a-b) A skin biopsy showing focal ulceration with mononuclear cell infiltration consisting predominantly of neutrophils with granulation tissue, which was in keeping with PG.

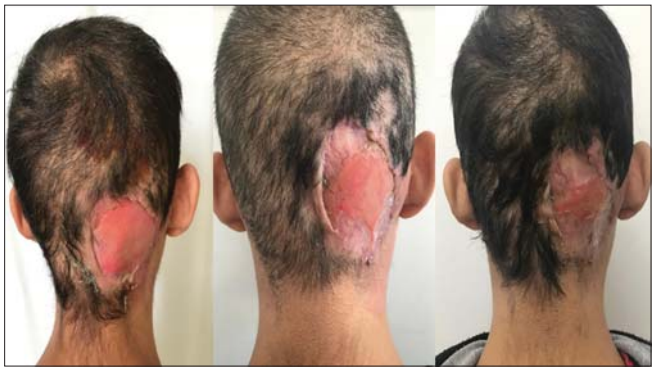

Figure 4: The evolution of the healing process after one month of initiating adalimumab.

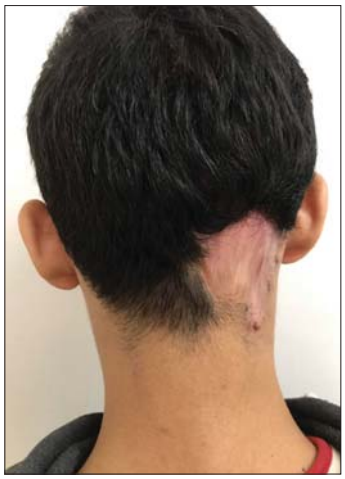

Figure 5: The complete healing of the ulceration after seven months, with scarring alopecia.

Ulcers in MP frequently begin as papulopustular lesions and evolve into destructive ulcers within a short lapse of time. They bear the typical appearance of irregular and undermined edges without the classical erythematous halo around them.

MP is a disease of young adults between the ages of 15 and 45 and is seen mostly in males. Although the ulcers are generally seen in the periauricular region, they may appear on any part of the body. In our case, no other parts of the body were involved upon physical examination, but cribriform scars on the limbs from previous ulcers suggested that that patient had developed PG on the lower body before the onset of the MP.

Although lesions in MP appear spontaneously, they may be induced or aggravated by trauma (pathergy). The evolution of the disease is progressive and chronic. In some cases of MP, temporary neurological dysfunction, such as cranial nerve palsies, sensorimotor loss, or even cranial osteolysis, has been reported [4]. We did not observe such symptoms in our case.

Although the exact nosological status of MP or PG, in general, remains unclear, its association with autoimmune diseases suggests the involvement of some dysregulation in the immune system. Immunohistochemical studies on PG ulcers have shown that myeloperoxidase—a neutrophilic marker—is highly expressed in the wound bed, whereas CD3 and CD163—a pan T cell marker and a macrophage marker, respectively—are significantly higher in the wound edge, which indicates that, other than neutrophilic cells, T cells and macrophages are also involved in the pathogenesis of this disease [5].

On the other hand, a simultaneous evolution of the two pathologies—UC and PG—is found in 50% of cases [6]. In our patient, the course of pyoderma was, indeed, concomitant with a colitis flare-up, suggesting that the increased activity of the underlying disease may have led to the appearance of the MP, especially as the significant improvement of the ulcer was noted as soon as the treatment of the UC was initiated.

Although MP generally responds to corticosteroid therapy, relapses often occur as soon as the dose is tapered off. Dapsone, azathioprine, and clofazimine may be given in combination with corticosteroids. Good results have also been reported with cyclophosphamide, thalidomide, and isotretinoin in some cases [5].

Several case reports and reviews on the efficacy of adalimumab in the treatment of PG with IBD have been reported [1]. In a recent study [7], data from thirteen patients with PG associated with UC was analyzed. All of the patients received adalimumab at an induction dose of 160 mg / 80 mg with a maintenance dose of 40 mg every other week, the median period going from the first injection of adalimumab to the end of the healing process, which was 1.25 months. The end of the healing process in our patient was in keeping with the review of the literature.

CONCLUSION

Adalimumab may be an alternative first-line treatment of MP, making it possible to avoid the severe side effects of the long-term use of corticosteroids. Therefore, clinical trials are needed to evaluate the efficacy and safety of adalimumab as a first-line treatment option for PG.

Our case demonstrates the effectiveness of adalimumab in treating MP and suggests that the management of this type of aggressive pyoderma is based on the control of the underlying IBD disease.

Consent

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

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

Our Dermatology Online

Case Report

The skin as a window on internal disorders: Two cases of internal malignancy and hypervitaminosis B12

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ABSTRACT

Paraneoplasias are frequently the first sign of an underlying malignant tumor. Although relatively rare, they need to be recognized by dermatologists to make an early diagnosis and improve the neoplastic prognosis. We report two cases of internal malignancy: small cell carcinoma of the lung and cervical carcinoma in stage IIB, detected through paraneoplastic cutaneous manifestations. Raised vitamin B12 levels along with high levels of cobalamin—reported in patients with different types of cancer—were also described in the second case report.

Key words: Paraneoplastic cutaneous manifestations; Exfoliative dermatitis; Telogen effluvium, Hypervitaminosis B12; Tripe palms

INTRODUCTION

The skin often acts as a mirror of changes internal to the body. Neoplastic diseases affecting the internal organs can lead to different kinds of cutaneous manifestations, thus known as paraneoplastic manifestations [1]. These include exfoliative dermatosis, which may be caused by various drugs, underlying cutaneous disorders—such as psoriasis, atopic dermatitis, exposure dermatitis—cutaneous malignancies such as Sézary syndrome, and solid organ tumors. Determining the cause of erythroderma is essential, but is also quite challenging for the dermatologist [2]. Telogen effluvium (TE) can be due to several conditions, but a sudden onset of TE as the only presentation of complaint in a patient with undetected internal malignancy is notably rare. Pathophysiologically, tumor-related hypervitaminosis B12 is mainly linked to excessive synthesis of transcobalamin by the tumor or high haptocorrin levels due to a leukemoid reaction [3,4]. Thus, great suspicion should be exercised upon the diagnosis of hypervitaminosis B12.

CASE REPORTS

Case 1

A 70-year-old male presented with 4 weeks of generalized peeling of the skin, accompanied occasionally by mild itching. Upon examination, he was cachectic and had pallor, clubbing, and cervical lymphadenopathy and generalized exfoliation of the skin. The palms and soles showed a thickening velvety appearance, suggesting tripe palms (Fig. 1). A cutaneous and systemic examination was normal except for crepitations present on the right side of the chest. Thus, the patient was diagnosed with internal malignancy, keeping in mind the generalized exfoliative dermatitis and tripe palms as a paraneoplastic condition.

Upon further inquiry, the patient admitted to a history of appetite loss and a weight loss of 5–6 kg in 1 month. The patient denied fever, cough, chest pain, and dyspnea on exertion. Blood and urine reports were normal except for hemoglobin (9.9) and neutrophilia. A chest X-ray and CECT of the thorax showed a necrotic mass in the

How to cite this article: Radhika SR, Nandini AS, Sharath Kumar BC. The skin as a window on internal disorders: Two cases of internal malignancy and hypervitaminosis B12. Our Dermatol Online. 2020;11(4):397-399.

Submission: 18.12.2019; **Acceptance:** 19.04.2020

DOI: 10.7241/ourd.20204.17

upper right lung lobe with cavitation and mediastinal lymphadenopathy (Fig. 2). A skin biopsy was taken from the palm, showing features of tripe palms. FNAC (Fig. 3a) and a transcutaneous CT-guided lung biopsy were done and revealed small cell carcinoma of the lung (Fig. 3b). An upper GI endoscopy was also done to rule out GI malignancies, showing grade B esophagitis. Thus, the patient was referred to a medical oncologist for further management. The patient died within a few days of referral to a higher center.

Case 2

Upon further evaluation, the patient gave a history of itching over the vulval area for the past few months. Upon local genital examination, an irregular firm-to-hard mass was present in the anterior lip of the cervix, which bled on touch (Fig. 4). A horizontal group of superficial inguinal lymphadenopathy was also present. A cutaneous and systemic examination was normal. A biopsy of the mass was done, showing a carcinoma of the cervix (Fig. 5). Abdominal and pelvic USG showed mild and diffuse thickening of the urinary bladder wall and hydrometra secondary to the obstruction from the bulky cervix (enlarged and irregular). A chest X-ray was normal. CT of the pelvis showed a mass in the cervix causing upstream hydrometra, thickening of the entire length of the vagina, and infiltration. After the clinical examination and investigation, the patient was diagnosed with a carcinoma of the cervix in stage IIB. The patient underwent 5 weekly cycles of cisplatin (CT) with concurrent EBRT at a dose of 45 Gy in 25 fractions to the pelvis with a 15 MV beam for 5 weeks. The patient tolerated the treatment well.

Figure 1: Generalized exfoliation of the skin with tripe palms and soles.

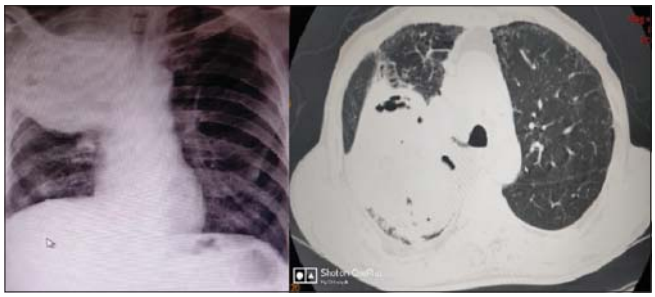

Figure 2: A chest X-ray with an opacity in the upper right and middle zone with air-fluid levels. CECT of the thorax showing a necrotic mass in the upper right lung lobe with cavitation and mediastinal lymphadenopathy.

DISCUSSION

A study done on 139 malignant patients demonstrated the association between hypervitaminosis B12 and solid neoplasms [13]. Hepatocellular carcinoma (HCC), secondary liver tumor, breast cancer, colon cancer, stomach cancer, and pancreatic tumor were some of the relevant carcinomas associated [14,15]. The exact pathophysiology of underlying cancer causing high plasma B12 levels has not been well understood. B12 circulates by binding to either haptocorrin or transcobalamin. Cancer may, thus, affect the metabolism of vitamin B12

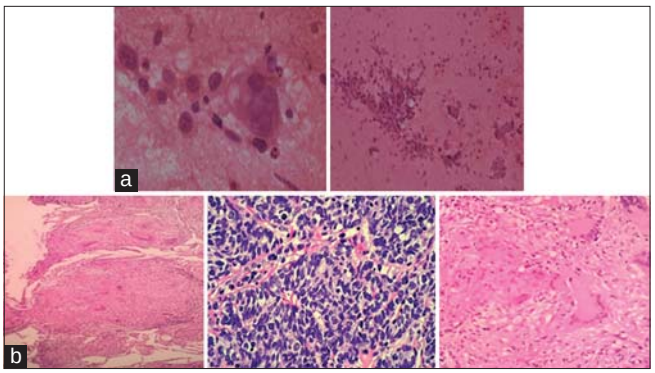

Figure 3: (a) FNAC of the lung showing atypical cells in clusters, individual cells with a high NC ratio, and multinucleated giant cells. (b) A lung biopsy showing nests of tumor cells around a blood vessel, individual cells with minimal cytoplasm, hyperchromatic nuclei, atypical cells arranged in clusters with a high nucleus-cytoplasmic ratio, a moderate amount of cytoplasm, a vesicular nucleus, and prominent nucleoli.

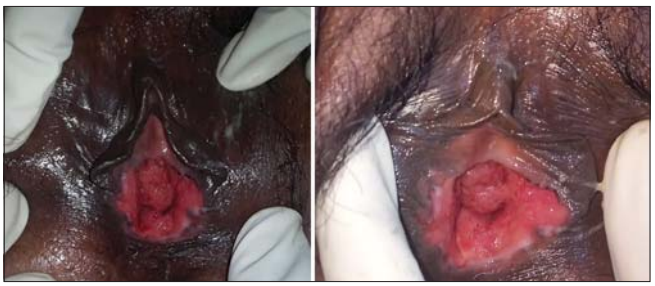

Figure 4: An irregular firm-to-hard 2x3 cm mass present over the anterior lip of the cervix.

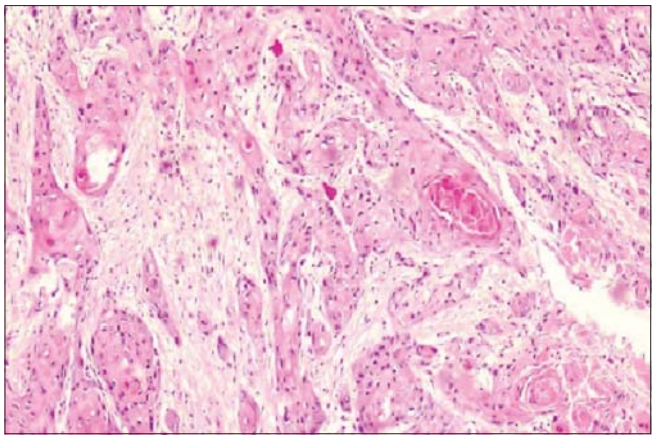

Figure 5: H&E stain showing malignant squamous cells that form irregular nests invading the stroma, laminated keratin pearls in the center of the nest, and individual cells with abundant eosinophilic keratinized cytoplasm.

by affecting the levels of these binding proteins, in turn leading to hypervitaminosis B12. These protein alterations may involve inflammation cells that can produce either haptocorrin or transcobalamin. This potential underlying inflammation could explain the association between high plasma B12 levels and the higher mortality risk, and also the risk of venous thromboembolism in carcinoma patients [16]. J.F.H. Arendt et al. [4] conducted a population-based cohort study using data from Danish medical registries, including 25,017 patients with cancer and varied cobalamin levels, and a comparison cohort of 61,988 cancer patients without a plasma cobalamin measurement. The conclusion was that cancer patients with elevated cobalamin levels had higher mortality rates than patients without elevated cobalamin levels. According to another study, which was conducted in UK primary care, concluded that elevated plasma B12 levels were associated with higher yearly cancer risk than normal B12 levels, also suggesting that some cancers may affect B12 metabolism [16].

CONCLUSION

This paper highlights the importance of generalized exfoliation, tripe palms, sudden-onset hair loss, and high levels of vitamin B12 as paraneoplastic conditions. The importance of a detailed medical history, general physical examination, and evaluation with an age-appropriate workup for malignancies is stressed. Due suspicion for malignancy in patients with dermatoses of unclear etiology permits an early diagnosis and appropriate treatment. The skin, thus, acts as a window on internal disorders, and hypervitaminosis B12 ought to be considered as a cancer manifestation.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients have given consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

Extramammary Paget's disease: A report of two cases and a review of literature

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ABSTRACT

Extramammary Paget's disease (EMPD) is a rare, slow-growing intraepithelial adenocarcinoma in the anogenital and axillary regions of the body clinically mimicking inflammatory and infective diseases. Surgical excision is basically performed as a treatment for EMPD. Generally, the prognosis is poor. Herein, we report two cases of extramammary Paget's disease involving the vulval region in a 70-year-old female and the inguinal region along with the left part of the scrotum in a 57-year-old male. Neither had any underlying malignancy or metastasis.

