Volume 12, Number 2 April 2021
p. 101- 229
Issue online since Thursday April 01, 2021

ISSN: 2081-9390
DOI: 10.7241/ourd

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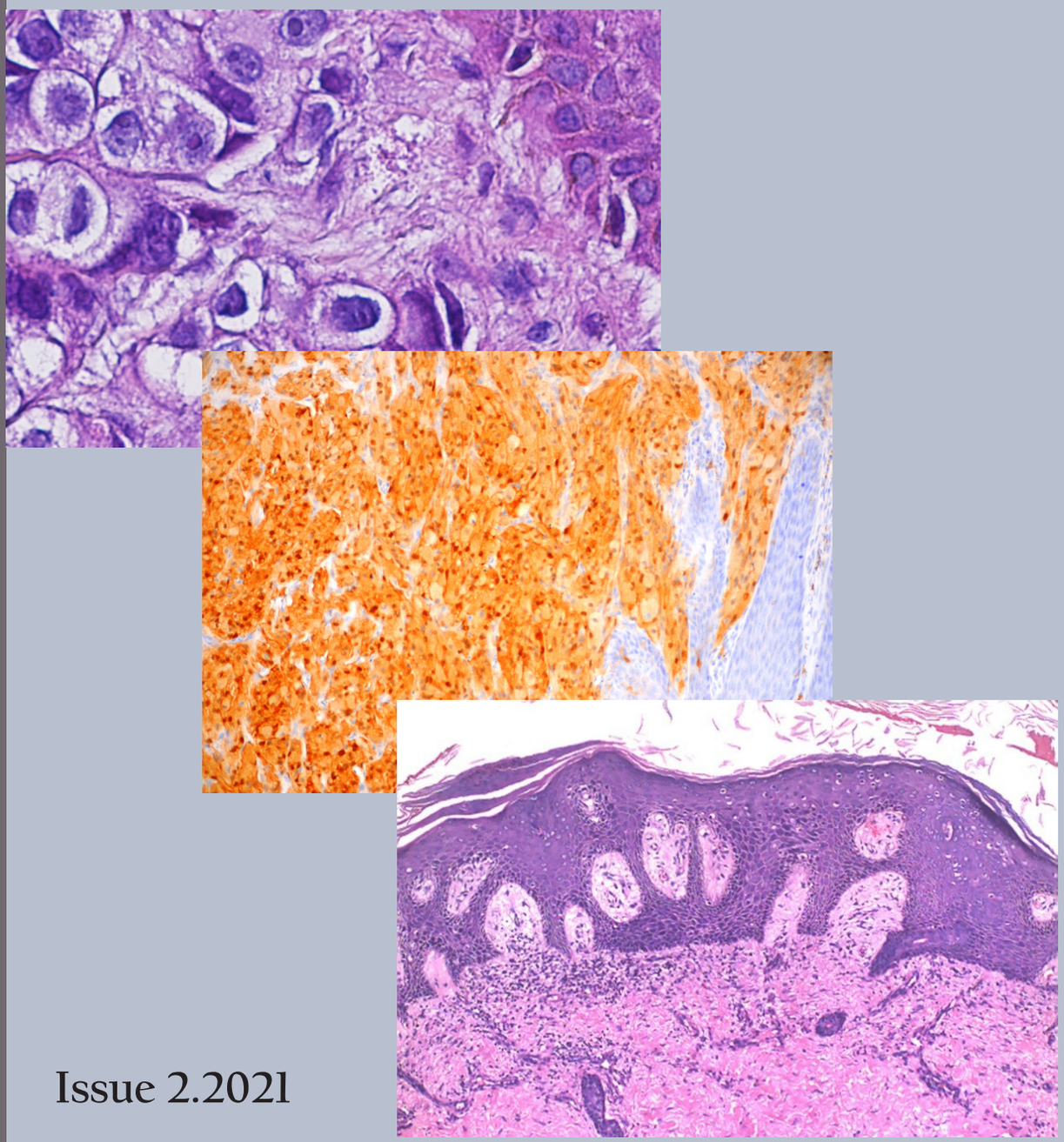

Issue 2.2021

Editorial Pages

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

Quarterly
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Universal Impact Factor for year 2012 is = 0.7319
system of opinion of scientific periodicals INDEX COPERNICUS (8,69)
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Editorial Board

Contents

Our Dermatology Online

Original Article

Mucocutaneous disorders in HIV/AIDS at a tertiary care hospital in Nepal: An observational study

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ABSTRACT

Background: Mucocutaneous manifestations in HIV infections are common. However, they have not, so far, been studied in Nepal. The aim of this study was, therefore, to describe mucocutaneous manifestations in Nepalese HIV patients. **Materials and Methods:** The following is a hospital-based, descriptive, cross-sectional study conducted in the Department of Dermatology and Venereology and Antiretroviral Treatment (ART) Center of Tribhuvan University Teaching Hospital (TUTH) from May 2017, through October 2018. Patients aged 16 years and above diagnosed with HIV were included in the study, for whom history and clinical examinations were performed. The study variables were age, sex, a clinical diagnosis of dermatological problems, clinical stages of HIV/AIDS, as per the World Health Organization (WHO) classification criteria, and the CD4 count. **Results:** A total of 52 patients were included in the study. The mean age upon presentation was 38.77 ± 10.9 years. The mean CD4 count was 464.27 ± 255.13. Females were more affected than males (female:male = 1.4:1). Mucocutaneous manifestations were the following: fungal infections (10; 19.3%), viral infections (6; 11.6%), parasitic infestations (3; 5.8%), bacterial infections (4; 7.7%), sexually transmitted infections (2; 3.8%), seborrheic dermatitis (3; 5.8%), idiopathic pruritus (3; 5.8%), recurrent oral ulcers (3; 5.8%), urticaria (3; 5.8%), pruritic papular eruptions (2; 3.8%), eczemas (2; 3.8%), acne (2; 3.8%), angular cheilitis (2; 3.8%), xerosis cutis (2; 3.8%), and others (5; 9.6%). **Conclusions:** The study showed that fungal infections are common in HIV patients, followed by viral infections and parasitic infestations. Seborrheic dermatitis, idiopathic pruritus, recurrent oral ulcers, and urticaria were found to be common inflammatory skin diseases in HIV.

Key words: Antiretroviral agents; CD4+T lymphocytes; HIV; Skin diseases; World Health Organization

INTRODUCTION

Mucocutaneous manifestations are common in HIV infections and may sometimes be their earliest manifestations. A variety of skin disorders occur during the course of HIV, such as infectious skin diseases, noninfectious skin diseases, and malignant skin conditions [1]. It is reported that almost 90% of people living with HIV (abbreviated to PLHIV) will develop skin symptoms during the course of the disease [2]. These manifestations not only act as markers but also reflect the underlying immune status and help to determine the stage of the disease. Treatment of HIV used to be based on clinical HIV staging and the CD4 count, the former applied to the majority of mucocutaneous manifestations. At present, the World Health Organization (WHO) recommends treating all HIV patients with antiretroviral therapy (ART), regardless of staging and the CD4 count [3]. Because of the "test and treat" policy, authors have seen the changing nature of mucocutaneous manifestations in HIV, probably because of early diagnosis and treatment, and this has not yet been documented. To the best of our knowledge, no studies on mucocutaneous manifestations in HIV infection have been conducted in Nepal. The following study was, therefore, undertaken to determine the pattern of various mucocutaneous manifestations in Nepalese patients with HIV/AIDS.

MATERIALS AND METHODS

The following is a hospital-based, descriptive, cross-sectional study conducted in the Department of

How to cite this article: Rajput PS, Das AK, Paudel U, Parajuli S. Mucocutaneous disorders in HIV/AIDS at a tertiary care hospital in Nepal: An observational study. Our Dermatol Online. 2021;12(2):101-105.

Submission: 14.05.2020; **Acceptance:** 30.07.2020

DOI: 10.7241/ourd.20212.1

Dermatology and Venereology and Antiretroviral Treatment (ART) Center of Tribhuvan University Teaching Hospital (TUTH) from May 2017, through October 2018. This center is one of the tertiary care centers for treatment of people living with HIV (PLHIV) located in Nepal. Patients aged 16 and above, diagnosed with HIV—irrespective of their ART status—and complaining of skin and venereal problems were included in the study. These patients were diagnosed based on the Nepal national algorithm for the diagnosis of HIV. In Nepal, three rapid test kits are used for the diagnosis of HIV: Determine HIV-1/2 (Assay 1), Uni-Gold HIV-1/2 (Assay 2), and Stat-Pak HIV-1/2 (Assay 3) [3]. The diagnosis of HIV is given only when these three assays are positive in serial testing. History and clinical examinations were performed on these patients, and the following variables were studied: age, sex, a clinical diagnosis of dermatological problems, clinical stages of HIV/AIDS, as per the WHO classification criteria, and the CD4 count. Any active lesion or scarring of the skin and mucosa observed in HIV-positive patients were labeled as mucocutaneous manifestations of HIV. Dermatological diagnoses were confirmed by two consultant dermatologists after performing examinations of all patients in daylight. In the case of more than one diagnosis, each manifestation was counted separately. Skin problems before the diagnosis of HIV and patients with systemic diseases were excluded from the study. All these findings were documented in a pro forma. Investigations were pursued only in cases deemed relevant and necessary for diagnosis. All the data was processed by the software SPSS Statistics, version 20.0. Descriptive analysis of the data was performed. Ethical approval was taken from the Institutional Review Committee of the Institute of Medicine before the study.

RESULTS

Out of the 52 patients who participated in the study, 31 (59.6%) were females and 21 (40.4%) were males (female:male = 1.4:1). The mean age upon presentation was 38.77 ± 10.9 years. Overall, infectious skin diseases (n = 27) were almost as common as noninfectious skin diseases (n = 25) (Table 1). Fungal infections (19.3%) were the predominant manifestations among infections, whereas seborrheic dermatitis, idiopathic pruritus, recurrent oral ulcers, and urticaria were the predominant manifestations among noninfectious skin disorders, each accounting for 5.8% of all manifestations

Table 1: Patterns of mucocutaneous disorders in HIV

Infectious skin diseases	Stage 1 (n)	Stage 2 (n)	Stage 3 (n)	Stage 4 (n)	Frequency n (%)
Fungal	1	4	1	4	10 (19.3)
Viral	0	1	1	4	6 (11.6)
Parasitic	0	2	1	0	3 (5.8)
Bacterial	0	0	3	1	4 (7.7)
Sexually Transmitted Infections	0	0	0	2	2 (3.8)
Non-infectious skin diseases					
Seborrheic dermatitis	0	1	0	2	3 (5.8)
Idiopathic Pruritus	0	1	2	0	3 (5.8)
Recurrent oral ulcers	0	2	0	1	3 (5.8)
Urticaria	1	0	1	1	3 (5.8)
Pruritic papular eruptions	0	1	0	1	2 (3.8)
Eczemas	1	1	0	0	2 (3.8)
Acne	1	1	0	0	2 (3.8)
Angular cheilitis	0	1	1	0	2 (3.8)
Xerosis cutis	0	0	0	2	2 (3.8)
Others	3	1	0	1	5 (9.6)
Total	7	16	10	19	52 (100)

(Table 1). Clinical staging (as per the WHO) of these patients was done, showing that 7 (13.5%) patients were in stage 1, 16 (30.8%) in stage 2, 10 (19.2%) in stage 3, and 19 (36.5%) in stage 4. One patient with each of the following diseases was in stage 1: pityriasis versicolor, miliaria rubra, chronic spontaneous urticaria, dyshidrotic eczema, lipodystrophy, rosacea, and acne. Onychomycosis (n = 1), idiopathic pruritus (n = 1), oral or vaginal candidiasis (n = 1), tinea corporis/cruris (n = 1), recurrent oral ulcers (n = 2), scabies (n = 2), allergic contact dermatitis (n = 1), pruritic papular eruptions (n = 1), angular cheilitis (n = 1), herpes simplex (n = 1), acne (n = 1), and melasma (n = 1) were seen in stage 2. Idiopathic pruritus (n = 2) and folliculitis (n = 2) were more common in stage 3, followed by one per case of tinea, bacillary angiomatoses, chronic spontaneous urticaria, angular cheilitis, pediculosis, and herpes zoster. Seborrheic dermatitis (n = 2), herpes labialis (n = 2), pityriasis versicolor (n = 2), verruca vulgaris (n = 2), and xerosis cutis (n = 2) were commonly seen in stage 4 (advanced HIV), followed by one per case of oral or vaginal candidiasis, tinea, condyloma acuminata, recurrent oral ulcers, molluscum contagiosum, chronic spontaneous urticaria, pruritic papular eruptions, polymorphic light eruptions, and acute paronychia. These cutaneous findings are shown in Table 1.

The mean CD4 count in our study was 464.27 ± 255.13, ranging between 10 and 964. 10 patients (19.2%) had a CD4 count of less than 200, and 42 patients (80.8%) had a CD4 count of more than 200 (Table 2).

Table 2: Mucocutaneous manifestations in relation to the CD4 count

Mucocutaneous manifestations	CD4 less than 200 (n)	CD4 more than 200 (n)
Fungal	1	9
Viral	2	4
Parasitic	0	3
Bacterial	2	2
STIs	0	2
Noninfectious skin diseases	5	22
Total	10	42

DISCUSSION

In our study, overall infectious skin diseases in HIV patients (n = 27) were almost as common as inflammatory skin diseases (n = 25). Fungal diseases (n = 10) were common skin infections, followed by viral (n = 6) and bacterial (n = 6) infections. Different types of inflammatory skin diseases were seen, among which seborrheic dermatitis, idiopathic pruritus, recurrent oral ulcers, and urticaria were the predominant cutaneous presentations. We feel that, because of the early introduction of antiretroviral therapy (ART) in all the patients, general dermatoses unrelated to HIV were as common as those related to HIV.

Seborrheic dermatitis is a manifestation of stage 2 HIV and accounts for a 1–10% prevalence in the general adult population [4]. Seborrheic dermatitis was present in 5.8% of our cases, which is a smaller percentage than that reached by other studies (up to 11.9%) [5]. Similarly, onychomycosis was present in 3.8% of our cases, again, less frequently than in other studies (2–50%) [6].

Pruritus, which is usually caused by immune dysregulation [7], was seen in 5.8% of our cases. Even the prevalence of pruritus in our study was lower compared to other studies, which estimate it at approx. 12–45% [8].

The lower prevalence of the dermatoses observed in our study could be attributed to the early initiation of ART in our patients, but a lower sample size could also be a contributing factor.

In our study, fungal infections were common among the infectious skin diseases. Tinea cruris, tinea corporis, onychomycosis, and pityriasis versicolor together accounted for 15.4% of the cases. This is similar to a study that estimated it at approx. 16.3% [2], but, still, higher than other studies [9], possibly because our agricultural society is more exposed to soil, water, and animals, which are common sources of these infections.

Bacillary angiomatosis occurs commonly in HIV patients with severe immune suppression [10,11]. It is a rare entity with a prevalence of as low as 1.2 per 1000 HIV cases. We had one such case (1.9%) of bacillary angiomatosis in our study. The reason for the higher prevalence of this condition needs further research in the future.

Sexually transmitted infections (STIs) are one of the important manifestations of HIV. The prevalence of condyloma acuminata in HIV ranges from 8.8% to 53% [12,13]. 1.9% of our cases suffered from condyloma acuminata. The fact that our patients were well-educated on barrier contraceptive measures along with receiving positive prevention at our ART center could have contributed to the lower rates of STI in our study.

5.8% of our cases had recurrent oral ulcerations seen in clinical HIV stage 2. 3.8% had herpes labialis, similar to the report by an Indian study [1]. HIV selectively infects, depletes, and/or dysregulates different human immune systems, particularly mucosal sites, and damages mucosal barriers [14]. Such damage to the mucosal epithelium was perhaps the cause of the recurrent oral ulcerations and herpes labialis seen in our patients.

The frequency of pruritic papular eruptions (PPEs) was 3.8% in our study. PPEs usually appear as papules and plaques that are usually widespread, skin-colored to erythematous, and usually bearing signs of excoriations [15]. Their presence after at least 6 months of ART has been proposed as one of the several markers of treatment failure [15]. The frequency of PPEs has been reported by some studies to be as high as 56% [16]. The frequency of PPEs appears to be low in our case because all the patients were on ART prior to the inclusion in the study.

Xerosis was seen in 3.8% of our cases. The prevalence of xerosis in HIV varies from 2.8% to 73.3% [2]. It is one of the most common skin manifestations in HIV and is a common cause of pruritus in HIV patients. Impaired water metabolism in the viable epidermis and reduced dermal lipids are responsible for HIV-associated xerosis [17].