Key words: Extra mammary Paget's disease; Vulva; Scrotum

INTRODUCTION

Mammary Paget's disease was first described by James Paget in 1874 [1]. It was in 1889 when Crocker described the first case of extramammary Paget's disease (EMPD), involving the scrotum and penis [2], and believed that the tumor derived from the sweat and sebaceous glands or hair follicles. EMPD mostly involves the vulva and anus, and is rarely found on the scrotum and penis [3]. In simple terms, it is an intraepithelial adenocarcinoma clinically presenting itself as a chronic eczema-like rash mainly in the external genital and axillary regions. EMPD is classified into primary (disease confined to the epidermis and dermis) and secondary (involvement of the visceral organs). It is most commonly mistaken for eczema or contact dermatitis. Other differential diagnoses to be considered are SCC, melanoma, and other benign papulosquamous diseases. In its early stages, EMPD is not invasive or metastatic, hence surgical excision gives satisfactory results. EMPD in its advanced progression is often difficult to treat and control, despite the availability of various therapeutic options, such as surgery, radiotherapy, and/or chemotherapy, including docetaxel and trastuzumab [4,5].

CASE REPORTS

Case 1

A 70-year-old female presented herself to us with a mildly pruritic erosive lesion with crusting on the vulva persistent for the last two years (Fig. 1). In the past, the patient applied a topical steroid on the lesion but with no improvement in the size of the lesion. The lesion started as a reddish mildly pruritic macule to gradually become slightly scaly and eventually erode, which was further aggravated after the application of topical steroids. The patient was a known diabetic. The patient's medical history was unremarkable and she denied any history of malignancy. A physical examination revealed a healthy geriatric female without systemic symptoms. A histopathological examination of a biopsy specimen from the skin lesion revealed an acanthotic epidermis with suprabasal atypical cells present in clusters or singly migrating toward the superficial epidermal layer. These cells had pale cytoplasm with a high nuclear-cytoplasmic ratio and prominent nuclei. Some of these cells showed a clear halo around the nucleus. The dermis showed dense lymphocytic infiltration (Fig. 2). Findings were consistent with EMPD of the vulva.

How to cite this article: Gupta N, Sarkar TK, Bhargava S. Extramammary Paget's disease: A report of two cases and a review of literature. Our Dermatol Online. 2020;11(4):400-402.

Submission: 04.11.2019; **Acceptance:** 09.01.2020

DOI: 10.7241/ourd.20204.18

Staging workup, which included chest radiography and computed tomography of the abdomen, revealed no features of metastasis. The patient underwent radiation therapy followed by vulvectomy with a 2-cm margin to the macroscopic normal tissue and primary closure. Surgical margins were histopathologically negative and the wound healed without complications. A follow-up after two years revealed no signs of recurrence.

Case 2

A 57-year-old male presented himself with a ten-month history of an itchy, erythematous macule on the left groin, which was misdiagnosed as tinea cruris and was treated accordingly (Fig. 3). As the lesion failed to resolve, the diagnosis was changed to seborrheic dermatitis and the patient was treated with topical corticosteroids for several months. However, the lesion progressed to an erosive mass with extension to the left lateral scrotum. The medical history was unremarkable, except a history of transurethral resection of the prostate for benign prostatic hypertrophy without evidence of malignancy. Histopathology confirmed the diagnosis of EMPD. The patient was also evaluated for metastasis but with no evidence of it. The patient underwent a wide excision of the skin lesion without recurrence to date.

DISCUSSION

EMPD is a rare, slow-growing intraepithelial adenocarcinoma occurring in the age group of 50–80 years most commonly located on the vulva followed by the perianal region. Other rarer locations include the axilla, eyelids, scrotum, and penis. It shows a female preponderance, with a ratio of 1.4:1 [6-8]. Several theories have been proposed for the pathogenesis of EMPD. One theory suggests that the disease is the result of multiple foci of malignant transformation of a population of cells with a common embryological origin, while another theory suggests that it is the result of a metastasis of underlying malignant cells to the epidermis [9,10]. Some other investigators believe that Paget's cells are either derived from or differentiate toward exocrine and apocrine gland cells, thus supporting the view that EMPD is an intraepithelial metastasis of an underlying exocrine gland adenocarcinoma [8-10], which warrants a search for underlying malignancy. The patient may be asymptomatic or may show pruritus (most commonly), a burning sensation, or pain. The lesion is typically sharply demarcated and eczematous with crusting, scaling, and rarely ulceration. Clinically, EMPD is to be differentiated from fungal infections, contact dermatitis, SCC, LSC, psoriasis, Bowen's disease, and melanoma [6,7,9,10]. However, failure to treatment gravitates toward the

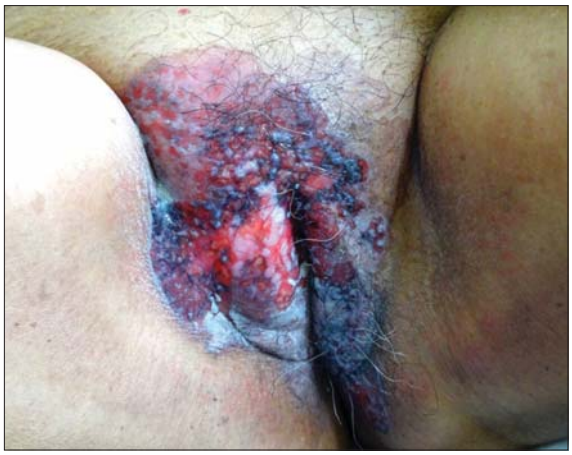

Figure 1: A mildly pruritic erosive lesion with crusting on the vulva in the first patient.

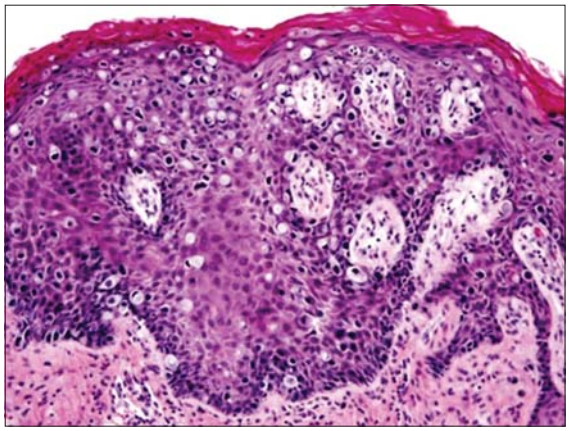

Figure 2: Histopathology showing an acanthotic epidermis with suprabasal atypical cells present in clusters or singly migrating toward the superficial epidermal layer; the cells with pale cytoplasm with a high nuclear-cytoplasmic ratio and prominent nuclei; some of the cells showing a clear halo around the nucleus.

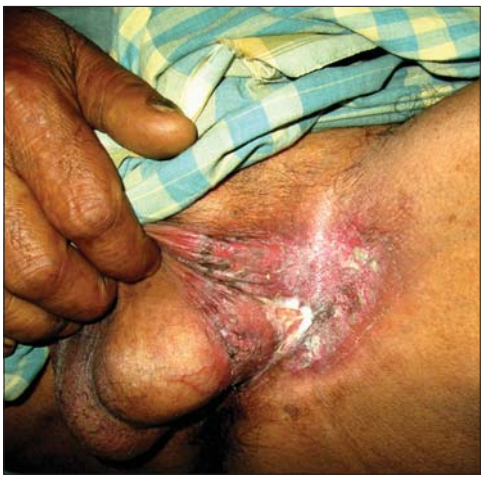

Figure 3: A mild itchy and erythematous plaque on the left groin in a 57-year-old male.

diagnosis of EMPD. Histologically, the presence of Paget's cells (large vacuolated cells containing basophilic or amphophilic finely granular cytoplasm, a large nucleus with atypia, and a prominent nucleolus nucleus) in the epidermis and/or adnexal epithelium confirms the diagnosis. The Paget's cells may be dispersed singly or form clusters, glandular structures, or a solid nest. In most of the cases (more than 90%), tumor cells contain cytoplasmic mucin, staining positively with mucicarmine and a periodic acid–Schiff reagent [11]. A few cases may show the presence of melanin granules [12], which may be due to: 1) chemotactic factors produced by the neoplastic cells, generating a proliferation of dendritic melanocytes; and 2) Paget's cells phagocytosing melanin from the melanocytes. These cases mimic melanoma both clinically and histologically. However, in EMPD, the atypical cells with melanin are situated in the suprabasal layer, whereas, in melanomas, the malignant cells usually also surround the dermoepidermal junction [13]. The diagnosis may further be confirmed by immunohistochemistry, being positive for CK7, EMA, and CEA. Paget's cells express HER2/neu receptors and c-erb-2 oncogene, indicating a biological origin similar to that of breast carcinoma [14]. EMPD also has a high risk of noncontiguous malignancy. 24% of patients with EMPD of the penis, scrotum, or groin develop malignancy of the genitourinary tract, including prostate, bladder, and rectal carcinoma [15], while vulval EMPD has concomitant urogenital malignancies in 15% of patients. Also, 33% of cases of perianal EMPD may develop colorectal adenocarcinoma. Therefore, a routine study for carcinoembryonic antigen and low molecular weight cytokeratin is to be done if secondary EMPD and internal adenocarcinoma are suspected. Since prognosis for localized EMPD is better than that for the invasive form of the disease, the treatment differs. Noninvasive EMPD can be treated with a wide local excision with a large margin, Mohs micrographic surgery (lesser recurrence), laser therapy, radiation, topical imiquimod, photodynamic therapy, and CO2 laser vaporization [7]. Lymph node dissection is performed only if there is clinical evidence of involvement. Invasive EMPD requires adjuvant therapy, such as radiotherapy or systemic chemotherapy. Chemoradiotherapy with 5-fluorouracil and mitomycin-C is effective. Also, monthly or weekly therapy with docetaxel and trastuzumab has proven to be effective.

CONCLUSION

EMPD must always be kept in mind as a differential diagnosis if a dermatitis involving sites such as the vulva or scrotum fails to respond to conventional treatment options. A prompt skin biopsy will help to reach a diagnosis for correct and timely management of EMPD.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

Angiokeratoma circumscriptum neviforme: Extensive involvement of lower limb

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ABSTRACT

Angiokeratomas are a rare group of disorders characterized by ectasia of preexisting papillary dermal vessels. It presents itself with discrete and/or confluent hyperkeratotic plaques. Among the variants of angiokeratoma, angiokeratoma circumscriptum is the least common and its nevoid distribution is still rarer, typically present since birth or very early childhood. Herein, we report a case of multiple verrucous plaques on the right leg in a blaschkoid distribution extending up to the thigh in a 27-year-old male diagnosed as angiokeratoma circumscriptum neviforme (ACN) on clinical and histopathological grounds..

Key words: ACN; Blaschkoid; Verrucous

INTRODUCTION

Angiokeratomas are characterized by ectasia of superficial or papillary vessels with overlying hyperkeratosis [1], first described by Mibelli in 1889 and termed angiokeratoma circumscriptum by Dammert. The mechanism of development remains unknown [2]. Angiokeratomas may be localized or generalized. The localized forms have been classified into solitary angiokeratoma, angiokeratoma of Fordyce, angiokeratoma of Mibelli, and angiokeratoma circumscriptum neviforme (ACN). Among these, ACN is the rarest, characterized by the presence of hyperkeratotic papules developing into verrucous bluish-black plaques commonly on the lower limbs in a segmental distribution. A lack of spontaneous regression makes the elimination of ACN imperative by the use of an appropriate modality (diathermy, curettage, electrocautery, cryosurgery, deep excision followed by grafting, CO2/argon/KTP laser) [2,3].

CASE REPORT

A 27-year-old male presented himself to us with a history of multiple erythematous macules on the right leg distributed in a linear pattern, encroaching the thigh since childhood. Later, the lesions gradually progressed to form papules and plaques. Subsequently, the lesions became hyperkeratotic, then static. Although the hyperkeratotic lesions extended to the inner thigh, the scrotum was spared. A history of occasional pain and bleeding was present. There were no symptoms suggestive of systemic involvement. A family history was absent, neither was there a history of bleeding from other sites. An examination revealed the presence of multiple purplish verrucous hyperkeratotic plaques arranged in a blaschkoid fashion extending from the ankle to the inner thigh (Fig. 1a and b). The lesions were firm and tender, and no pulsation was felt. The rest of the leg was normal, and there was no asymmetry in the size of the legs. No bruit was heard on auscultation. The rest of the general and systemic examination was within normal limits. A complete hemogram and biochemistry were within normal limits. An X-ray revealed no bone or soft tissue abnormalities. An incisional biopsy for a histopathological examination revealed compact hyperkeratosis, acanthosis, and elongation of rete ridges. The papillary dermis showed the presence of multiple dilated, thin-walled, congested capillaries without extension to the deep dermis or subcutis (Fig. 2).

How to cite this article: Sarkar TK, Gupta N, Bandyopadhyay D, Bhargava S. Angiokeratoma circumscriptum neviforme: Extensive involvement of lower limb. Our Dermatol Online. 2020;11(4):403-405.

Submission: 11.11.2019; **Acceptance:** 18.01.2020

DOI: 10.7241/ourd.20204.19

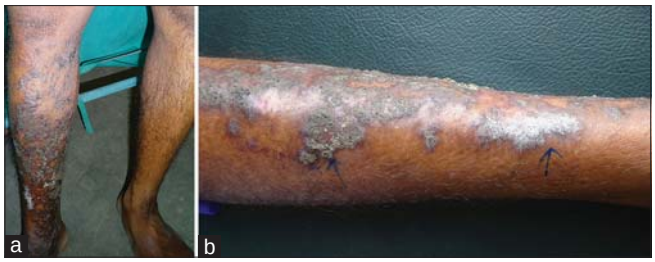

Figure 1: (a) Linear, verrucous, well-circumscribed plaques extending from the ankle to the inner thigh of the right side. (b) A close-up view of the linear verrucous lesions on the leg.

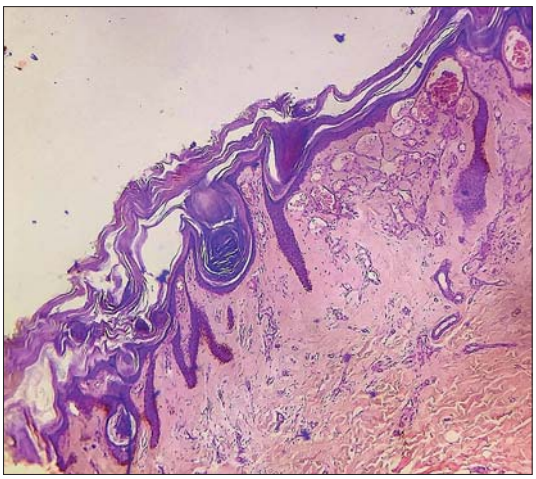

Figure 2: A photomicrograph showing compact hyperkeratosis, acanthosis, and elongated rete ridges, as well as the papillary dermis with dilated thin-walled vascular spaces containing erythrocytes (H&E, 40×).