Herpes zoster was seen in 1.9% of our cases. It occurs more frequently in older people and those with cellular

immunodeficiency [18]. In PLHIV, a prevalence of 8% has been found [19]. The lower frequency of herpes zoster in our study could again be attributed to early ART in our study population.

Parasitic infestations accounted for 5.8% of our cases and included scabies and pediculosis. The prevalence of scabies has been reported by other studies to be 0.4–5.1% [2]. Scabies can be seen in an atypical form as crusted scabies in patients with HIV. Our cases of scabies had a presentation as of immunocompetent patients.

Some of our patients displayed acne and polymorphic light eruptions, which are common in the general Nepalese population, and, according to the authors, might not be significant presentations, or it might be that HIV displays the prevalent dermatoses of the general population.

Our study showed that 10 patients (19.2%) had a CD4 count of less than 200, and 42 patients (80.8%) had a CD4 count of more than 200. Surprisingly, all the manifestations (infectious and noninfectious skin diseases) were seen in patients with a higher CD4 count, except for bacterial infections (equal number of infections in the two groups). This is an important finding as it suggests and proves that starting ART in the early stages of HIV prevents mucocutaneous manifestations.

This study shows the pattern of cutaneous manifestations in HIV patients of a Nepalese center and is the first study to have been conducted in Nepal. The lower frequency of mucocutaneous manifestations in our study compared to the known manifestations of HIV can be attributed to a smaller number of HIV cases in our study, which was one of its limitations. Furthermore, because of multiple diagnoses, a statistical correlation between different study variables was not ascertained. Moreover, all the patients were on ART, which could have contributed to immune restoration and, consequently, less frequent manifestations of skin diseases. This points toward the changing mucocutaneous manifestations in HIV in a post "treat all patients" scenario. However, further studies with large numbers of HIV patients and their correlation with staging and the CD4 count will be required in the future to prove these important observations.

CONCLUSION

Our study showed a variety of mucocutaneous manifestations in different stages of HIV. The pattern of skin diseases seems to be distributed widely, ranging from infectious to inflammatory, with infectious diseases being in our study as common as inflammatory skin diseases. The frequency of all mucocutaneous manifestations appeared to be smaller compared to other studies because of the possible role of the "treat all" policy, proving the observation of the changing nature of skin diseases in HIV patients.

ACKNOWLEDGMENT

We would like to thank Dr. Amod Poudyal of the Central Department of Public Health of the Institute of Medicine for statistical help.

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

Sodium metabisulfite hypersensitivity in urticaria

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ABSTRACT

Background: Sodium metabisulfite is a recognized, but rare, trigger of urticaria, wherein the IgE mechanism has been sporadically proven. The aim of this study was to identify the potential reaction to sodium metabisulfite (MBS) based on a placebo-controlled oral challenge in patients with urticaria and suspected hypersensitivity to food additives. **Materials and Methods:** A total of 110 adult patients (76 females and 34 males with a mean age of 46 years) were included in the study between 2017 and 2019. All subjects underwent MBS skin prick tests (SPT) and patch tests (PT). Patients with a positive skin test or suspected MBS hypersensitivity were qualified for a placebo-controlled oral challenge (OC). **Results:** Skin testing was positive in 24 patients: SPT in 20% (n = 22), PT in 5% (n = 6). Out of 64 oral challenges, 13 positive results were obtained. Patients with a positive challenge typed sulfite foods twice as often as a culprit compared to those with a negative OC. **Conclusions:** In patients with urticaria, both the IgE and non-IgE mechanism of MBS hypersensitivity has been demonstrated. Skin tests with a detailed medical history of potentially guilty foods may be helpful in determining sulfite hypersensitivity.

Key words: Sulfites; Sodium metabisulfite; Urticaria; Food additive hypersensitivity

INTRODUCTION

Sulfites are a group of inorganic salts that, in a certain environment, liberate sulfur dioxide. A range of them—such as sodium and potassium metabisulfite, sodium sulfite, and sodium and potassium bisulfite—are used in the food, beverage, cosmetic, medicine, rubber, and photographic industry as a preservative and a bleaching and antioxidative agent [1-3]. They are key preservatives of wine, beer, grapefruit juice, dried fruits, and seafood and are widely used in the production of processed foods [4-6]. The acceptable daily intake (ADI) for sulfites, in terms of sulfur dioxide, is 0.7 mg per 1 kg of body weight per day, but their intake is often exceeded. According to the European Union regulation, the total amount of sulfur dioxide in wine must not exceed 150 mg/L for red wines and 200 mg/L for white and rose wines, and is higher for sparkling and sweet wines (up to 235 and 400 mg/L respectively). Although producers are obliged to label products with a sulfite concentration of over 10 mg/L appropriately, they are not obliged to disclose the total amount of the substance [5].

The hypersensitivity symptoms described after sulfites ingestion may include rhinitis [7], asthma [6,8-10], urticaria [11-13], systemic rash [14-16], intestinal disorders, dizziness [7], headache [17], and anaphylaxis [7,18-20]. Sulfites are thought to be the main food additive exacerbating asthma, which affects 3–10% of the population [20]. Numerous studies have reported sensitization to take place through the skin, for instance, after the application of an anti-fungal or anti-hemorrhoid medicine, hair dye, or facial cream or after contact with animal feed, caused by prolonged occupational exposure [7,20]. Contact allergy is also a proven and well-known sulfite side effect [1,7,21-23].

The mechanisms lying behind these reactions are only partially known [24]. Some of the patients may not be able to metabolize sulfiting agents well enough due to a deficiency of the enzyme sulfite oxidase, which

How to cite this article: Sadowska B, Sztormowska M, Gawinowska M, Chelminska M. Sodium metabisulfite hypersensitivity in urticaria. Our Dermatol Online. 2021;12(2):106-112.

Submission: 04.01.2021; **Acceptance:** 01.02.2021

DOI: 10.7241/ourd.20212.2

may lead to hypersensitivity symptoms [9,20]. An interesting thesis is the possibility of suppression of the Th1-type immune response by sulfites, resulting in the advantage of the Th2 mechanism [25]. The immunological background of the reaction has been proven in some cases [26], but other authors question this link [4].

Several observations indicate that the asthma phenotype is more common than urticaria in sulfite hypersensitivity [5,8,9]. The subject of the present study was to assess the frequency of sodium metabisulfite hypersensitivity in patients with urticaria and suspected hypersensitivity to food additives, with an identification of the IgE and non-IgE dependent reactions.

MATERIALS AND METHODS

Patients

The study included patients with a duration of urticaria of more than six weeks, hospitalized with a suspicion of hypersensitivity to food additives, at the Department of Allergology of the Medical University of Gdańsk, Poland, between 2017 and 2019. A group of 110 patients was qualified for the study (Table 1). Before hospitalization, all participants completed a detailed questionnaire regarding the duration and nature of urticaria, eating habits, the use of an elimination diet, the allergy diagnostics performed, as well as the assessment of the effectiveness of the current treatment.

Patients had not been taking antihistamines for seven days and systemic glucocorticoids for one month prior to hospitalization. Spirometry was performed for any coexisting asthma or chronic obstructive pulmonary disease. Written consent was obtained. The study protocol was approved by the local bioethics committee (NKBBN/546/2016-2017) and was in line with the principles of ethics and the Declaration of Helsinki.

Skin Testing

All patients underwent MBS skin tests. Sodium metabisulfite from Euro-Win Ltd., Jaslo, Poland, was used in the study. To prepare SPTs, it was diluted with saline and glycerol at a 1:1 ratio to obtain a 1% solution (i.e., a concentration of 10 mg/mL). A positive and negative control was performed (histamine hydrochloride 10 mg/mL and saline from Allergopharma). A wheal diameter of a minimum of 3 mm with surrounding erythema larger than the negative control and representing the average of the two largest perpendicular dimensions was considered positive. A negative MBS SPT was obtained in 100 patients from the control group without urticaria who were consulted at the outpatient clinic.

Table 1: Patient characteristics.

Number of patients		n = 110
Average age (in yrs.)		46.1
Females / males		69% / 31%
Atopy		64.6%
Asthma		22.7%
Systemic symptoms		56.4%
Past use of glucocorticoids		42.7%
Adrenaline prescription		40.9%
Manifestation of urticaria	Urticaria + angioedema	50.9%
	Urticaria only	32.7%
	Angioedema only	16.4%
Duration of disease	Average duration (in yrs.)	7.2
	Up to 5 years	53.6%
	More than 5 years	46.4%
Onset of symptoms*	More often at night	26.4%
	Until noon	4.6%
	In the afternoon	19.1%
	Other	58.2%
Symptoms location*	Face	83.6%
	Hands	36.4%
	Forearms and arms	52.7%
	Trunk	52.7%
	Feet	34.6%
	Legs	39.1%
	Genitals	20.9%
AH1 treatment efficacy	Good	22.7%
	Partial	35.5%
	Bad	41.8%

* Multiple responses were allowed.