DISCUSSION

Angiokeratomas are telangiectasias of preexisting dermal capillaries and veins with hyperkeratotic surfaces [4]. It is three times more common in females than in males. Angiokeratoma is classified as localized or widespread. Angiokeratoma corporis diffusum is a systemic variety caused by a deficiency in any of several enzymes, resulting in the deposition of glycosphingolipids. Localized angiokeratomas are classified as angiokeratoma of Fordyce, located in the genital region, angiokeratoma of Mibelli, located on acral parts following exposure to cold, solitary and multiple angiokeratoma, and angiokeratoma circumscriptum, which is rare. Angiokeratoma circumscriptum neviforme is still a rarer variety of angiokeratoma, occurring at an early age. ACN is seen usually in infancy or early childhood, although late-onset cases have been reported [5]. ACN presents itself as bluish-black papules and nodules grouped to form a verrucous and hyperkeratotic plaque. Lesions are most commonly seen on the thighs and the gluteal region but may also occur on the neck [6]. Uncommon sites, such as the tongue, oral cavity, elbow, penis, and trunk, have also been reported [7-9]. Lesions are segmental or linearly arranged. The pathogenesis of ACN remains unknown but several causal factors, such as trauma, developmental anomaly, subcutaneous hematomas, pregnancy, and tissue asphyxia, have been suggested. Angiokeratoma circumscriptum have been reported to coexist with angiokeratoma of Fordyce and caviar spots (angiokeratoma of the tongue), Cobb syndrome, Klippel–Trénaunay syndrome, nevus flammeus, cavernous hemangioma, and traumatic arteriovenous fistula [3,10-12]. Clinically, angiokeratoma may mimic verrucous hemangioma, melanoma, pigmented basal cell carcinoma, and sometimes lichen planus hypertrophicus; in these cases, histopathology helps to differentiate between the conditions. HPE with ACN shows epidermal hyperkeratosis, papillomatosis, and/or acanthosis, along with the presence of dilated blood vessels limited to the papillary dermis, unlike verrucous hemangioma, in which dilated capillaries extend deeper into the reticular dermis and subcutaneous tissue. In our case, correlating clinical features with the features of HPE confirmed the diagnosis of ACN. Treatment with diathermy, cryosurgery, curettage, and electrocautery is done for smaller lesions. Larger lesions require deep surgical excision or laser ablation with carbon dioxide [9], argon laser, or potassium titanyl phosphate (KTP) laser [2]. We planned carbon dioxide laser for this patient. Scanty case reports of this entity in the world literature prompted us to report this case.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Our Dermatology Online

Case Report

Tuberous sclerosis complex and psoriasis: A possible common pathophysiology

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ABSTRACT

Tuberous sclerosis is a rare genodermatosis characterized by multisystemic disorders: cutaneous, cerebral, ocular, bony, digestive, pulmonary, sometimes severe, especially renal and cardiac. The association of this condition with psoriasis, to our knowledge, has never been described, which may suggest a common pathophysiology. The case of a 45-year-old male, and similar cases in the family, provides an association with skin psoriasis and tuberous sclerosis as skin and kidney manifestations. This association in a single patient suggests a possible common pathophysiology, including the common activation of mTOR. More studies are needed to prove the relationship between these two entities.

Key words: Tuberous sclerosis; Psoriasis; Bourneville–Pringle disease

INTRODUCTION

Tuberous sclerosis complex (TSC), also known as Bourneville disease or Bourneville–Pringle disease, is an autosomal dominant genetic disorder with various clinical manifestations that affects the brain, skin, kidneys, heart, and other organs [1]. The association of STB with psoriasis is very rare and suggests a common pathophysiology. We report such a rare case of tuberous sclerosis in a 45-year-old male with psoriasis.

CASE REPORT

A 45-year-old male with no significant pathological antecedent presented himself to the urology department with low back pain. The patient had had asymptomatic cutaneous lesions since the age of six years with extension and increase in number and size, as well as similar cases in the family (father, four brothers, granddaughter, nephews, and nieces), with no notion of consanguinity in the parents, and pruriginous, erythematous, squamous lesions evolving by pushed remission since the age of ten years. The patient did not report epileptic seizures, psychomotor disorders, or other possible associated signs. A dermatological examination revealed multiple angiofibromas (Fig. 1a) symmetrically distributed over the centrofacial areas, fibrous cephalic plaques (Fig. 1b) sitting at the level of the forehead and scalp, a shagreen plaque with a 10-cm long axis (Fig. 1c) sitting at the left axillary level, multiple skin tags around the neck, and periungual fibromas (Figs. 1d and 1e). Erythematous squamous plaques sitting at the knees and elbows were bilateral and symmetrical with a methodical scratching of positive pitcher; the body surface was 4% (Fig. 2). The patient did not show any symptoms of cardiovascular, endocrine, respiratory, immune, or musculoskeletal disorders. Ultrasonography and abdominal CT revealed a multicystic kidney without pylocelical dilation with pylocelictic stones. The diagnosis of STB was retained and was associated with psoriasis. The patient benefitted from a double "J" probe uplift in the urology department and application of a topical corticosteroid on the psoriasis plaque with an improvement.

How to cite this article: Rasso A, Oukarf S, Sow A, Elloudi S, Baybay H, Farih MH, Mernissi FZ. Tuberous sclerosis complex and psoriasis: A possible common pathophysiology. Our Dermatol Online. 2020;11(4):406-408.

Submission: 26.09.2019; **Acceptance:** 30.01.2020

DOI:10.7241/ourd.20204.20

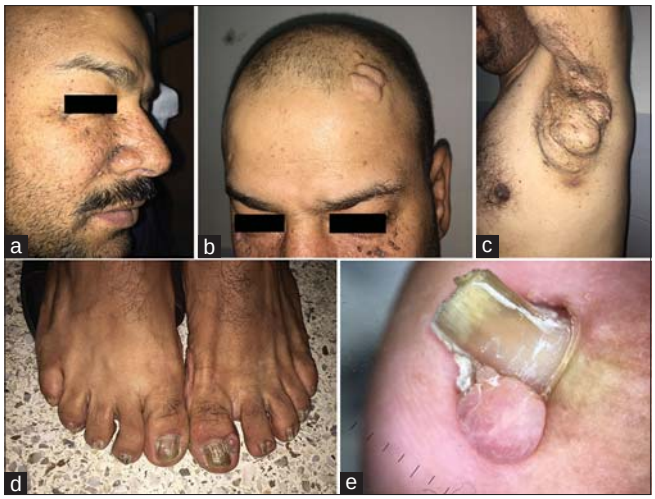

Figure 1: Clinical manifestations of tuberous sclerosis complex: (a) angiofibromas, (b) fibrous plaques, (c) a shagreen plaque, and (d) ungual fibromas and (e) their dermoscopy.

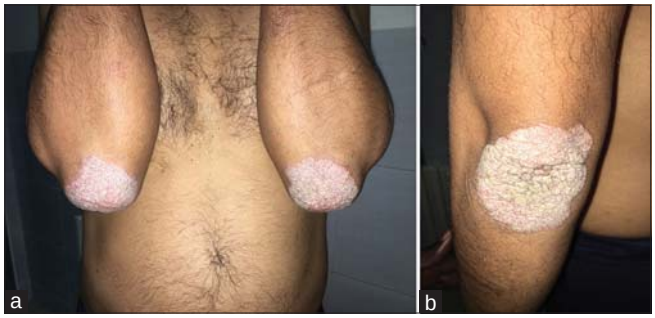

Figure 2: Bilateral and symmetrical psoriatic plaques sitting at the knees and elbows.

Table 1: The diagnostic criteria of tuberous sclerosis [6]

Major features
1. Facial angiofibromas or forehead, plaque pits in dental enamel
2. Nontraumatic ungula or periungual fibroma
3. Hypomelanotic macules (three or more)
4. Shagreen patch (connective tissue nevus) migration lines
5. Multiple retinal nodular hamartomas
6. Cortical tuber
7. Subependymal nodule
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangiomyomatosis (LAM)
11. Renal angiomyolipoma (renal AML)
Minor features
1. Multiple, randomly distributed
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial
5. Gingival fibromas
6. Nonrenal hamartoma
7. Retinal achromic patch
8. Confetti-like skin lesions
9. Multiple renal cysts

Definite TSC: either two major features or one major feature and two minor features. Probable TSC: one major and one minor feature. Possible TSC: either one major feature or two or more minor features. Note: Cortical tubers together with cerebral white matter radial migration lines are considered one feature. In patients with LAM or renal AML, other features are required for diagnosis

DISCUSSION

Tuberous sclerosis complex (TSC) is one of a group of related disorders known as neurocutaneous syndromes or phakomatoses with an incidence rate of approx. 1 in 5000–10,000 live births [2,3]. It is an autosomal dominant disease with high penetrance caused by genetic mutations in one of the TSC1 or TSC2 genes [2], which results in the overactivation of mammalian target of rapamycin complex 1 (mTOR), a key intracellular regulator of cell growth and proliferation, leading to hamartomatous lesions in several organs [3,4]. TSC is a multisystem disorder with various clinical manifestations. The wide spectrum of clinical features results from the formation of hamartomas in various organs. Hamartomas are frequently present in the skin, brain, kidneys, heart, and, less frequently, in the lungs, retina, gingiva, bones, and gastrointestinal tract [5]. The diagnosis is based on the association of major criteria and minor criteria (Table 1) [6]. The diagnosis is made when two major criteria, or one major and two minor, are fulfilled. The diagnosis and management of TSC is often challenging. The treatment involves addressing the symptoms caused by the hamartomas. Inhibitors of the mTOR pathway, such as rapamycin, have an immunosuppressive and antiproliferative action. This drug is effective in reducing the volume of the tumors.

On the other hand, psoriasis is a chronic autoimmune inflammatory skin disorder, following the proliferation and abnormal differentiation of keratinocytes, which are under the influence of several factors whose genetic component remains the most likely [7], including mutation of the genes of the chemokine, including MCP1, CCR2, and CCR5. The PSORS2 locus is a gene that is the active transcription factor in inflammation and immunity located in the region of the gene encoding the RAPTOR protein, a protein associated with mTOR regulation. Thrombin/threonine protein kinase (mTOR) regulates growth and cell proliferation in response to environmental stimuli. It is overexpressed preferentially at the psoriatic level of lesional and nonlesional skin [8]. In psoriasis, dysregulation of cytokines and growth factors may lead to the activation of the mTOR signaling system, which initiates the proliferation of keratinocytes and synovial cells responsible for psoriatic arthritis. For the first time, we explored how a dual kinase inhibitor of mTOR signal proteins may be an equally effective

therapeutic agent for psoriasis. The association with TSC in our patient suggests the genetic predisposition of psoriasis vulgaris [9]. It blocks IL-2-induced LT proliferation via mTOR inhibition.

CONCLUSION

To our knowledge, this is the first report that describes the association of psoriasis with STB in a patient. These inflammatory diseases are chronic with mainly cutaneous manifestations and share a hereditary character and a common pathophysiology, but with different mutations.

Consent

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

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

Our Dermatology Online

Opinion Article

Challenges of teledermatology in rural Australia

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ABSTRACT

People staying in rural and remote areas of Australia face a higher prevalence of health conditions because of the reduced access to healthcare, including primary healthcare. This may be complicated by the lack of ability of public hospitals to schedule across telehealth resources. Some of the remote care facilities, too, face difficulties to locate and connect to other facilities that provide telemedicine services. Up to 15% of all general practice consultations are dermatology cases. One of the ways of providing increased specialty access for the underserved and patients with no access to dermatological care is through teledermatology. Over the past decade, there has been an increase in the popularity of the use of teledermatology in supporting patient care. Teledermatology allows the diagnosis of skin conditions by virtue of the visual nature of the field of dermatology, making it a good match for telemedicine. According to the journal *Rural* and *Remote Health*, the success and sustainability of telehealth services in rural and remote Australia are also influenced by key factors such as adaptability, economics, and vision. Teledermatology has the potential to bring a number of advantages, for instance, a reduction in the waiting and travel times for patients and their family members. However, there also exist challenges in delivering healthcare to the rural areas of Australia.

Key words: Telemedicine; Telehealth; Remote consultation

People staying in rural and remote areas of Australia face a higher prevalence of health conditions because of the reduced access to healthcare, including primary healthcare. This may be complicated by the lack of ability of public hospitals to schedule across telehealth resources. Some of the remote care facilities, too, face difficulties to locate and connect to other facilities that provide telemedicine services [1]. Up to 15% of all general practice consultations are dermatology cases [2]. One of the ways of providing increased specialty access for the underserved and patients with no access to dermatological care is through teledermatology [3,4]. Over the past decade, there has been an increase in the popularity of the use of teledermatology in supporting patient care [5]. Teledermatology allows the diagnosis of skin conditions by virtue of the visual nature of the field of dermatology, making it a good match for telemedicine [4]. According to the journal *Rural* and *Remote Health*, the success and sustainability of telehealth services in rural and remote Australia are also influenced by key factors such as adaptability, economics, and vision [6]. Teledermatology has the potential to bring a number of advantages, for instance, a reduction in the waiting and travel times for patients and their family members. However, there also exist challenges in delivering healthcare to the rural areas of Australia [1].

In 2003, Tele-Derm National was made open-access by the Australian College of Rural and Remote Medicine (ACRRM) for doctors Australia-wide. By the use of this service, all general practitioners registered in rural and remote Australia are able to get dermatological opinion through teleconsultation as well as online education in dermatology [7,8]. The Tele-Derm service in Australia is delivered through the "store and forward" modality [7]. Contrary to the popular belief, a face-to-face consultation service, which is the traditional mode of consultation, is not necessarily better than teledermatology [8]. Care provided by teledermatology is often more effective, efficient, and of higher quality [4], and allows the provision of services where none exists [8]. According to the clinical questionnaires of a pilot study by Biscak et al., 100% of doctors working

How to cite this article: Lim TLC. Challenges of teledermatology in rural Australia. Our Dermatol Online. 2020;11(4):409-411.
Submission: 01.04.2020; **Acceptance:** 05.06.2020
DOI: 10.7241/ourd.20204.21

in the remote areas of Queensland, Australia, found the "store and forward" services advantageous. Additionally, 97% of them reported that they would use such services more than once. Only one answered "possibly" on the questionnaire. The study, therefore, revealed that the role played by teledermatology services in the delivery of healthcare to remote Australia is significant [9]. Nevertheless, through the "store and forward" modality, the patient's diagnosis will depend entirely on a medical history and digital images, which are stored, transferred, and standardized, rather than on videoconferencing. Even though the "store and forward" modality is independent of space and time, there is still a need to wait for dermatological opinion [4]. In Australia, cases are reviewed within 24 hours of submission [2], which is different from real-life interaction through videoconferencing, which allows direct doctor–patient interaction with more in-depth clinical history taking and immediate dermatological opinion. However, the digital images used for the "store and forward" modality are normally higher in resolution [4]. The drawback of this technology-oriented "store and forward" care is that it has not been able to comprehensively address the concerns and reservations of patients. Besides, there is a reduction in the unique doctor–patient relationship [9].

Although telemedicine has the potential to make a positive impact on patients, experienced providers of telemedicine in Australia have also identified barriers to the implementation of telemedicine [10]. According to the journal *Australian Family Physician*, the poor uptake of teledermatology may be due to the fact that the existence of teledermatology services is still not widely known to doctors and patients [2]. Besides the issue of funding, the other major barrier identified is the amount of time needed to conduct telemedicine consultations. This may increase the workload of rural Australian doctors [10]. It places a far greater responsibility on the referring doctors because the referring doctor still has to conduct the necessary investigations, management plans, and appropriate follow-ups once the diagnosis is confirmed [2]. In rural and remote Australia, access to the Internet is also significantly poorer and there can be a lack of equipment. Furthermore, doctors of rural Australia show a preference for traditional approaches and are skilled at teleconferencing, telephone, and facsimile. This preference might either mean they do not show much interest in learning IT (information technology) skills or face trouble acquiring such soft skills [10]. Some doctors might also face difficulties in resolving technology-related issues [11]. All this suggests that the implementation of teledermatology may become unsuccessful if doctors fail to understand the service, resulting, in turn, in its poor implementation. There may also be other barriers affecting the implementation of teledermatology [4]. Teledermatology is unsuitable for certain dermatologic conditions, for instance, lesions in the hair-bearing area and melanocytic lesions in patients with high-risk factors. Counseling through teledermatology is deemed unsuitable for patients diagnosed with melanoma or requiring total body skin examinations [11]. It is possible that erroneous diagnoses may occur, resulting in clinical inadequacies [9].

Moreover, according to the journal *Telemedicine Journal and e-Health*, factors such as the level of complexity of skin diseases, the patient's preferences, and the distance to accessible dermatologists may influence the decision of the primary healthcare provider to refer the patient for teledermatology [3]. The same journal also described a challenge in assessing outcomes in teledermatology in rural patients, which is the loss to follow-up with referring doctors [7]. Moreover, it may be challenging for doctors to follow-up on patients who are medically complex [11]. Security, privacy, ethical, and legal issues may also occur [4]. It is understandable that patients may be anxious over the possibility of doctors misdiagnosing and mismanaging them [2].

In conclusion, proper implementation of teledermatology, policies, and practice solutions are essential in dealing with the challenges and barriers affecting teledermatology in the rural communities of Australia. In addition, further research and more studies must be conducted to determine the perceived barriers to the implementation of teledermatological services, patient satisfaction, and the impact of teledermatology on quality of life.

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

Our Dermatology Online

Clinical Image

Nevus lipomatosus superficialis

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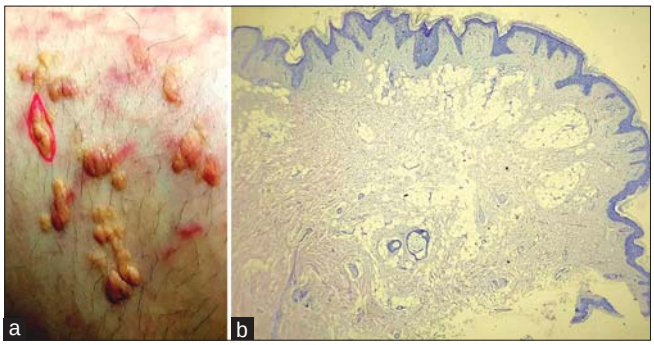
Nevus lipomatosus superficialis (NLS) is a rare type of connective-tissue nevus that appears before the age of 20 with an equal sex ratio and that usually manifests itself as soft, yellowish or skin-colored papules or plaques on the buttocks or the trunk, solitary or multiple with varying configurations. An NLS consists of mature adipose tissue within the dermis. No treatment is required [1-3].

A 16-years-old female presented to a dermatology clinic complaining of multiple yellowish papules and plaques confined to the right lower lateral trunk that had been visible since the age of 4. An examination of the skin revealed multiple soft yellowish papules and plaques of different sizes in a zosteriform distribution located on the lower lateral trunk (Fig. 1a). An incisional biopsy was taken for histopathological examination and revealed adipose tissue present throughout the dermis (Fig. 1b). The diagnosis of nevus lipomatosus superficialis was confirmed. The patient was referred to a plastic surgery clinic for further treatment.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients have given consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.



Figures 1: (a) Nevus lipomatosus superficialis. (b) Mature adipose tissue in the dermis (H&E, ×10).

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

How to cite this article: Abdullah M, Lateef A. Nevus lipomatosus superficialis. Our Dermatol Online. 2020;11(4):412.

Submission: 28.03.2020; **Acceptance:** 02.07.2020

DOI: 10.7241/ourd.20204.22

Our Dermatology Online

Clinical Image

Acquired vulvar lymphangioma: An enigma

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A 44-year-old female developed multiple solid dusky-red and skin-colored labial papules and plaques with rough surfaces and warty excrescences (Fig. 1). The overlying skin was hyperpigmented, indurated, and rugose. The lesions had developed over a couple of years and were asymptomatic. There was no crusting or oozing. There was a long medical history of vulval lymphedema secondary to filariasis. An excisional biopsy of a papule showed papillated epidermal hyperplasia and focal parakeratosis. The papillary dermis showed a "Swiss-cheese"–like appearance secondary to lymphedema and superficial sciatic thin-walled vascular spaces with a proteinaceous fluid characteristic of lymphangiectasias (Fig. 2). The patient was treated with vulvectomy and has shown no sign of recurrence to date.

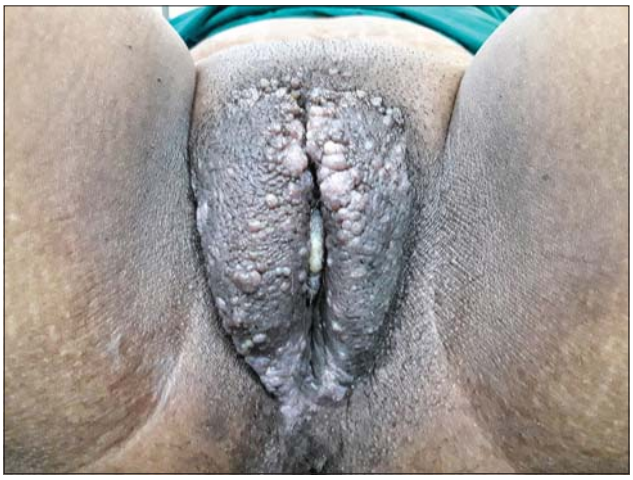

Figure1: Numerous sessile dusky-red and skin-colored warty papules and plaques in the vulva in a background of hyperpigmented and rugose skin.

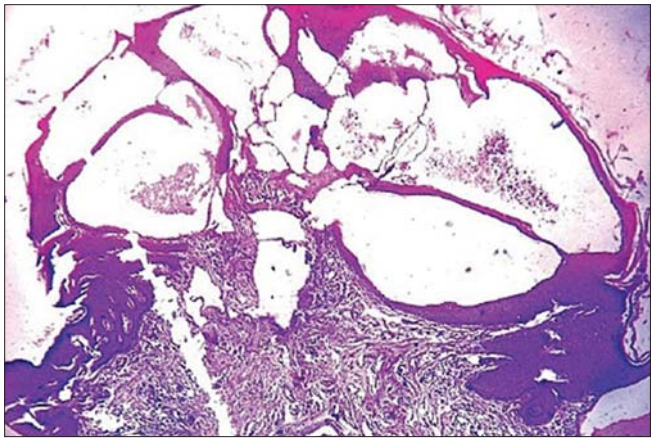

Figure 2: Acanthosis and hyperkeratosis of the epidermis along with numerous dilated lymphatic channels in the upper dermis containing proteinaceous eosinophilic material (H&E, 100×).

Lymphangioma circumscriptum, or acquired lymphangioma, is the most common form of cutaneous lymphangioma and may occur at any age [1]. Congenital lymphangiomas are hamartomatous malformations of lymphatic vessels, whereas acquired lymphangiomas arise due to acquired obstruction of lymph vessels following surgery, infection—such as erysipelas and tuberculosis—or radiation treatment. The sites of predilection for acquired lymphangioma are the proximal extremities, trunk, axilla, and oral cavity, especially the tongue [2]. The female external genitalia are a very rare site for lymphangioma circumscriptum [1-3]. The differential diagnosis of lesions in the genitalia includes condylomata lata, genital warts, molluscum contagiosum, herpes zoster, seborrheic keratosis, and even leiomyoma [3].

In spite of the absence of a standard therapy for lymphangiomas, various modalities of treatment have been suggested, such as observation, surgical excision of the skin and subcutaneous tissues, surface ablation with laser (CO_2, Er:YAG), sclerotherapy, and superficial radiotherapy. Intense pulse light and pulse dye laser may also be tried. Surgical excision is the treatment of choice with a high success rate for lesions confined to the superficial dermis [1,3].

Consent

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

How to cite this article: Varma R. Acquired vulvar lymphangioma: An enigma. Our Dermatol Online. 2020;11(4):413-414
Submission: 07.02.2020; **Acceptance:** 19.04.2020
DOI: 10.7241/ourd.20204.23

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Letter to the Editor

Seasonal variation in Google search interest for melasma

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Sir,

Melasma is a common chronic acquired disorder of hyperpigmentation found worldwide. The relationship between sun exposure and melasma exacerbation is commonly reported, as is the use of broad-spectrum sunscreens in treating melasma [1]. However, the seasonal variations in the prevalence or incidence of melasma are not well established, having only been examined in a single-center study in Nepal [2]. In the absence of large-scale clinical epidemiological studies, we used *Google* search data to conduct an ecological study of seasonal patterns of public interest in melasma.

Google Trends was queried for the search term "melasma" from January 1, 2011 to December 31, 2019 among users in the United States (US). *Google Trends* outputs search interest data that is normalized by time and geographic region. The single maximal search interest value in each query is set as "100", and all other points are scaled proportionally. There are mechanisms in place to detect and filter irregular activity. Searches made very infrequently, duplicate searches from the same person over a short period and searches with special characters are filtered out [3]. Data from January 1, 2020 and after was excluded to minimize the effect of the novel coronavirus-19 pandemic on search results. The data was acquired on May 13, 2020 [4].

Cosinor analysis, which models seasonal patterns using a sinusoidal equation, was performed on the dataset [5]. Cosinor analyses yield two p values, a sine and cosine p value. If either p-value is less than the established value of significance, the model detects significant seasonality. Using the Bonferroni correction to address the multiple comparison problem, the level of significance was established at $p<0.025$ [5] In addition to providing a seasonal peak and nadir, the model also provides an amplitude which is half the extent of predictable variation in a cycle. Cosinor analysis was performed in R version 3.6.3 with "season" package [6,7].

A time series of monthly normalized search interest for melasma in the US showed clear seasonal variations that cycled annually (Figs. 1a and 1b). Cosinor analysis showed that this seasonality in the US was statistically significant (sin $p<0.001$, cos $p<0.001$), with an amplitude of 22.1, a peak in June, and a nadir in December (Fig. 1c).

This exploratory study shows that in the US, a country with a primarily temperate climate, *Google* search interest for melasma peaked in the summertime. This pattern of seasonality of public interest in melasma is unsurprising, given prior clinical reports of UV as a trigger for melasma and a short theoretical latency period between exposure and disease exacerbation [1]. However, we cannot exclude another confounding variable driving these seasonal differences. A limitation of the cosinor model is that it assumes a sinusoidal pattern, which must be symmetric and may be too restrictive in certain cases [5]. Furthermore, how well seasonal variations in public interest, as measured by *Google* search interest, mirror differences in incidence requires further epidemiological or clinical studies.

Consent

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

How to cite this article: Muddasani S, Wu SZ, Fleischer Jr. AB. Seasonal variation in Google search interest for melasma. Our Dermatol Online. 2020;11(4):415-416.
Submission: 30.05.2020; **Acceptance:** 01.09.2020
DOI: 10.7241/ourd.20204.24

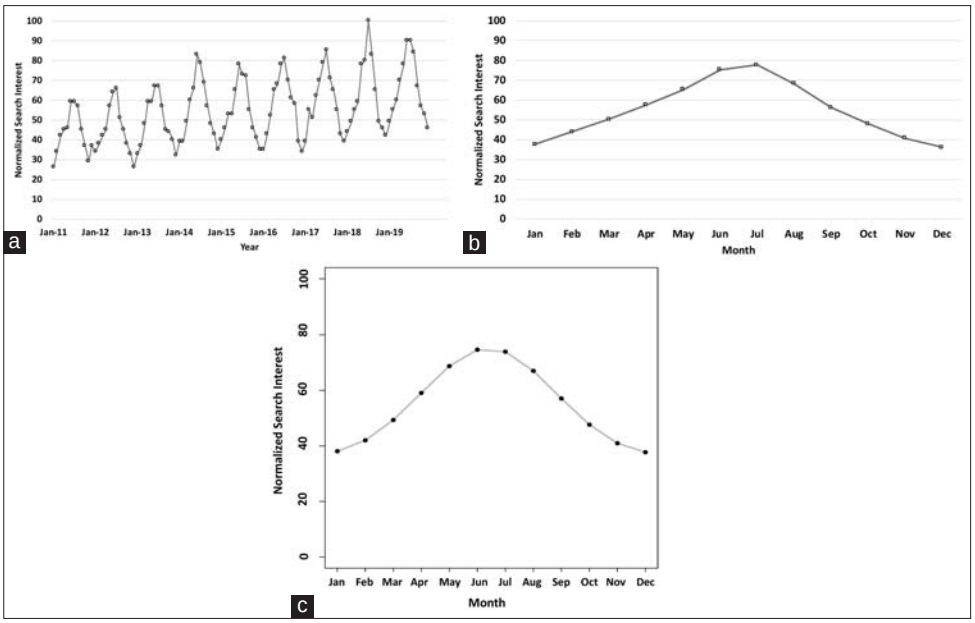

Figure 1: Graphical representations of normalized search interest, A. normalized search interest time series, B. mean normalized search interest for each month of the year, C. cosinor models of normalized search interest, Jan=January, Feb=February, Mar=March, Apr=April, May=May, Jun=June, Jul=July, Aug=August, Sep=September, Oct=October, Nov=November, Dec=December.

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Source of Support: Nil, **Conflict of Interest:** Dr. Fleischer is a consultant for Boerhringer-Ingelheim, Dermavant, Incyte, Qurient, SCM Lifescience and Syneos. He is an investigator for Galderma, Menlo and Trevi. He has no other potential conflicts including Honoraria, Speakers bureau, Stock ownership or options, Expert testimony, Grants, Patents filed, received, pending, or in preparation, Royalties, or Donation of medical equipment.

Letter to the Editor

Two cases of perianal basal cell carcinoma

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Sir

Herein, we report two cases.