Patch tests were performed with commercial sodium metabisulfite (S-011, Chemotechnique Diagnostics, Vellinge, Sweden), and MBS on a petrolatum vehicle prepared by the pharmacy, both in a 1% concentration. The tests were performed using IQ-Ultra chambers (Chemotechnique Diagnostics, Vellinge, Sweden) and rated on days D2, D3, D4, D5, D6, and D7. Readings were performed according to the International Contact Dermatitis Research Group criteria. Some of the readings were carried out on an outpatient basis. An intravenous line single-blind oral challenge with MBS was then performed.

Oral Challenge

Patients with any positive skin test or a history suggesting the possibility of sulfite hypersensitivity were qualified for a single-blind placebo-controlled

oral challenge. OCs were performed according to the following protocol: placebo, 10 mg, 20 mg, and 100 mg capsules were administered in 30-minute intervals, followed by 200 mg after two hours. After the last dose, the patients underwent a minimum of two hours of observation, and immediate contact with the hospital was recommended within the next 24 hours should any symptoms appear. A test was considered positive according to objective symptoms, such as urticaria, angioedema, conjunctivitis, rhinitis, and bronchoconstriction confirmed in spirometry within 24 hours after the challenge. In the case of a hypersensitivity reaction, the participants were given antihistamines, glucocorticoids, and intramuscular adrenaline as needed.

Statistical Analysis

The significance of the association among variables was analyzed with a chi-squared test and Fischer's exact test. *P* values below .05 were considered significant.

RESULTS

Questionnaire

Almost every second patient (48%) experienced symptoms less than once a month, while 16% reported the frequency of urticaria from eight to thirty days. Based on this data and on medical history, we classified 65% of the cases as chronic inducible urticaria (CindU), 57% as chronic spontaneous urticaria (CSU), and 22% into the CindU + CSU group. Atopy, defined as a minimum of one positive skin prick test or serum IgE for airborne or food allergens, was established in 65% of the subjects. Seventy percent of the patients were convinced that it was the food that caused the symptoms. The following foods, potentially with sulfites, were listed as guilty by 24 patients before the study: wine, beer, dried fruits, olives, cakes, herring fillets, and restaurant meals.

Skin Prick Test (SPT)

A positive sodium metabisulfite SPT was obtained in 20% of the participants (MBS SPT (+), n = 22), among which one result was prolonged with a maximum skin reaction observed only after 3.5 hours (Fig. 1). Unlike the MBS SPT (-) patients, no statistically significant difference in sex, asthma, and atopy prevalence was observed in the MBS SPT (+) patients. The location of urticarial symptoms was more common in the lower limbs in the MBS SPT (+) patients than in the MBS SPT (-) (59 vs. 34%, $p < .032$). Out of the 20 patients with a positive skin prick test, the oral challenge was positive in 40% (n = 8, $p < .009$).

Patch Test (PT)

Although patch tests are not a feasible test for the diagnosis of urticaria *per se*, they may show evidence of concomitant type I and type IV allergy reactions. A positive patch test (MBS PT (+)) was noted in six patients (5.5%; 5 females and 1 male). The tests were positive on D3 through D5 in all six patients and up to D7 in two. The results were similar on both vehicles, commercial and pharmacy prepared (Fig. 2). All six patients had a history of angioedema and urticaria, and three of them suffered from throat edema in the

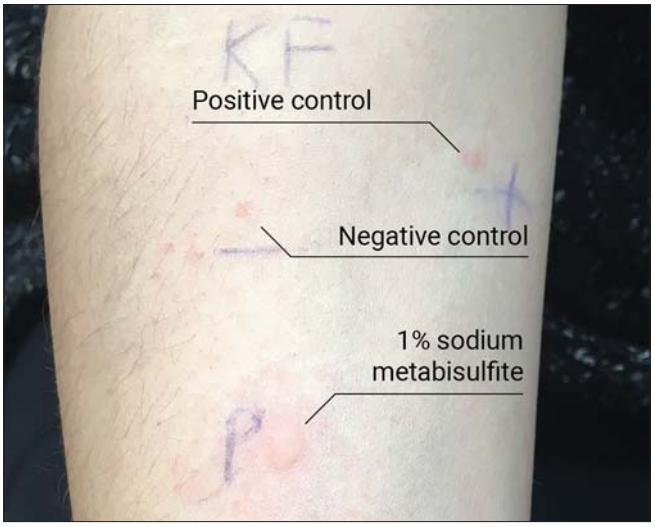

Figure 1: Sodium metabisulfite (MBS) skin prick test (SPT) after 3.5 hours.

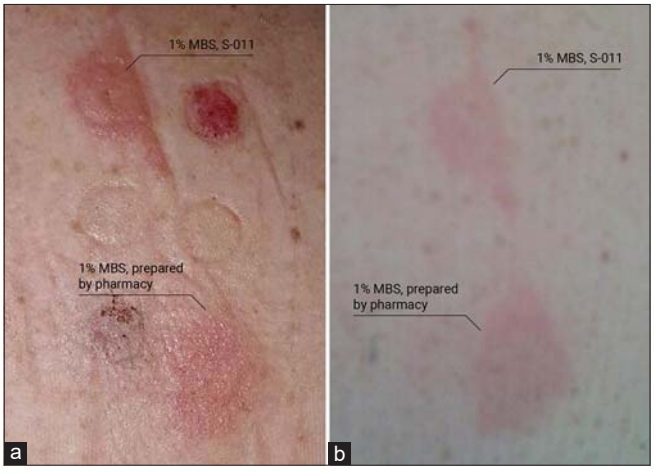

Figure 2: Positive sodium metabisulfite patch tests (PT) (a) after 48 hours and (b) after 120 hours.

past. In this group, next to the typical facial location, compared to the group with a negative patch test, urticaria symptoms more often affected the hands (83% vs. 34%; $p < .015$), feet (83% vs. 32%; $p < .012$), and genitals (67% vs. 18%; $p < .013$). This group was dominated by people over 50 years of age and their complaints had persisted for over five years (n = 5; 83%). In addition, as many as five patients had used parenteral glucocorticoids (83% vs. 40%; $p < .039$). In this group, the sodium metabisulfite SPT was positive in four subjects (67%; $p < .033$), and the challenge test was positive in 2 out of the 6 patients.

Oral Challenge (OC)

An oral challenge with sodium metabisulfite was carried out in 64 out of the 110 patients. Two MBS SPT (+) patients were not challenged; one refused to participate while the other had contraindications (forced expiratory volume in one second (FEV1) below 70%). A positive result was obtained in 13 patients (MBS OC (+)).

Reactions occurred with 10 mg, 20 mg, 100 mg, and 200 mg doses in one, three, four, and five patients, respectively. These included urticaria, angioedema, rhinoconjunctivitis, shortness of breath not supported by spirometry, flatulence, pruritus, tachycardia, headache, and weakness (Table 2). All these patients were treated with a double antihistamine dose (prednisone in three and intramuscular adrenaline in two). All objective symptoms resolved within two hours of intervention.

Unlike the MBS OC (-), the MBS OC (+) patients slightly more often indicated that the food was the culprit (92% vs. 74%; $p < .17$), including 46% with complaints about food containing potential sulfites. A subsequent analysis of the causative agents reported in the questionnaires showed that the MBS OC (+) patients, unlike the MBS OC (-), more often indicated that physical exertion induced urticaria (38% vs. 12%; $p < .023$). Alcohol, stress, heat, dermographism, infection, prolonged pressure, water, sweating, vibrations, sex cycle, and drugs were similarly often a reaction cofactor in both groups, while cold and UV radiation were slightly more often indicated as the cofactor (23% vs. 10% in both groups; p insignificant). The MBS SPT was positive in 62% of the patients with a positive challenge, and only in 24% of those with a negative challenge ($p < .009$).

DISCUSSION

In our study, we determined that hypersensitivity to sodium metabisulfite occurred in 12% of the studied patients with urticaria and suspected to have hypersensitivity to food additives. We confirmed that the clinical significance of sulfites is underestimated [20].

Several mechanisms are thought to play a role in the observed sulfites hypersensitivity, but IgE mediated reactions have rarely been documented so far [11,27,28].