CASE 1

A 71-year-old female presented with a perianal mass seen for the past 10 years, growing slowly over 12 months prior to presentation. Her past medical history included primary biliary cirrhosis, dyslipidemia, gastroesophageal reflux disease, and osteoporosis. A dermatological examination revealed a reddish exophytic nodular lesion approx. 30 × 25 mm in size in the perianal region at the 9 o'clock position (Fig. 1a). Aside from the perianal lesion, the anal canal was normal. A biopsy of the perianal region was performed, since the preliminary diagnosis was skin cancer, as squamous cell carcinoma or melanoma. The tumor was composed of a proliferation of basaloid cells with peripheral palisading in the dermis, and a mild mucin deposition was noted around the tumor (Figs. 1b–1d). Histological findings revealed superficial basal cell carcinoma (BCC). The patient was referred to another hospital for further treatment.

CASE 2

An 80-year-old female presented with an itchy brownish lesion on the right side of the perianal region seen for the past year. She had a history of angina pectoris, uterine fibroid, and uterine prolapse. There was no medical history of radiotherapy, chemical exposure, or trauma to the genital area. There was no remarkable family history of skin disease or skin cancer. A physical examination revealed a single brownish patch with slight itching near the anus (Fig. 2a). Dermatoscopy showed a large bluish-gray ovoid nest, multiple bluish-gray globules, and arborizing vessels (Fig. 2b). An incision biopsy was performed, showing basaloid cells with peripheral palisading in the superficial area of the dermis (Fig. 2c). The tumor was excised completely with a 2–4 mm clear margin. After the excision, there was no evidence of recurrence during a 3-month follow-up period.

Chronic exposure to the sun is a significant predisposing factor for BCC. More than 80% of BCC cases occur on sun-exposed areas, such as the head and neck [1]. Consequently, BCC of areas that are not sun-exposed, such as the axilla, nipple, or the genital and perianal areas, are extremely rare. It is estimated that perianal BCC accounts for only 0.08% of all BCCs [2]. In Japan, Hamada investigated 412 cases of BCC, and only 2 (0.5%) perianal BCCs were identified. Nagamatsu reported 2 (2.4%) BCCs located in the preanal area out of the 83 studied.

These regions are usually well covered and not exposed to sunlight. The etiologic factors for perianal BCC have not yet been clearly defined but, according to previous reports, the possible causes include radiation therapy, alternation in immune surveillance, exposure to coal tar or arsenic, sexually transmitted diseases, burns, traumatic scars, and chronic skin irritation [3,4]. Neither of our two cases had any of these etiologies. BCC occurs mainly in middle-aged and elderly patients, but the average age is slightly higher for perianal BCC, compared to the other types of BCC [5]. Moreover, most patients are men, and lesions are usually less than 2 cm in diameter [6]. Case 1 presented with a large ulcerated nodule 30 × 25 mm in size. Case 2 presented with a hyperpigmented plaque with central ulceration. Our cases showed, thus, one nodular and

How to cite this article: Matsumura N, Irie K, Endo M, Miura T, Kato Y, Ohtsuka M, Yamamoto T. Two cases of perianal basal cell carcinoma. Our Dermatol Online. 2020;11(4):417-419.

Submission: 15.02.2020; **Acceptance:** 23.04.2020

DOI: 10.7241/ourd.20204.25

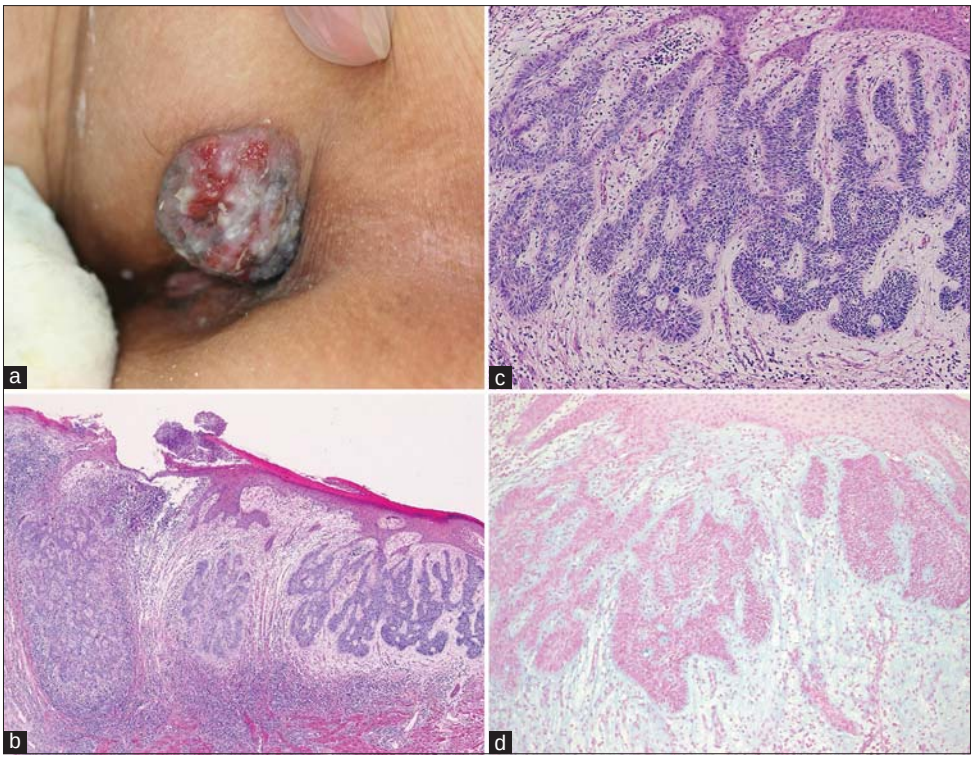

Figure 1: (a) A reddish exophytic nodular lesion approx. 30 × 25 mm in size with central ulceration. (b) Anastomosing cords of basaloid cells connecting to the epidermis (H&E, ×40). (c) A proliferation of basaloid cells with peripheral palisading in the dermis (H&E, ×100). (d) Mucin pooling around the tumor. Alcian blue and colloidal iron stain positive around the peritumoral space.

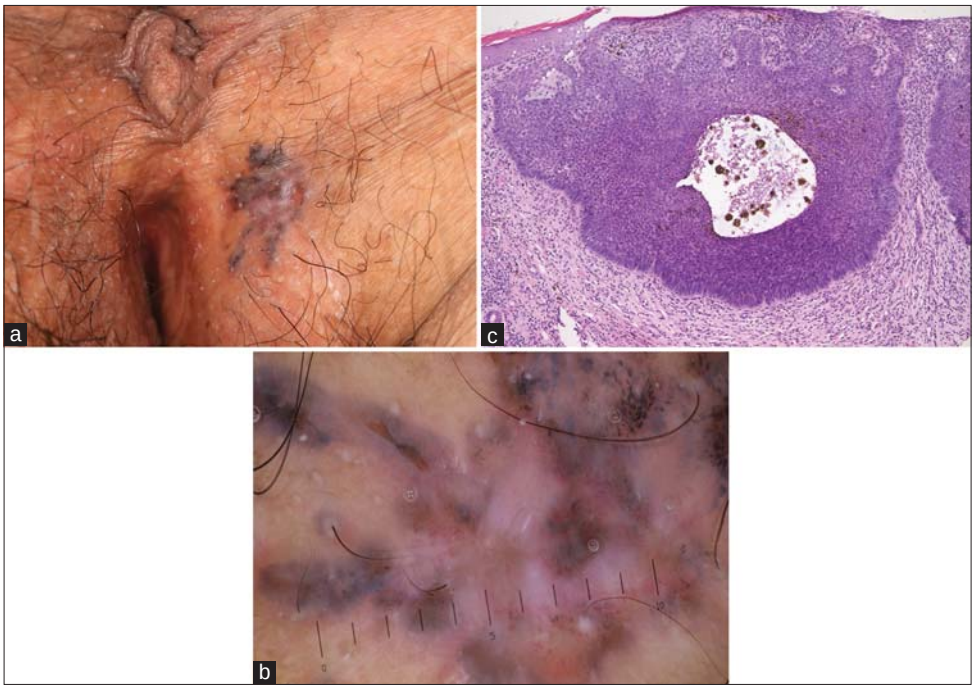

Figure 2: (a) A single brownish patch with slight itching near the anus. (b) A large bluish-gray ovoid nest, multiple bluish-gray globules, and arborizing vessels. (c) Basaloid cells with peripheral palisading in the superficial area of the dermis (H&E, ×40).

one superficial BCC. A literature review revealed that the most common type of perianal BCC is nodular, followed by superficial [2].

According to the National Comprehensive Cancer Network (NCCN), a BCC in the perianal region is considered high-risk. Treatment options for

perianal BCC include wide local excision and Mohs micrographic surgery. Case 2 was treated with a 2–4 mm excision with a clear margin, and no recurrence was observed during a 3-month follow-up period. A standard 4 mm margin excision should be considered in select tumors. In summary, because perianal BCC is so uncommon and the lesions are located in an inconspicuous area, Aldana insists that a biopsy should be considered for suspicious lesions in the perianal and genital areas [7]. Increased awareness of perianal BCC may contribute to the prevention of delayed diagnosis.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients have given consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Letter to the Editor

A case of eczema herpeticum with Hailey–Hailey disease: A potential diagnostic pitfall

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Sir,

We report the case of a 48-year-old female with a medical history of Hailey–Hailey disease. The patient had been followed since the age of 30 years for Hailey–Hailey disease, which had affected the axillary and inguinal region (Fig. 1a). The presence of intraepidermal clefts in the epidermis with dyskeratotic cells and acantholysis with the characteristic appearance of a dilapidated brick wall was confirmed histologically (Fig. 1b). The patient was treated with topical corticosteroids and dapsone 100 mg/day. She was referred for painful lesions and a burning sensation in the groin present for the last two days. A physical examination revealed multiple vesiculopustules on erythematous plaques with linear ulcerations in the inguinal region (Fig. 2). She had no fever and no lesions elsewhere. A skin biopsy revealed Hailey–Hailey disease with herpetic eczema. The patient was treated with acyclovir 500 mg three times a day administered intravenously for ten days with a favorable outcome.

Hailey–Hailey disease is a rare genodermatosis with autosomal dominant inheritance and incomplete penetrance [1]. Clinically, it presents itself as flaccid vesicles and fissures in intertriginous areas [2] with superficial linear erosions with crusts and maceration. Heat, sweating, and friction often exacerbate the disease. In addition to the classic bacterial and fungal infections, which may complicate the course of Hailey–Hailey disease, a herpes simplex infection may worsen Hailey–Hailey lesions [2]. Herein, we report a case of Hailey–Hailey disease with coexistent herpes virus infection located in the inguinal region. Hailey–Hailey disease with coexistent HSV (herpes simplex virus) infection is rarely reported in the literature. In fact, Hailey–Hailey disease is a primary acantholytic disease which could be complicated by a secondary acantholytic disorder, such as a herpes virus infection [3]. The diagnosis should be suspected clinically when lesions of the inguinal region become painful with acute flaring of multiple vesiculopustules associated with painful erosions. The diagnosis suspected clinically should be confirmed by viral culture, PCR, and a skin biopsy. Skin cytology, as reported by de Aquino Paulo Filho [2], is a rapid diagnostic tool showing giant viral multinucleated cells that could guide the early diagnosis of an HSV infection. The risk factors include rupture of the epidermal barrier and the use of corticosteroids [1-5]. Indeed, the disruption of the stratum corneum and the fragility of the epidermis in Hailey–Hailey disease make it easy for HSV to infect and proliferate [6]. Rapid diagnosis of this complication is advised for quick treatment and to avoid systemic complications. In fact, it is a potentially life-threatening viral infection that may be disseminated, leading to visceral involvement and death [4]. Therapy should be initiated without delay if there is a high suspicion or a positive Tzanck smear with high-dose intravenous antiviral drugs such as acyclovir [2]. Timely recognition of this complication helps to improve the prognosis of the disease [4].

In summary, this case is being reported to increase awareness of the rare association between Hailey–Hailey disease and HSV infection, which may be severe and which frequently alters the quality of life of affected patients.

How to cite this article: Zaouak A, Bouhajja L, Hammami H, Fenniche S. A case of eczema herpeticum with Hailey–Hailey disease: A potential diagnostic pitfall.Our Dermatol Online. 2020;11(4):420-421.

Submission: 27.10.2019; **Acceptance:** 10.01.2020

DOI: 10.7241/ourd.20204.26

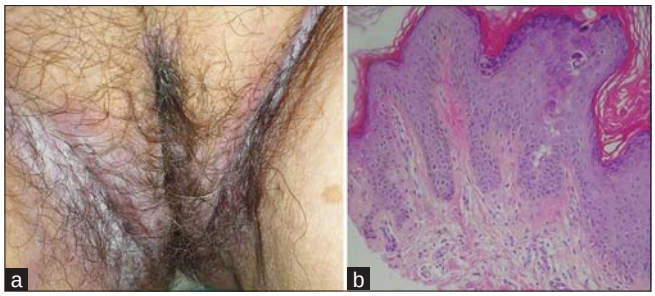

Figure 1: (a) White plaques in the inguinal region with linear fissures. (b) Intraepidermal clefts in the epidermis with dyskeratotic cells and acantholysis with the characteristic appearance of a dilapidated brick wall (H&E, 100×).

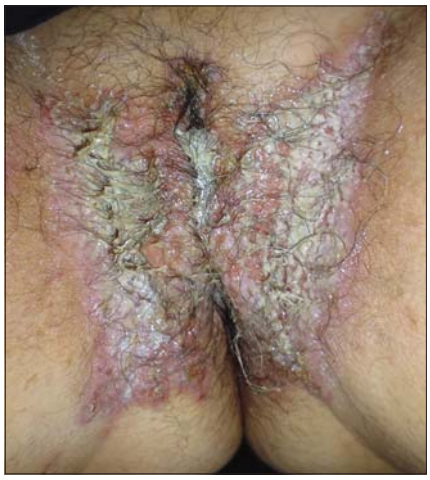

Figure 2: Multiple vesiculopustules with small erosions on an erythematous base in the inguinal region.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Letter to the Editor

Trichofolliculoma: A new dermoscopic pattern

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Sir,

Trichofolliculoma is an uncommon benign hair-follicle hamartoma usually appearing in adulthood as a solitary papule or nodule on the face or scalp. In some cases, the lesion manifests itself as a central dilated pore with a small tuft of white hairs, which corresponds histologically to a primary dilated hair follicle with secondary immature hair follicles emerging from it. The dermoscopic features of trichofolliculoma have rarely been described and are usually nonspecific. We report a new dermoscopic pattern of trichofolliculoma.

A seventeen-year-old female presented herself with a two-year history of a small itchy papule on the right cheek. The patient described occasional discharge of whitish filamentary material from the center of the lesion. A physical examination revealed a skin-colored pinhead-sized papule with a central dilated pore (Fig. 1).

A dermoscopic examination revealed a pinkish structureless lesion with a tuft of thin fuzzy white hairs emerging from a central opening surrounded by a horny plug (Fig. 2).

An excisional biopsy was performed as the patient was very annoyed by the itching. A histological examination revealed a dysmorphic hair follicle with a central invagination filled with keratinous material and multiple secondary follicles radiating around it. These elements were consistent with the diagnosis of trichofolliculoma (Fig. 3).