In the current study, we demonstrated that, in patients with urticaria and MBS hypersensitivity, the underlying IgE mechanism is as common as the non-IgE. Assuming that a positive SPT result in an MBS OC (+) patient is evidence of IgE-dependent reactions, we confirmed the allergic mechanism in 62% of the patients (8 out of the 13) with a hypersensitivity reaction to MBS.

In our study, we noted a relatively high percentage of MBS positive skin prick tests (20%) in patients with urticaria. This finding may be explained by the strict selection of patients with suspected hypersensitivity to food additives, wherein most of them suffered from CindU.

Yang et al. obtained positive skin tests with potassium metabisulfite in five patients, which correlated with three positive challenges out of four carried out among 35 patients with hypersensitivity reactions after restaurant meals, wine, or drinks [18].

Reports of hypersensitivity to sulfites in urticaria are divergent. Jimenes-Aranda et al. found hypersensitivity to sodium metabisulfite, sodium bisulfite, and potassium bisulfite in 36%, 33%, and 31% of patients, respectively [28]. Montaño García and Orea reported a positive response after an MBS challenge in 6% of patients [29]. On the other hand, Rajan et al. showed that after the administration of various food additives, including 100 mg of MBS, patients with urticaria experienced no symptoms in a double-blind challenge [30]. One's country's eating habits and the actual sulfite content in the foods available may be important. A patient from the UK was described complaining of a rash as a result of diet changes after a visit to Italy, such as the consumption of seafood, wine, grapes, and fries [15].

Table 2: Characteristics of the patients with a positive sodium metabisulfite oral challenge

No. of patients	Age	Sex (F/M)	U/AE	Drug hypersensitivity	Food as the culprit	MBS in food as the culprit	ASST	Asthma	Atopy	MBS SPT (mm)	MBS PT	MBS dose responsible for the reaction in the OC (mg)				Onset of reaction after the final dose (minutes)	Reactions during the OC	Treatment management in the OC
												10	20	100	200			
1	67	F	U/AE	-	YES	-	NEG	YES	YES	3	(-)	x				10	rhinitis, conjunctivitis, headache, weakness, mouth edema	AH1
2	72	F	U/AE	-	YES	YES	NEG	-	YES	3	(-)		x			15	cheek edema, rhinitis, dyspnea, flatulence	AH1
3	39	F	U	-	YES	-	POS	-	YES	6	(-)			x		40	neck/arm urticaria, generalized itchiness	AH1, GK
4	50	F	U/AE	YES	YES	YES	NT	YES	YES	3	(+)			x		10	face urticaria, generalized itchiness	AH1, GK, ADR
5	21	M	U/AE	-	YES	-	NT	-	YES	3	(-)			x		10	weakness, face urticaria	AH1
6	35	F	U	-	YES	-	POS	-	YES	3	(-)			x		15	neck urticaria	AH1
7	30	F	U/AE	-	YES	YES	POS	-	YES	4	(+)				x	120	generalized urticaria and itchiness	AH1
8	30	F	U/AE	-	YES	YES	POS	-	YES	3/6*	(-)				x	120	arms/trunk urticaria	AH1
9	44	F	U/AE	-	YES	YES	NEG	YES	-	0	(-)		x			10	face/cleavage urticaria, HR 90/min, feeling hot	AH1
10	47	F	U/AE	YES	YES	-	POS	YES	YES	0	(-)		x			5	face urticaria, cleavage urticaria (next 20 mg dose)	AH1
11	60	F	AE	YES	-	-	NT	-	YES	0	(-)				x	10	tongue edema	AH1, GK, ADR
12	24	M	U	-	YES	-	POS	-	YES	0	(-)				x	120	trunk/arms urticaria	AH1
13	39	M	U/AE	YES	YES	YES	NEG	-	-	0	(-)				x	7h	trunk/thigh urticaria	AH1

F - female; M - male; U - urticaria; AE - angioedema; MBS - sodium metabisulfite; ASST - autologous serum skin test; SPT - skin prick test; PT-Patch test; OC - oral challenge test, Neg - negative result; Pos - positive result, NT - not tested; * result after 30 minutes and 3.5 hours; AH1 - antihistamines; GK - glucocorticoids; ADR - adrenaline; hrs - hours

Table 3: Skin prick test and patch test sensitivity and specificity in patients with sulfite hypersensitivity

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-	OR	95% CI
SPT	61.5	76.5	40.0	88.6	2.62	0.50	5.2	1.43 - 18.91
PT	15.4	92.2	33.3	81.0	1.96	0.92	2.1	0.35 - 13.18
SPT or PT	61.5	72.6	36.4	88.1	2.24	0.53	4.2	1.18 - 15.14
SPT and PT	15.4	96.1	50.0	81.7	3.92	0.88	4.4	0.56 - 35.17

PPV - positive predictive value; NPV - negative predictive value; LR - likelihood ratio; OR - odds ratio; SPT - skin prick test; PT - patch test

Asero described a thirty-year-old female, in whom severe pruritus was observed after four hours of the administration of 10 mg sodium metabisulfite [31]. In our study, paroxysmal pruritus associated with urticaria was also the main ailment in a thirty-year-old female patient (No. 7), who was refractory to treatment even with four antihistamines tablets daily. After stopping consuming muesli with dried fruits for breakfast, she gradually reduced the treatment to only one tablet per week. Our study showed that subsequent sulfite elimination correlated with the improvement of urticaria in five patients with a positive challenge.

According to the European Food Safety Authority (EFSA), the most sulfite-sensitive individuals may show reaction to ingested metabisulfite in quantities ranging from 20 mg to 50 mg [5]. Reports show that a single restaurant meal may contain 20–200 mg of sulfites [32], and their prohibited addition to products, such as lettuce or fruit salads, has been demonstrated [18,20]. The present study observed mouth edema with rhinitis, conjunctivitis, and headache in female patient No. 1 with asthma and a positive MBS SPT, occurring within 10 minutes of administering a 10 mg dose of MBS. In addition, tearing, watery nasal discharge, and mild shortness of breath were seen up to 10 minutes after the application of a skin prick test, with the symptoms resolving spontaneously after 30 minutes; the patient had an associated airborne reaction after the exposure to sodium metabisulfite.

The results of the current study may be compared to those obtained by Ban et al. [9], who used doses ranging from 40 mg to 200 mg for the oral challenge. The authors showed that, in the group with urticaria and MBS hypersensitivity, the dose causing wheals during a challenge was, on average, 188 mg after 100 minutes of the first dose. Our study determined that the average dose followed by symptoms was 113 mg, with the reaction time of 164 minutes of the first dose of MBS.

We ascertained a percentage of 5.5% (n = 6) of positive sodium metabisulfite PTs, which was consistent with other studies (2.2–7%) performed in the last ten years [3,7,33-35]. As the reaction was more prominent on D3 and D4 than on D2, we excluded irritancy. Similarly to some studies [20], we detected more positive MBS patch tests in females than males (5:1 ratio). However, we were not able to establish the primary source of sulfite sensitization.

We noticed that urticarial symptoms were relatively more severe in the MBS PT (+) patients and lasted longer than in the rest. Similarly to other studies [7,11], we determined that the patients with sulfite contact allergies may also have shown symptoms after their ingestion and that patch tests may be useful to diagnose immediate reactions to sulfite-containing foods [7,20]. Our study found two patients (No. 4 and 10) with a positive sodium metabisulfite SPT, PT, and challenge test. Table 3 shows the sensitivity and specificity of skin tests, wherein a positive oral challenge was regarded as the gold standard.

No group with a positive MBS test differed in terms of the coexistence of allergic rhinitis, dermatitis, asthma, or drug hypersensitivity. We found that sulfite hypersensitivity usually accompanies other allergic diseases and is rarely an isolated complaint.

Our study concluded that sodium metabisulfite hypersensitivity appears often enough to be screened in chronic urticaria and that more than half of the diagnosed urticarial cases were IgE-dependent reactions, sometimes coexisting with positive sodium metabisulfite patch tests.

ACKNOWLEDGMENTS

The authors would like to acknowledge Mikołaj Rybaczuk, M.A., for statistical analysis.