Trichofolliculoma is a benign hair-follicle tumor first described by Meischer in 1944 [1]. It is mostly seen in adulthood but may also occur in children or even newborns [2]. It manifests clinically as a solitary papule affecting the face and scalp, sometimes with a dilated pore and a small tuft of hair in the middle. However, these specific features are not always present and the clinical aspect may be very misleading.

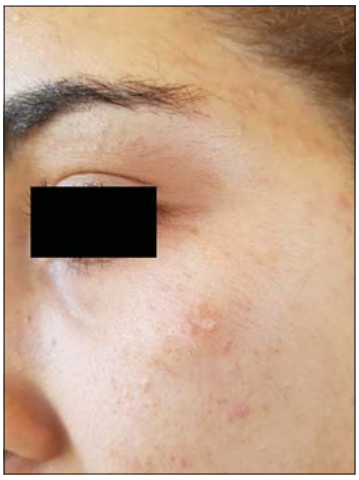

Figure 1: The clinical aspect of the lesion with no particular orientation.

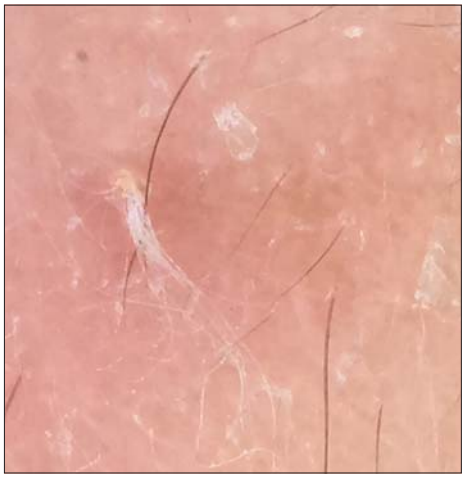

Figure 2: A pinkish structureless lesion with a tuft of thin white hairs emerging from a central opening.

How to cite this article: Mai S, Meziane M, Znati K, Senouci K. Trichofolliculoma: A new dermoscopic pattern. Our Dermatol Online. 2020;11(4):422-423.
Submission: 21.11.2019; **Acceptance:** 22.01.2020
DOI: 10.7241/ourd.20204.27

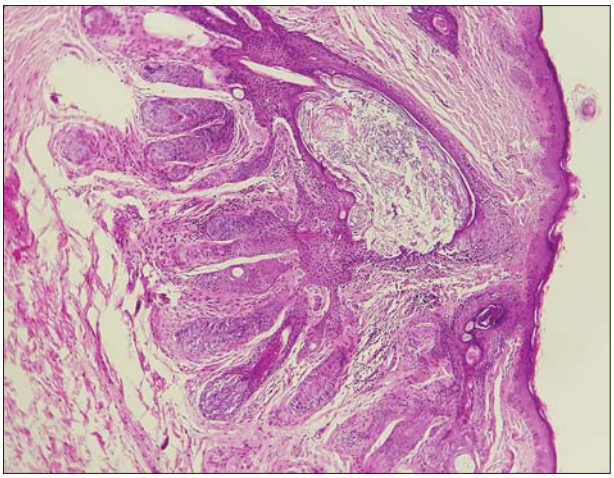

Figure 3: Multiple secondary hair follicles radiating from a primary dysmorphic follicle with a central cavity filled with keratin and sebum.

Dermoscopy may be particularly helpful to exclude differential diagnoses, especially malignant tumors. The dermoscopic features of trichofolliculoma have rarely been described in the literature. Panasiti et al. described a case with a "firework" pattern with a central brown zone and radial dark brown projections [3]. Jégou-Penoui et al. reported a case of a pinkish hemispherical well-limited papule with a central disruptor and fine peripheral serpiginous vascularization with a centripetal disposition [2]. Garcia-Garcia et al. reported a late-stage lesion that appeared as a well-defined, bluish nodule with a white-pink central area, shiny-white structures, dotted vessels, and a central scale [4].

This particular aspect of a white hair tuft that may be observed clinically has never been described on dermoscopy before.

Consent

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

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

Our Dermatology Online

Letter to the Editor

Solitary fibrous tumor of the inguinal region displaying heterogeneous echogenicity and its correlation with histopathologic findings

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Sir,

Solitary fibrous tumor (SFT)—first documented by Klemperer and Rabin in 1931 as a primary neoplasm of the pleura [1]—represents a rare fibroblastic neoplasm composed of cellular areas and a less cellular zone of thick hyalinized collagen intermingled with numerous vessels. SFT is anatomically ubiquitous and classically benign, and malignant transformations have been reported [2]. The NAB2–STAT6 gene fusion, which is associated with nuclear relocation of STAT6 protein, has recently been identified as the defining driver mutation of SFT [3]. Herein, we report a case of SFT of the inguinal region and evaluate the correlation between ultrasonographic and histopathologic findings.

A 63-year-old male presented with a three-month history of a painless and mobile subcutaneous mass in the right inguinal region. Color Doppler revealed a well-circumscribed, ovoid, heterogeneous echoic mass 21 × 31 × 14 mm in size with peripheral color flow signals (Fig. 1a). Magnetic resonance imaging (MRI) showed low signal intensity on T1-weighted image and high signal intensity on T2-weighted image. Computed tomography (CT) of the chest, abdomen, and pelvis showed no evidence of metastasis. The patient underwent excision of the lesion, which was located in the subcutaneous fat just below the superficial fascia (Fig. 1b). Histopathologic findings revealed an encapsulated tumor composed of cellular areas with patternless bland spindle cells without nuclear atypia and less cellular zones with abundant collagen fibers (Figs. 1c – 1e). There were numerous vessels including a staghorn-like vascular network (Fig. 1d) and clustering dilated vessels on the periphery (Fig. 1f). Immunohistochemical staining showed cytoplasmic expression of CD34 (Fig. 1g) and nuclear translocation of STAT6 protein (Fig. 1h), whereas expression of Bcl-2 and CD99 was partial, and staining for AE1/AE3, desmin, S100 protein, c-KIT, factor VIII, and CD31 was negative (Fig. 1i). Based on these results, the patient was diagnosed with SFT. Since the surgical excision, there has been no recurrence for more than two years.

We have evaluated the correlation between ultrasonographic and histopathologic findings. In ultrasonography (USG), hypoechoic lesions matched the distribution of cellular areas in histology, whereas hyperechoic lesions matched the distribution of less cellular zones with abundant collagen fibers (Figs. 1a – 1e). Peripheral color flow signals in color Doppler ultrasonography corresponded to the clustering dilated vessels (Figs. 1a, 1c, and 1f).

The ultrasonographic findings of SFT have not been described due to its rarity and ubiquitous locations. Since the proportion of cellular areas and less cellular zones in SFT varies, the heterogenous pattern of SFT may vary from case to case. There have been several reports describing the ultrasonographic and color Doppler findings of SFT: solitary, homogenous hypoechoic lesions of the pleura in three cases [4]; an ovoid, hypoechoic lesion of the breast with peripheral and internal color flow signals [5]; and a mosaic echo

How to cite this article: Kajita A, Kawakami Y, Miyake T, Oda W, Yamasaki O, Morizane S. Solitary fibrous tumor of the inguinal region displaying heterogeneous echogenicity and its correlation with histopathologic findings. Our Dermatol Online. 2020;11(4):424-426.

Submission: 29.06.2020; **Acceptance:** 01.10.2020

DOI: 10.7241/ourd.20204.28

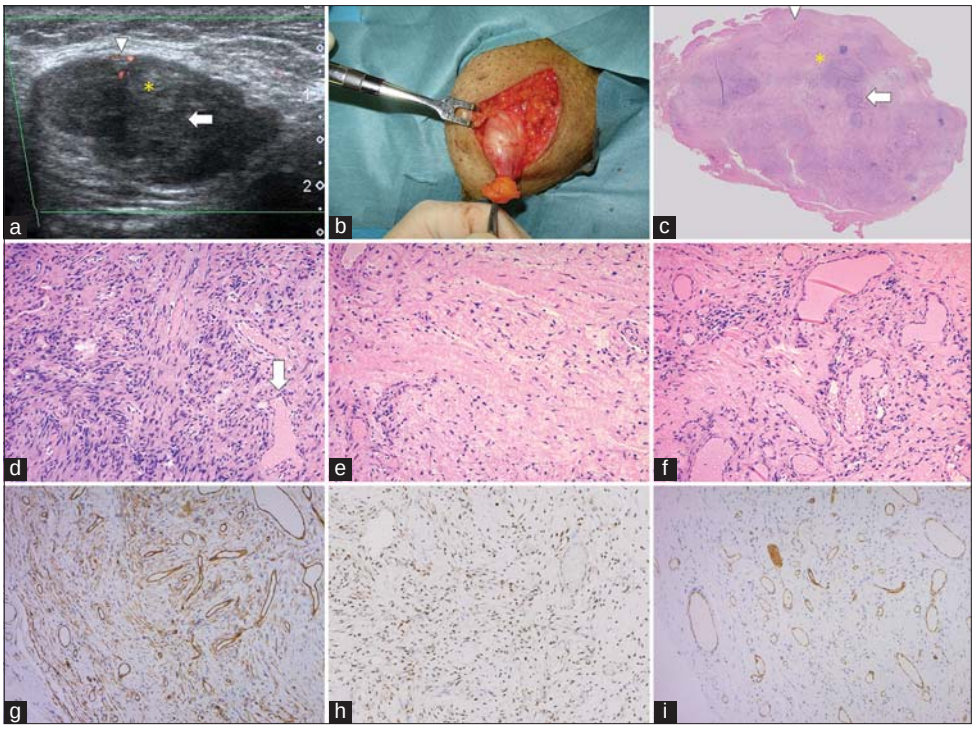

Figure 1: (a) Color Doppler USG showing an ovoid lesion with hypo- (arrow) and hyperechoic lesions (asterisk) and peripheral color flow signals (arrowhead).(b) Intraoperative findings showing an encapsulated subcutaneous tumor just below the superficial fascia. (c) An overview section displaying an encapsulated tumor composed of cellular areas (arrow) matching the distribution of hypoechoic lesions in USG and less cellular zones (asterisk) corresponding to the distribution of hyperechoic lesions in USG, as well as clustering dilated vessels on the periphery (arrowhead) matching the distribution of color signals on color Doppler (H&E). (d) A high-power view of a cellular area (arrow in Fig. 1c) showing patternless spindle cells and numerous vessels, including staghorn-like vessels (arrow) (H&E; original magnification: 100×). (e) A high-power view of a less cellular zone (asterisk in Fig. 1c) showing abundant collagen fibers (H&E; original magnification: 100×). (f) A high-power view of the peripheral region (arrowhead in Fig. 1c) showing clustering dilated vessels (H&E; original magnification: 100×). (g) Tumor cells showing positivity for CD34 (original magnification: 100×). (h) Tumor cells showing nuclear expression of STAT6 (1:200; sc-621; Santa Cruz) and vascular endothelial cells showing negative expression (original magnification: 100×). (i) Tumor cells showing negative expression of CD31, staining only vascular endothelial cells (original magnification: 100×).

pattern with rich blood flow signals in a subcutaneous tumor of the hip [6]. Two of them reported correlations between ultrasonographic and histopathologic or macroscopic findings. In both, the vasculature of the lesions in histologic or macroscopic findings matched the distribution of color flow signals on color Doppler [5,6]. Heterogeneous echoic masses with color flow signals in USG observed in our case have also been reported in other subcutaneous tumors, such as angiolipomas, superficial metastatic melanomas, and eccrine spiradenomas [7]. Ultrasonographic findings do not necessarily predict the preoperative diagnosis of SFT. Nevertheless, because the MRI of SFT is relatively nonspecific [5], it is important to accumulate ultrasonographic findings of SFT.

Consent

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

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

Our Dermatology Online

Letter to the Editor

Cutaneous blastomycosis as a malodorous wound

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Sir,

A 70-year-old male presented himself with a nonhealing wound over the right lower extremity, which had grown slowly over the course of six months (Fig. 1). Additional symptoms included pain accompanying movement of the leg and a malodorous smell. The patient had a notable history of living in a rural area in Indiana for many years and working as a farmer. No one in his household displayed similar lesions. Histopathologic findings showed broad-based budding yeast surrounded by neutrophils (Fig. 2). Gomori methenamine silver and periodic acid–Schiff stains and a fungal culture confirmed the diagnosis of *Blastomyces dermatitidis*. Despite the absence of respiratory complaints, subsequent CT imaging of the chest showed a 2.7 × 1.1 × 1.2 cm soft tissue density in the anterior upper lobe of the right lung. The patient was placed on a prolonged course of oral itraconazole with a slow resolution of the pulmonary and cutaneous ailments.

Cutaneous blastomycosis typically manifests itself after hematogenous spread from a primary source in the lungs, even in the absence of florid pneumonia [1]. Less often, *Blastomyces dermatitidis* can directly infect the skin, resulting in cutaneous blastomycosis [2]. These skin lesions are most often described as ulcerative or verrucous; however, they present themselves in a wide array of ways, including nodules, pustules, papules, and abscesses [3]. The most frequent extrapulmonary site is the skin, occurring in about 12% to 18% of cases. The face and extremities are commonly involved. In patients with multiple systems affected, approximately 77% have skin involvement. As many as 50% of blastomycosis cases may be without symptoms, with cutaneous involvement as the only sign of infection [4].

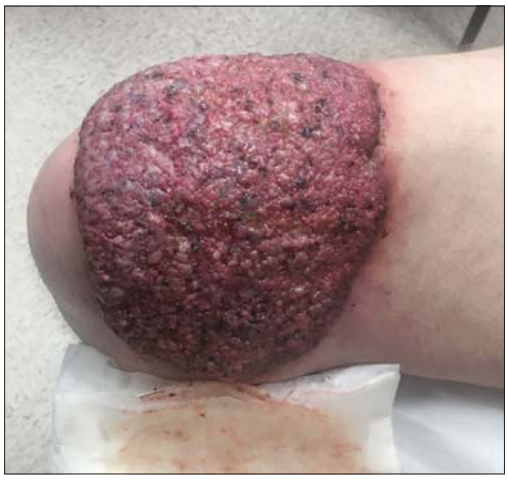

Figure 1: A gross image of the patient with cutaneous blastomycoses showing notable hyperkeratotic, verrucous, mounded nodules with a gray to violaceous border.

Although local blastomycosis outbreaks have been reported, most cases are sporadic. Endemic areas include the Midwestern states, as in the case of our patient, the Southeastern states, the Mississippi and Ohio River Basins, and the Canadian provinces near the Great Lakes. Despite initial reports of endemic cases affecting mostly middle-aged men performing outdoor occupations, a review of the reported outbreaks showed that such cases were not limited by sex, age, race, or occupational and seasonal predilections. Exposure to soil through work or recreational activities, typically near bodies of water, appears to be the most common factor associated with infection [5].