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

Papular mucinosis (papular lichen myxedematosus): Clinical and histopathological evaluation

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ABSTRACT

Background: Papular mucinosis is a variety of mucinosis characterized by excessive production of mucin by fibroblasts and deposition in the dermis. It manifests itself with fleshy papules or plaques in different sites of the body and taking different clinical morphological cutaneous features. **Objective:** The objective is to report and evaluate the different clinical and histopathological features of the disease in Iraqi patients. **Patients and Methods:** This is a case series and a clinical descriptive study in which ten patients with papular mucinosis were reported during the period from 2012 through 2019. The age ranged from 4 to 56 years, with seven females and three males. Clinical evaluation regarding histories of the disease and examination was carried out. General investigation was done and skin biopsy for histopathological assessment was conducted. **Results:** Nine patients were adults, with their age ranging from 20 to 56 years, a mean of around 35 years, and only one 4-year-old child. It is a disease with a female predominance, as observed in 7 (70%) females. The common sites of involvement were the face but the rash may extend to affect the neck and upper arms. The rash appeared in the form of skin-colored or red fleshy papules and plaques or in diffuse erythematous orange peel-like forms. The rash was asymptomatic in most patients. The pathology of the disease clarified the diffuse deposition of mucin in the dermis, as was demonstrated with H&E staining. **Conclusion:** Papular mucinosis is a rare disease characterized by mucin deposition in the skin affecting mostly adult females. The face is commonly involved together with other areas such as the neck and upper arms, but the trunk and lower limbs are spared. It manifests itself with different clinical morphological cutaneous features. Papular granuloma annulare must be considered as an important differential diagnosis in all cases of papular mucinosis.

Key words: Lichen myxedematosus, Papular mucinosis, Mucin

INTRODUCTION

The cutaneous mucinoses are a heterogeneous cluster of disorders in which an atypical amount of mucin conglomerates in the skin, either diffusely or focally [1].

Mucin is an element of the dermal extracellular matrix and is usually manufactured in little quantities by fibroblasts. It is a jelly-like, amorphous compound of acid glycosaminoglycans. The acid glycosaminoglycans may be connected to both sides of the protein core, as in the case of dermatan sulfate and chondroitin sulfate, or they may be free, as in the case of hyaluronic acid, which is the most important constituent of dermal mucin. Mucin is capable of holding water in quantities of up to 1000 times its weight, playing an important role in maintaining the water and salt equilibrium of the dermis. In routinely stained sections, the existence of either a blue-staining material between separated collagen bundles or empty spaces within the dermis are important hints of mucin deposition. For verification, special stains can be utilized, such as Alcian blue, toluidine blue, and colloidal iron [2].

Pathogenesis

The exact pathogenesis of mucinosis is unknown. The most agreed hypothesis is that circulating cytokines, such as tumor necrosis factor alpha, transforming

How to cite this article: Sharquie K, Jabbar RI. Papular mucinosis (papular lichen myxedematosus): Clinical and histopathological evaluation. Our Dermatol Online. 2021;12(2):113-119.

Submission: 06.08.2020; **Acceptance:** 11.10.2020

DOI: 10.7241/ourd.20212.3

growth factor beta, and Interleukin-1, intensify the reproduction of fibroblasts and glycosaminoglycan production. *In vitro*, the serum of patients with scleromyxedema can enhance the production of DNA by fibroblasts [3].

Classification

Cutaneous mucinoses may be classified as primary, in which mucin deposition is the major histological feature that leads to clinically unique lesions, and secondary, in which mucin constitutes an additional associated histological finding. Primary mucinoses are then subdivided into degenerative–inflammatory forms and hamartomatous–neoplastic forms. The degenerative–inflammatory forms are further subdivided into dermal and follicular [4].

Classification of Primary Mucinoses

A-Degenerative–Inflammatory Mucinoses:

1. Dermal
   a. Scleromyxedema
   b. Localized variants of lichen myxedematosus (LM):
      • Discrete papular mucinosis
      • Acral persistent papular mucinosis
      • Cutaneous mucinosis of infancy (CMI)
      • Nodular mucinosis
   c. Self-healing cutaneous mucinosis
      • Juvenile type
      • Adult type
   d. Scleredema
      • Nondiabetic (types I and II)
      • Diabetic (type III)
   e. Mucinoses associated with altered thyroid function
      • Localized (pretibial) myxedema
      • Generalized myxedema
   f. Reticular erythematous mucinosis
   g. Papulonodular mucinosis associated with autoimmune connective tissue disease
   h. Digital mucous cyst (myxoid cyst)
   i. Cutaneous focal mucinosis
   j. Miscellaneous mucinoses

2. Follicular
   • Follicular mucinosis
   • Urticaria-like follicular mucinosis

B. Hamartomatous–Neoplastic Mucinoses:
   • (Angio)myxoma
   • Mucinous nevus

Classification of Secondary Mucinoses (Associated with Histological Deposition of Mucin)

1. Epithelial mucinosis
   • Basal cell carcinoma
   • *Rare:* Squamous cell carcinoma, verruca, seborrheic keratosis, keratoacanthoma, mycosis fungoides.
2. Dermal mucinosis
   • Granuloma annulare
   • Lupus erythematosus, scleroderma and dermatomyositis
   • Epithelial tumors (e.g., basal cell carcinoma, eccrine carcinoma)
   • Mesenchymal tumors (e.g., myxosarcoma, myxoid lipoblastoma)
   • Neural tumors (e.g., neurofibroma, lobular neuromyxoma)
   • Other tumors (e.g., cutaneous metastases, mucinous carcinoma of the eyelid)
   • Hypertrophic scarring
   • Obesity-associated lymphedema
   • *Rare:* chronic graft-versus-host disease, cutaneous reactions to interferon, herpes zoster, venous insufficiency.
3. Follicular mucinosis
   • Eczematous dermatoses
   • Mycosis fungoides
   • *Rare:* lupus erythematosus, insect bites, familial reticuloendotheliosis, side effect of imatinib.

Scleromyxedema

Scleromyxedema is a rare cutaneous disorder characterized by dispersed eruption of hard, waxy, dome-shaped or flat-topped papules and nodules 2 – 3 mm in size that may amalgamate to form plaques and that involve the head, neck, trunk, and extremities. The scalp and mucosa are usually uninvolved [5]. Papules are generally arranged linearly and the neighboring skin exhibits a sclerodermoid manifestation. There is no significant gender predominance: males and females are equally affected. It most commonly occurs in adults between the fifth and sixth decades of life [6]. Mucin deposition in the dermis is responsible for the skin features. A sclerodermoid eruption with multiple papules, edema, and erythema—as well as papular induration over the ears and glabella—confer a leonine facies [7,8]. Skin thickening in chronic scleromyxedema can lead to decreased articular motion and difficulty in opening the mouth. Itching and dysesthesia are usual complaints as well [6,7].

Patients with scleromyxedema may have a number of systemic manifestations, such as muscular, rheumatologic, neurologic, renal, pulmonary, and cardiovascular [7].

Diagnostic criteria for scleromyxedema are as follows: a) histological triad of mucin deposition, fibroblast reproduction, and fibrosis; b) monoclonal gammopathy, predominantly IgG λ and less commonly IgG κ; c) absence of thyroid diseases [4].

Pathology

Scleromyxedema is characterized by a triad of pathologic features: [9]
- a diffuse accumulation of mucin in the upper and mid reticular dermis;
- an increase in collagen deposition;
- a noticeable proliferation of irregularly arranged fibroblasts.

Localized Variants of Lichen Myxedematosus (LM)

In the localized variants of LM, patients show small, firm, waxy papules (or nodules and plaques created by coalescence of the papules) that involve several sites, usually the upper and lower limbs and/or the trunk. The skin is the only site of involvement and these variants, in contrast to scleromyxedema, are not accompanied by sclerosis, paraproteinemia, or systemic involvement, nor are they accompanied by a thyroid disorder [10].

The diagnostic criteria of the localized variants of LM include a papular or nodular eruption and the histopathological triad (mucin accumulation, fibroblast reproduction at different grades) without monoclonal gammopathy or thyroid diseases [4].

Epidemiology

The exact incidence and prevalence rates of the localized variants of lichen myxedematosus remain unknown [4].

CLINICAL FEATURES

Discrete Papular Lichen Myxedematosus (DPLM)

DPLM is characterized by 2 – 5 mm papules, numbering from several to hundreds and affecting the extremities and trunk in a symmetrical fashion [12]. The involved skin is not indurated and the face usually uninvolved. Progression occurs slowly and without systemic involvement. Although prognosis is good, spontaneous resolution is rare [12,13].

Acral Persistent Papular Mucinosis (APPM)

In APPM, multiple ivory to skin-colored papules involve exclusively the dorsal aspects of the hands and extensor surfaces of the distal forearms and show a female predominance (female : male = 3 : 1). Lesions are persistent but without systemic involvement [14].