Two types of these cutaneous lesions are commonly distinguished [6]. They may appear as papules that progress to hyperkeratotic, verrucous, mounded nodules with a gray to violaceous border and with or without surrounding pustules, as in our patient. Less commonly, they may also develop a superficial ulcer

How to cite this article: Hekman D, Rahnama-Moghadam S. Cutaneous blastomycosis as a malodorous wound. Our Dermatol Online. 2020;11(4):427-428.
Submission: 23.06.2020; **Acceptance:** 11.10.2020
DOI: 10.7241/ourd.20204.29

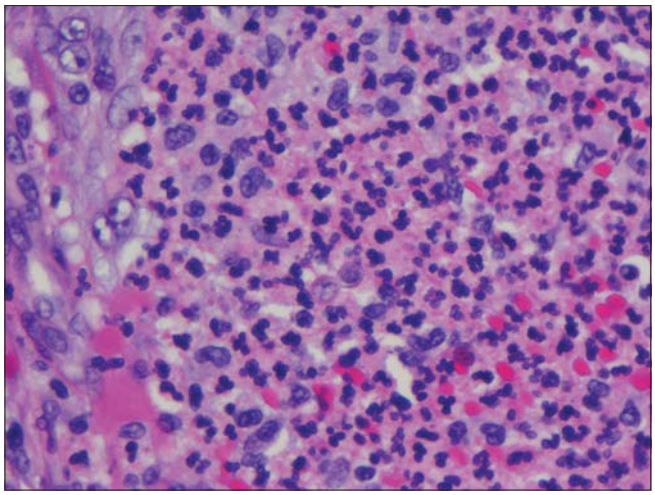

Figure 2: Histopathologic findings from a lesion showing broad-based budding yeast surrounded by neutrophils.

surrounded by an elevated border and an underlying base of friable granulation tissue. Differential diagnosis includes pyoderma gangrenosum and squamous cell carcinoma.

Diagnosis is confirmed by culturing tissue samples of the organism and/or visualizing thick-walled, broad-based budding organisms on pathology slides. Wet mounts obtained by touching a glass microscope slide to the wet exudate of the wound surface and stained for fungal spores may visualize organisms as well. Currently, serologic testing has not proven effective in diagnosing blastomycosis.

Since there is no operative national surveillance, the incidence of infection remains unknown. In the endemic area of Wisconsin, the average annual incidence rate between 1986 and 1995 was 1.4 cases per 100,000 persons. Accurate diagnosis of blastomycosis with appropriate evaluation is important, especially as its mortality falls at around 4%, even with treatment [7].

Consent

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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

Letter to the Editor

Generalized lichen amyloidosis

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Sir,

Lichen amyloidosis (LA) is a primary cutaneous amyloidosis characterized clinically by papular lesions with a usual localization on the legs. The generalized form is uncommon. We report a new atypical case of lichen amyloidosis characterized by generalized lesions and successfully treated with a new therapeutic combination: acitretin and trichloroacetic acid at 50%.

A 57-year-old female with a history of high blood pressure under treatment consulted for very itchy papular lesions evolving for the last six years and treated with emollients, dermocorticoids, and antihistamines but without improvement. The lesions were initially located on the legs but then gradually spread to the rest of the body. A dermatological examination found papular, flesh-colored lesions 2–3 mm in diameter, some of them keratotic, rough on palpation, resting on hyperpigmented plates, associated with scratching lesions, and located on the arms, forearms, thighs, legs, back, and neck (Figs. 1 and 2). A skin biopsy revealed an acanthotic and papillomatous epidermis and orthokeratotic hyperkeratosis with amorphous and cracked eosinophilic deposits in the papillary dermis (Fig. 3) easily visible with standard staining and birefringent with the Congo red stain. The rest of the biological and morphological assessments revealed no association with endocrine neoplasia. The diagnosis of generalized lichen amyloidosis was established. The patient was treated with acitretin 25 mg daily in combination with trichloroacetic acid at 50% (one application every fifteen days). There was a decrease in the pruritus from the first month and a good evolution of the cutaneous lesions after one year of follow-up.

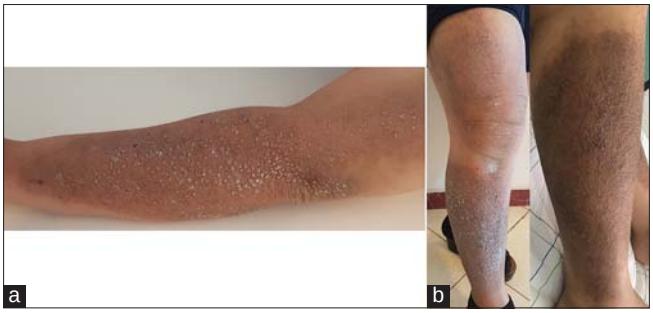

Figure 1: (a-b) Generalized lichen amyloidosis: multiple papules on hyperpigmented plaques on the upper and lower limbs.

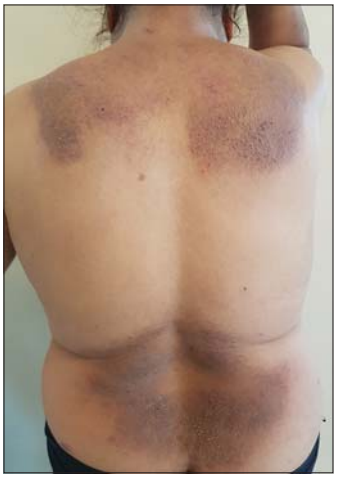

Figure 2: Generalized lichen amyloidosis: multiple papules on hyperpigmented plaques on the back.

The generalized form of lichen amyloidosis is rare and often associated with other dermatoses that aggravate the pruritus, such as lichen planus [1], chronic urticarial [2], atopic dermatitis, prurigo, and mycosis fungoides. In our patient, data from the interview, a clinical examination, and additional examinations could not reveal an associated aggravating factor.

How to cite this article: Maouni S, Mezni L, Znati K, Meziane M, Ismaili N, Senouci K, Benzekri L. Generalized lichen amyloidosis. Our Dermatol Online. 2020;11(4):429-430.

Submission: 11.12.2019; **Acceptance:** 17.02.2020

DOI: 10.7241/ourd.20204.30

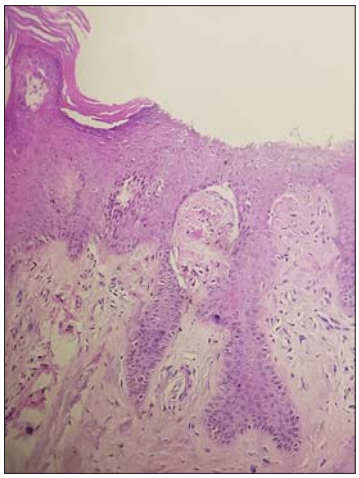

Figure 3: Generalized lichen amyloidosis and histologic findings: an acanthotic and papillomatous epidermis with orthokeratotic hyperkeratosis; globular eosinophilic deposits throughout the papillary dermis (H&E, 100×).

Two theories have been proposed to explain the mechanism of cutaneous amyloidosis: the apoptotic theory, which involves the transformation of keratin from apoptotic keratinocytes into amyloid bodies, and another theory, which proposes that the cutaneous amyloid deposits result from direct secretion by keratinocytes [3]. The therapeutic management of this clinical form is very delicate and several therapeutic methods have been proposed by the literature. Oral retinoids were prescribed in some cases, but the clinical course was variable depending on the genetic terrain and the extent of the disease. Indeed, acitretin works through its anti-inflammatory and anti-proliferative action by promoting keratinocyte differentiation and through its action on apolipoprotein E, which allows a reduction in amyloid deposits [4,5].

Given the synergistic effects of the two treatments and the good clinical response observed in our patient, this therapeutic combination may be recommended in the treatment of cases of generalized LA resistant to usual treatments.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Letter to the Editor

Congenital erythropoietic porphyria and its rarity in Indian siblings

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Sir,

Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disorder of heme biosynthesis with an estimated prevalence of 1 in 1,000,000 or less [1]. CEP is the rarest of bullous porphyrias. Only less than 200 cases have been reported worldwide, and a clinician may not happen to diagnose such a case in all their professional career [2,3].

Two male siblings, 6 and 15 years old, native residents of Uttar Pradesh, and born to a nonconsanguineous marriage presented themselves to the Department of Dermatology with a history of fluid-filled blisters in photo-exposed areas, which had healed with scarring and had been persistent from infancy, as well as reddish-brown discoloration of the urine and the teeth. No history of photosensitivity, abdominal pain, neuropsychiatric symptoms, and acute attacks was present. There were no complaints *in utero* or perinatally, and both siblings were born by a normal vaginal delivery from a full-term pregnancy. Milestones were normal. An examination revealed several intact blisters in the acral areas, milia, atrophic and hyperpigmented scars in photo-exposed areas, erythrodontia (Fig. 1a) in both, hypertrichosis and sclerodermatous hands in the older sibling (Figs. 1b – 1e), and less severe presentations in the younger sibling than the older (Figs. 2a – 2c). The nails showed onycholysis and dystrophy. Both showed pink fluorescence of the teeth (Figs. 3a and 3b) and the urine (Figs. 3c and 3d) in a Wood's lamp examination and raised porphyrin levels in the plasma, urine, and feces. Histopathology of the vesicles showed a subepidermal split (Fig. 3e). Both parents and two other siblings—one male and one female—were normal, born chronologically in between the two affected siblings.

Congenital erythropoietic porphyria (CEP), also known as Gunther's disease, is due to deficiency of uroporphyrinogen III synthase, leading to overproduction of uroporphyrinogen I and coproporphyrinogen I, which accumulate in the bone marrow, in erythrocytes, the plasma, the bones, and the teeth [3]. Its clinical spectrum is highly variable, from nonimmune hydrops fetalis to mild late-onset cases. Its onset falls typically around infancy and early childhood. One of its first clues can be a burgundy-red discoloration of the urine and diapers stained red. Cutaneous lesions begin with itching and erythema, followed by painful vesiculobullous eruptions that leave pigmented scars. In most of the other photodermatoses, inflammation is usually not severe enough to produce blisters. The presence of large amounts of porphyrins very early in life—at the time of tooth and bone development—results in erythrodontia that fluoresces under Wood's lamp, which is almost pathognomonic of CEP [4]. Hypertrichosis can produce a werewolf appearance. Complications include hemolytic anemia, hypersplenism, hepatomegaly, bone marrow hypertrophy, pathological fractures, acral osteolysis, and ocular damage. Histopathology shows subepidermal blisters and thickened collagen bundles. Strict photoprotection remains the most important preventive measure and the first line of treatment. Treatment includes broad-spectrum sunscreen application, antioxidants, avoidance of other triggers, blood transfusions, and splenectomy in severe cases. Bone marrow and stem cell transplantation has been reported to be successful in some cases [3]. Gene therapy may provide a cure in the future. Although

How to cite this article: Brar SK, Alagappan A, Brar BK. Congenital erythropoietic porphyria and its rarity in Indian siblings. Our Dermatol Online. 2020;11(4):431-433.
Submission: 13.05.2020; **Acceptance:** 31.07.2020
DOI: 10.7241/ourd.20204.31

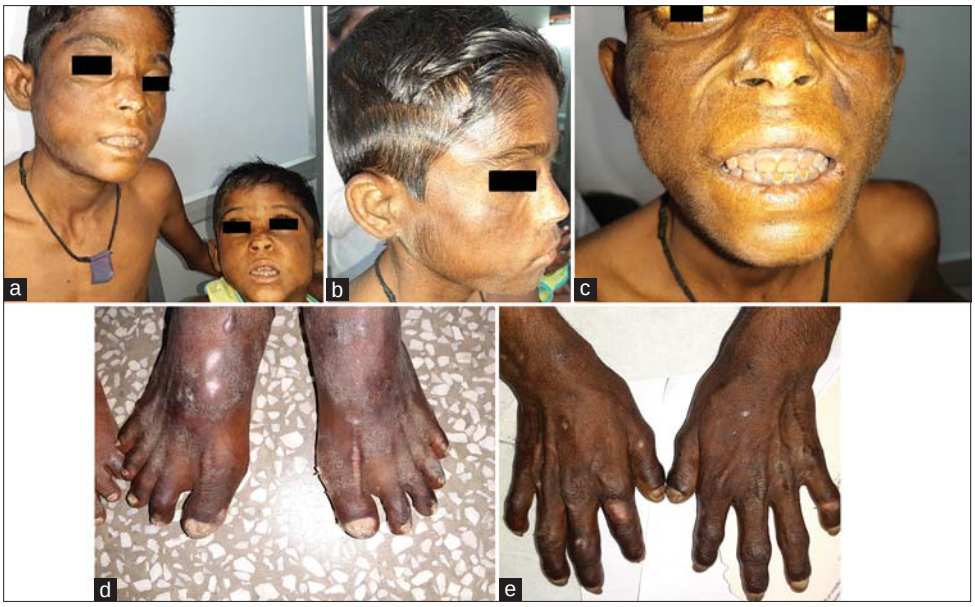

Figure 1: (a) Atrophic and hyperpigmented scars on the face with erythrodontia in both siblings. (b-c) Hypertrichosis on the face in the older sibling. (d-e) Sclerodermatous hands and feet with resorption of terminal phalanges in the older sibling.

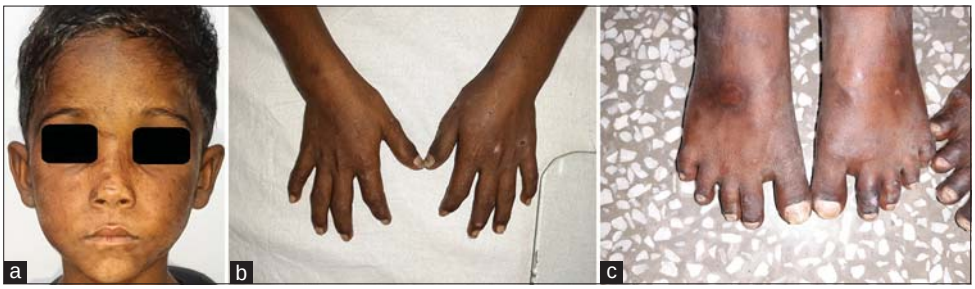

Figure 2: Milder involvement in the younger sibling with atrophic scars (a) on the face and (b-c) on the hands and feet.

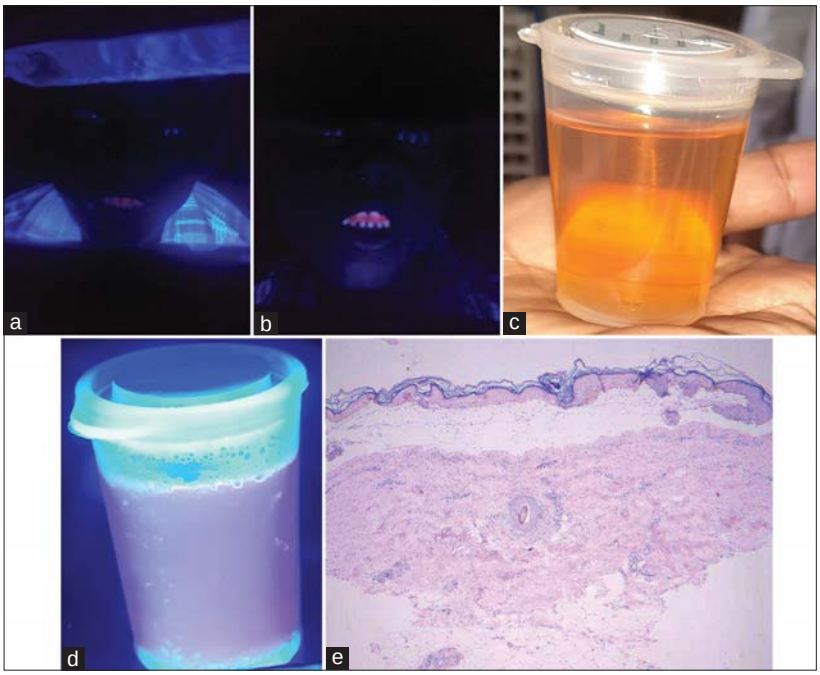

Figure 3: (a-b) Pink fluorescence of the teeth. A brownish discoloration of the urine (c) visible to the naked eye and (d) showing pink fluorescence in a Wood's lamp examination. (e) Histopathology of the vesicles with a subepidermal split (H&E, 100×).

CEP tends to be exceptionally severe in early childhood, most patients survive into adulthood with a life expectancy of around 40 to 60 years [5].

There have been several reports of CEP from India, but almost all of them are isolated cases, and a few reports in the world literature, as in Sudanese and Pakistan siblings, but, to the best of our knowledge, none in Indian siblings. The paucity of reports of CEP in siblings in the world and Indian literature has prompted us to report these two Indian siblings.

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

Letter to the Editor

Gout nodules in vitiligo without chronic gouty arthritis: A rare presentation

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Sir,

Gouty tophi present themselves as firm and skin-colored or yellowish papules or nodules with white chalky material. They may appear in any location on the body, but appear most commonly in the interphalangeal joints [1]. Clinically, they may resemble calcinosis cutis, rheumatoid nodules, xanthomas, and panniculitis. They indicate a chronic foreign-body granulomatous response to monosodium urate crystal deposits in the dermis and the subcutaneous tissue, and classically occur with untreated chronic gouty arthritis. Very rarely, in the absence of arthritis, they may be the first clinical sign of gout, which is known as gout nodulosis [2].

A 53-year-old male presented himself with multiple asymptomatic swellings over both ankles and feet persistent for four years prior. The patient had a history of depigmented patches over the face, hands, feet, and genitals since childhood, but no arthritis. His father and younger sister had vitiligo as well. The patient had been alcoholic for ten years and hypothyroid for five years, and had been taking 50 µg levothyroxine sodium daily. The cutaneous examination revealed multiple skin-colored to erythematous, firm, and nontender nodules 1 × 1 cm to 4 × 5 cm in size, present over both lateral malleoli, the first metatarsophalangeal joint, the lateral border of the left foot, and the palmar surface of the right index finger and left thumb (Figs. 1a – 1c). Depigmented patches were present over the face, ears, the palmar and dorsal surfaces of the hands, both feet, the scrotum, and the penis with areas of repigmentation. The complete blood count, liver function tests, serum creatinine, the fasting lipid profile, T3, T4, and TSH were normal. An abdominal ultrasound revealed left renal calculi with bilateral grade I renal parenchymal changes and grade II–III fatty changes in the liver. A radiograph of both ankles and feet showed soft tissue swellings with no evidence of erosion or joint space reduction. During a biopsy, chalky material came out from the nodule (Fig. 2). Histopathology showed compact hyperkeratosis, acanthosis, mild edema, and perivascular lymphocytic infiltrate in the upper dermis. The subcutaneous tissue was replaced by fibrillary hyaline pink material with palisading granulomas. Polarized microscopy of the chalky material proceeding from the biopsy site showed needle-shaped birefringent crystals, suggesting monosodium urate crystals (Fig. 3). This was further confirmed by a phosphotungstic acid test, in which the chalky material turned blue. Serum uric acid was high, at 8.2 mg/dL (normal range: 2.4–6 mg/dL). Serum calcium, phosphorous, and parathormone were normal.

Gouty nodules without chronic arthritis are very rare [3,4]. They may occur with renal insufficiency, hyperparathyroidism, or in patients receiving anti-inflammatory or diuretic drugs for a longer time. Our patient had hyperuricemia, but not renal problems, and had not received any anti-inflammatory or diuretic drugs. Also, his calcium and parathormone levels were normal. He developed gouty nodules with mild hyperuricemia, but with no arthritis and no other known cause of hyperuricemia. Kikuchi et al. reported hyperuricemia in vitiligo patients who have undergone narrowband UVB therapy. The immunomodulatory effect of UV radiation affects T lymphocytes, which attack melanocytes, resulting in increased nucleic

How to cite this article: Joshi D, Gayatridevi P, Rajitha A, Raghurama Rao G, Seetharam Anjaneyulu K. Gout nodules in vitiligo without chronic gouty arthritis: A rare presentation. Our Dermatol Online. 2020;11(4):434-435.

Submission: 25.05.2020; **Acceptance:** 31.07.2020

DOI: 10.7241/ourd.20204.32

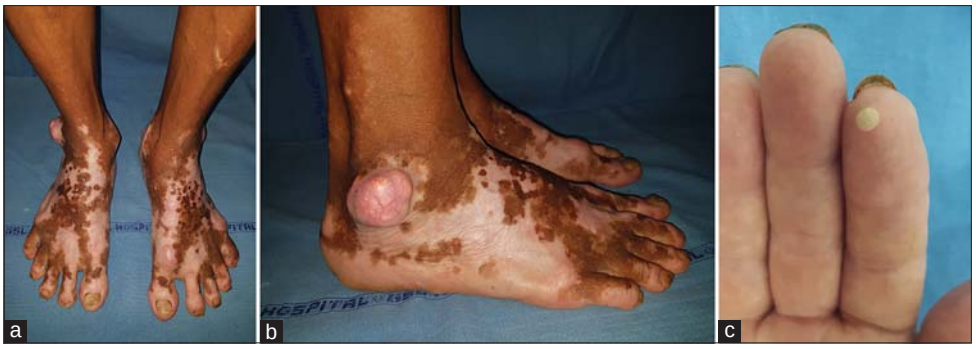

Figure 1: (a) Firm nodules over both lateral malleoli with vitiligo on both feet and ankles. (b) A nodule over the right lateral malleolus. (c) A nodule with white chalky material over the left index finger.

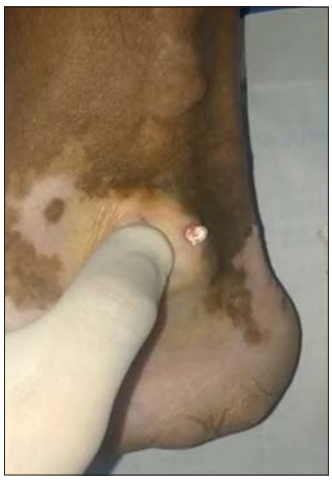

Figure 2: Chalky material from the nodule.

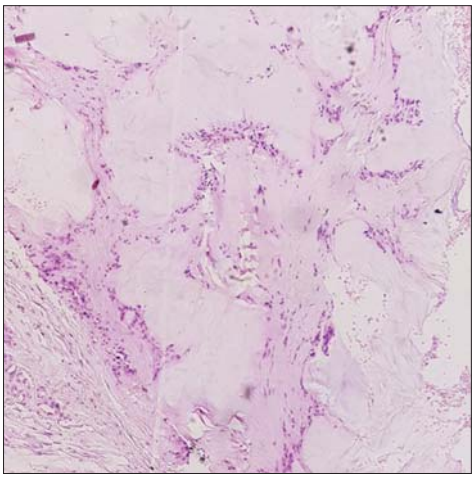

Figure 3: The subcutaneous tissue replaced by fibrillary hyaline pink material with palisading granulomas (H&E, 400×).

acid turnover, thus causing hyperuricemia [5,6]. Therefore, the sun exposure in our patient, who had had vitiligo since childhood, might have been responsible for the increased uric acid levels and gouty tophi. Inflammasomes are structures that mediate the generation of IL-1. The NALP3 inflammasome is involved in gout, whereas the NALP1 inflammasome in vitiligo [7]. Hence, the association of vitiligo with gout might be inflammation-mediated and induced by prolonged UV radiation.

Consent

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

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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

Letter to the Editor

Sternocostoclavicular involvement in psoriatic arthritis

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Sir,

The anterior chest wall is the mainly affected region in pustulotic arthro-osteitis (PAO) associated with palmoplantar pustulosis (PPP). By contrast, sternocostoclavicular arthritis is rare in psoriatic arthritis (PsA). We report two cases of Japanese patients with psoriasis that led to the development of arthro-osteitis in the anterior chest wall.

Case 1: A 28-year-old female developed chronic scaly erythemas on the occipital scalp and was diagnosed with psoriasis at the age of 16. Furthermore, she had been suffering from joint pain in the anterior chest wall, left shoulder, wrist, and toes for several years. A physical examination revealed keratotic erythematous plaques on the scalp, back, and left elbow (Fig. 1a). Neither of the palms or soles was involved. The Psoriasis Area and Severity Index (PASI) score was 4.5. Moreover, the anterior chest wall was painful and showed swelling (Fig. 1b). A laboratory examination showed a slight increase in C-reactive protein (CRP) (1.0 mg/dL); however, rheumatoid factor, antinuclear antibodies, and matrix metalloproteinase-3 were within the normal ranges. Technetium-99 bone scintigraphy revealed increased uptake in the thorax, right wrist, and right fourth toe (Fig. 1c). The patient was treated with topical corticosteroid and oral methotrexate 7.5 mg/week.

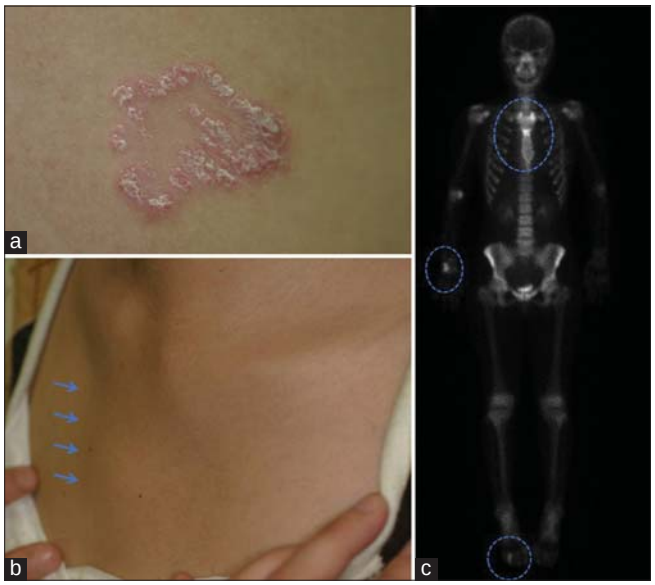

Figure 1: (a) A well-circumscribed scaly erythematous plaque. (b) Swelling of the anterior chest wall (at the arrow). (c) Bone scintigraphy showing increased uptake in the sternocostoclavicular areas, right wrist, and right toes.

Case 2: A 52-year-old female had developed generalized erythema, scales, and tiny superficial pustules, and had been treated on repeated admission in another hospital. The skin conditions had been compounded by a sore throat, fever-up, and joint pain. The patient was treated with etretinate (Tigason™) but without improvement and was thus referred to our hospital. A physical examination showed that the ill-defined scaly erythemas had spread and coalesced diffusely with superficial tiny pustules on the trunk and extremities (Fig. 2a). A histological examination revealed a Kogoj's spongiform abscess in the epidermis with perivascular inflammatory cell infiltration in the upper dermis. A laboratory examination showed increased levels of white blood cell count (13,600/μL) and CRP (5.6 mg/dL), whereas renal and liver functions were normal. Therapy with methotrexate 30 mg/week was started and then tapered with the improvement of skin lesions. The joint pain, however, was not completely controlled and the right clavicle showed a marked swelling. Technetium-99 bone scintigraphy revealed increased uptake in the thorax, right wrist, and right fourth toe (Fig. 2b).

Psoriasis and PPP share several similarities, although PPP is considered an entity distinct from psoriasis [1].

How to cite this article: Yamamoto T. Sternocostoclavicular involvement in psoriatic arthritis. Our Dermatol Online. 2020;11(4):436-437.
Submission: 02.06.2020; **Acceptance:** 14.09.2020
DOI: 10.7241/ourd.20204.33

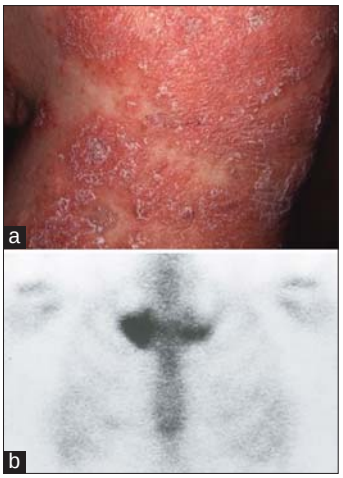

Figure 2: (a) A number of scaly erythemas with superficial tiny pustules on the trunk. (b) Bone scintigraphy showing increased uptake in the right clavicle.

An examination of 44 patients with PAO by bone scintigraphy revealed that the increased uptake of technetium was most frequently observed in the sternocostoclavicular region, which accounted for 82% (36/44) of cases [2]. As for the joint manifestation, enthesitis is the primary event of both PsA and PAO. PsA involves both peripheral and axial joints, with a predominance of peripheral involvement (60%) [3]. By contrast, PAO affects the anterior chest wall in the majority of cases, with less involvement of peripheral joints [1]. A recent retrospective study examined 104 cases of PsA, among which axial disease accounted for 43.2% (45/104) of cases [4]. Three cases of anterior chest wall involvement were described, but only one was psoriasis while the rest were cases of palmoplantar psoriasis and PPP.

In this report, we present two cases of plaque-type psoriasis vulgaris and generalized pustular psoriasis without a family history of psoriasis or PPP. Neither palms nor soles were involved, and neither patients had severe acne. In case 1, arthralgia was observed in not only the anterior chest wall but also the peripheral joints, whereas, in case 2, the patient complained of joint pain in the right clavicular region only. In our institute, we have had more than 80 cases of PsA in over ten years, but no other cases developed arthritis on the anterior chest walls. Although we have had a number of Japanese patients with PAO [5], sternocostoclavicular arthritis is rare in Japanese patients with PsA. In conclusion, these two cases suggest a close relationship between PsA and PAO.

Consent

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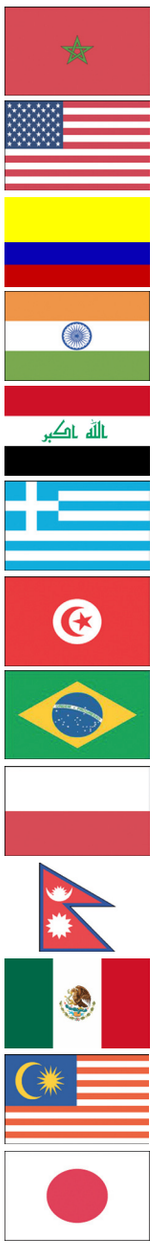
Source of Support: Nil, **Conflict of Interest:** None declared.



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