Cutaneous Mucinosis of Infancy (CMI)

In CMI, hard, opalescent papules involve the neck, upper arms (especially the elbows), and trunk [10]. In contrast to self-healing mucinosis, neither systemic manifestations nor spontaneous remission are observed. Of the handful of cases described to date, at least two have had a congenital linear variant, which might be better classified as an example of a mucinous nevus [15].

Nodular Lichen Myxedematosus

Nodular LM is characterized by firm, skin-colored nodules usually more than 6 mm in diameter with or without papules located on the trunk and extremities. Very few cases of nodular LM have been reported and the age of onset seems to be lower compared to APPM and DPLM [16-18].

Atypical Forms of Lichen Myxedematosus

Occasionally, patients with LM have abnormal manifestations or manifestations intermediate between scleromyxedema and localized LM [10].

Pathology

In the localized forms of LM, the histological changes are less distinctive than in scleromyxedema. Mucin accumulates in the upper and mid reticular dermis and fibroblast reproduction is variable; fibrosis is not noticeable and may even not seen. In acral persistent papular mucinosis, mucin accumulates focally in the upper part of the dermis with no increase in the number of fibroblasts [9].

Differential Diagnosis

Pathological examination of the skin assists in differentiating the localized types of LM from several papular lesions that can have the same appearance,

such as papular granuloma annulare, colloid milium, papular elastorrhexis, molluscum contagiosum, amyloidosis, and eruptive collagenomas [4].

Treatment

Localized LM does not require therapy, and a wait-and-see approach is recommended. Topical therapy with corticosteroids or calcineurin inhibitors may be of some benefit [11]. One patient with associated human immunodeficiency virus (HIV) infection had a complete remission after treatment with oral isotretinoin. Spontaneous remission may occur [19], even with an HIV infection [20].

Complete resolution of LM nodules has been reported with intralesional injection of triamcinolone acetonide at a dose of 0.02 – 0.05 mL (8 mg/mL) [18].

Destructive modalities, including carbon dioxide (CO2) laser, erbium-doped yttrium aluminum garnet (Er-YAG) laser, cryotherapy, electrocoagulation, and electrofulguration, are acceptable cosmetic treatments for the localized types [21].

Self-Healing Cutaneous Mucinosis

Self-healing cutaneous mucinosis was initially reported in children, with the age ranging from 1 to 15 years [2]. The same disorder, thereafter, appeared in several adults [22].

Clinical manifestations are as follows: a) an acute eruption of several papules, sometimes collecting into linear infiltrated plaques, on the face, neck, scalp, abdomen, and thighs; and b) mucinous subcutaneous nodules in the periarticular areas and the face with periorbital swelling. In addition, systemic symptoms (e.g., fever, muscle tenderness, and arthralgias) may occur with skin lesions, but paraproteinemia, bone marrow plasmacytosis, and thyroid disorders are absent. Spontaneous remission over a period of 1 – 8 months is characteristic. Histologically, papular lesions show mucin deposition in the dermis with mild inflammation and some increase in the number of fibroblasts, whereas nodules have deep mucinous deposits accompanied by bands of fibrosis and obvious reproduction of fibroblast-like cells and gangliocyte-like cells resembling proliferative fasciitis [23].

Patients and Methods

This is a case series and a clinical descriptive study in which ten patients with papular mucinosis were collected at the Dermatology Center in Baghdad Medical City, Baghdad, Iraq, during the period from July 2012 through December 2019.

The age ranged from 4 to 56 years. The patients were seven females and three males.

Formal approval was taken from each patient after the nature, course, prognosis, and aim of the study were explained to each of the patients prior to the commencement of the study.

A full history was taken from each patient, including sex, age, age of disease onset, duration of the disease, associated skin and systemic symptoms, and past medical and drug history.

Proper clinical examination was conducted to determine the sites, colors, sizes, clinical appearances, and morphological distributions of the lesions.

A biopsy was taken from five patients from selected sites and processed for histopathology with H&E staining.

Pathological and clinical pictures were studied together for clinical and pathological correlation.

Erythrocyte sedimentation rate, complete blood count, blood urea, and serum creatinine were measured for each patient.

RESULTS

Clinical Results

Nine patients (90%) were adults, with the age ranging from 20 to 56 years, a mean of around 35 years, and only one 4-year-old child. The disease shows a female predominance, as observed in 7 (70%) females. The common sites of involvement were the face but the rash may extend to affect the neck and upper arms, but not the trunk and lower limbs. Lesions appeared in the form of fleshy, skin-colored or red papules and plaques or in diffuse erythematous orange peel-like forms (Figs. 1 and 2).

The rash was asymptomatic in most patients and only 2 (20%) experienced mild itching.

A 4-year-old female showed an acute eruption of asymptomatic papulonodular skin lesions persistent for two months and involving the face, scalp, neck, trunk, and extremities with swelling under the eyes. Some lesions had healed spontaneously during the course of the disease. A skin biopsy revealed mucin deposition in the superficial

dermis. Clinical features and pathological findings of this case were matched together and diagnosed as self-healing juvenile cutaneous mucinosis (Fig. 3).

No systemic symptoms appeared in any patient except mild fever in case of self-healing juvenile cutaneous mucinosis. All results from laboratory investigations were normal.

Topical steroids were used with some beneficial results. In one case with a facial rash, diathermy was applied with favorable cosmetic results.

Pathological Results

Biopsies of the skin that stained with H&E clarified the diffuse deposition of mucin in the superficial and deep dermis and in direct contact with dermoepidermal junction. However, there was no increase in the fibroblast cells and no collagen deposition was noticed. The changes in the epidermis were variable, as acanthosis and hyperkeratosis were observed in some cases, while thinning of the epidermis in others (Figs. 1 and 3).

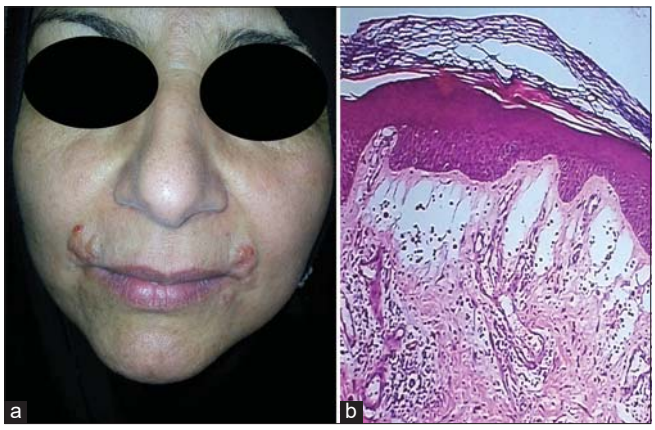

Figure 1: A 46-year-old female with (a) plaques of localized lichen myxedematosus around the mouth angles and (b) an H&E-stained section from the same patient showing mucin deposition in the papillary and reticular dermis together with hyperkeratosis and acanthosis of the epidermis (H&E, 10×).

DISCUSSION

To the best of our knowledge, this is the first study on localized lichen myxedematosus (papular mucinosis) showing ten cases with different variants of the condition, with previous studies being either case reports [5,11-13,18] or a study with one type of localized cutaneous mucinosis [24].

Lichen myxedematosus is a rare cutaneous disorder as confirmed by the present work: ten patients have been seen by one doctor during a period of eight years.

In this study, 9 (90%) patients were adults, with the age ranging from 20 to 56 years. The condition studied has a female predominance as 70% of our cases were females. These results cannot be compared to other studies because of the rarity of studies on localized lichen myxedematosus and because case reports of only one or two varieties have been recorded. The exact incidence and preponderance of the different varieties of localized lichen myxedematosus are unknown because of their rarity. A female dominance has only been reported in acral persistent papular mucinosis, which is comparable to our findings [4].

Figure 2: A 56-year-old female with even papulonodular plaques of localized lichen myxedematosus affecting (a) the face, (b) the posterior neck and upper trunk, and (c) the forearm.

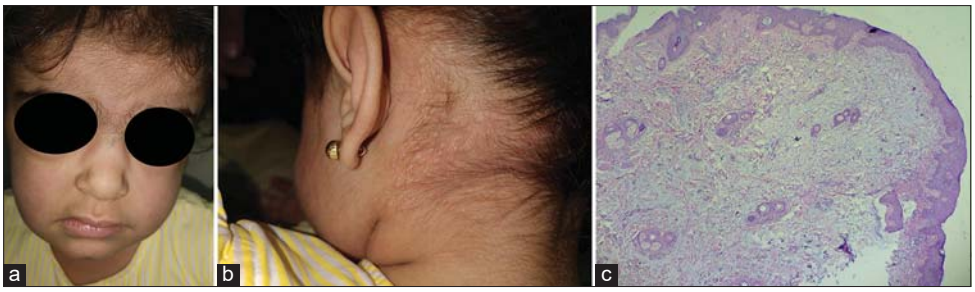

Figure 3: Self-healing juvenile cutaneous mucinosis in a four-year-old female involving (a) the face and forehead and (b) the postauricular and posterior neck. (c) An H&E-stained section showing diffuse mucin deposition in the papillary and reticular dermis with thinning of the epidermis (H&E, 10×).

In our work, the common sites of involvement were the face, but the rash may extend to affect the neck and upper arms. With the exception of a case of self-healing juvenile cutaneous mucinosis, the morphological distribution of lesions in most of our cases did not match any variant of localized lichen myxedematosus. This variability in morphological distribution cannot be explained but might have had a racial element or might have been a new entity of localized cutaneous mucinosis.

Histopathological results showed diffuse deposition of mucin in the papillary and reticular dermis and encroaching the dermoepidermal junction, and these results are comparable with what has been reported, but fibroblast cells proliferation and collagen deposition have not been observed in our work [9,11-15].

Regarding the differential diagnosis of papular lichen myxedematosus, papular granuloma annulare must be excluded [4].

Regarding the treatment of localized lichen myxedematosus, topical steroids, topical calcineurin inhibitors, and intralesional steroids have been used in previous reports. In our study, topical steroids were used with some beneficial results. In one case with a facial rash, diathermy was applied with favorable cosmetic results. Regarding the case of self-healing juvenile cutaneous mucinosis, no treatment was needed, except for reassurance of the parents as it is a self-limiting disease.

CONCLUSION

Papular lichen myxedematosus mucinosis is a rare disease characterized by mucin deposition in the skin, affecting mostly adult females. The face is commonly involved together with other sites such as the neck and upper arms. The condition presents itself with different clinical morphological cutaneous features. Granuloma annulare of the papular variety must be excluded in all cases of papular mucinosis.

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

Clinical and laboratory profiles of genital ulcers (sexually transmitted diseases) in a tertiary care center in northeastern India

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ABSTRACT

Background: Genital ulcers are defined as breaches in the continuity of the genital mucosa and/or skin. Sexually transmitted infections (STIs) that cause genital ulcer disease (GUD) are syphilis, chancroid, donovanosis, lymphogranuloma venereum (LGV), and herpes genitalis. This study aimed to investigate the clinical and laboratory profiles of STI-related genital ulcers. **Materials and Methods:** A cross-sectional two-year study was conducted on patients attending the Outpatient Department of Dermatology, Venereology and Leprosy in a tertiary care center in northeastern India. Selected were 95 patients who presented themselves with STI-related genital ulcers. Detailed history taking and examination were conducted with basic tests to assist the diagnosis. **Results:** The male-to-female ratio was 3.32:1, and the most common site was the glans and prepuce in males (28.77%) and the labia majora and minora in females (36.36%). 96.84% of patients had superficial ulcers. The KOH mount was positive in 26 patients. The Tzanck smear was positive in 31 patients. RPR was positive in four. HIV was positive in eleven. Herpes genitalis (96.84%) was the most common GUD. Mixed STIs were attested in 41.05% of patients. **Conclusion:** GUD can take various forms of presentation. The available laboratory tests should be utilized. The possibility of mixed infections should always be kept in mind.

Key words: Genital ulcer disease; Herpes simplex virus; HIV

INTRODUCTION

Genital ulcers are defined as breaches in the continuity of the genital mucosa and/or skin. Genital ulcer disease (GUD) may be due to sexually transmitted infections (STIs), such as syphilis, chancroid, donovanosis, lymphogranuloma venereum (LGV), herpes genitalis, or non-STIs, such as traumatic ulcers, Behçet's disease, lichen planus, erythema multiforme, lichen sclerosis et atrophicus, bullous diseases, Fournier gangrene, and squamous cell carcinoma [1].

Documenting the etiological agents of GUD remains especially difficult as the relevant diagnostic tests are often unavailable or are misused. The etiological agent may not be found due to the patient self-medicating or because of the contamination of the ulcers. However, bedside and laboratory tests are, in early lesions, fairly sensitive and specific. A clinical diagnosis may be misleading because the increasing number of HIV coinfections and mixed infections often alter the morphology of the ulcers and the textbook description of GUD may not always be present. The ulcers do not remain confined to the genitalia and may be seen in extragenital sites due to changes in sexual behavioral patterns. Clinical diagnoses have been observed to be incorrect in around 40% of patients with GUD when compared to laboratory tests [1].

In view of the above loopholes in the diagnosis and management of GUD, it is important that a clinical diagnosis is reinforced by the laboratory facilities

How to cite this article: Bachaspatimayum R, Zamzachin G, Devi TB. Clinical and laboratory profiles of genital ulcers (sexually transmitted diseases) in a tertiary care center in northeastern India. Our Dermatol Online. 2021;12(2):120-129.

Submission: 11.06.2020; **Acceptance:** 13.09.2020

DOI: 10.7241/ourd.20212.4

available at the institute of examination so that the newer trends of manifestation, if any, can be recognized and so that any HIV-correlated peculiarity of GUD can be detected. An accurate clinical diagnosis corroborated by laboratory findings will prevent inflicting unnecessary psychological trauma to the patient.

MATERIALS AND METHODS

A cross-sectional study was conducted on patients visiting the Outpatient Department of Dermatology, Venereology and Leprosy in collaboration with the Department of Microbiology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, for a two-year period from October 2011 through September 2013.

A total of 95 cases of both sexes and all age groups who presented themselves with STI-related genital ulcers at the Outpatient Department of Dermatology, Venereology and Leprosy, RIMS Hospital, were selected from among all cases displaying genital ulcers after excluding non-STI-related genital ulcers. Clinically diagnosed STI-related genital ulcers for which the minimum laboratory investigations could not be completed due to poor patient compliance were also excluded from the study group. Ethical approval for this study was received from the Institutional Ethical Committee, RIMS, Imphal, Manipur.

After receiving a written informed consent from each of the patients, a detailed history was taken and recorded in a uniform predesigned proforma, followed by a thorough local and systemic examination as well as investigations such as genital swabs for KOH, wet mounts, Gram stain, Giemsa stain, Tzanck smear, and blood samples for VDRL and routine tests, including urine examination, tests for HIV, HBsAg, anti-HCV Ab, serology for herpes simplex virus 1 and 2, and TPHA, wherever needed. The collected data was analyzed with descriptive statistics.

RESULTS

Among the total 95 cases studied, 73 (76.84%) were males and 22 were females (23.16%), giving a male-to-female ratio of 3.32:1. The most common age group was 21–30 years old (34.73%).

The most common presentation among male patients was painful genital sore (n = 22; 30.14%), followed by asymptomatic genital sores (n = 14; 19.17%). The healthcare-seeking behavior in female patients was mainly due to pain (n = 9; 40.90%) (Table 1).

Most of the male patients (n = 32; 43.83%) presented themselves between day 6 and 11, in contrast to the female patients, among whom the majority (n = 14; 63.63%) reported earlier, between day 0 and 5 after the onset of the disease. The mean duration of the disease was 11.88 ± 13.299 days in males and 11.14 ± 16.994 days in females (Table 2).

The most common site in males was the glans and prepuce (n = 21; 28.76%) (Table 3), while, in females, most ulcers appeared in both the labia majora and minora (n = 8; 36.36%) (Fig. 1).

Speculum examination of cervical lesions was skipped so as not to unnecessarily cause more paint to a suffering patient.

Table 1: Distribution of symptoms among males and females

Symptoms	Male n (%)	Female n (%)
Painful genital sore	22 (30.14)	9 (40.90)
Itching	9 (12.33)	3 (13.63)
Pain and itching	6 (8.22)	0 (0.00)
Pain and dysuria	5 (6.85)	1 (4.55)
Pain and discharge from the urethra or vagina	1 (1.37)	5 (22.72)
Asymptomatic rash around the urethral meatus	1 (1.37)	0 (0.00)
Pain with genital swelling	0 (0.00)	1 (4.55)
Genital sore with groin swelling	1 (1.37)	0 (0.00)
Genital sore with genital swelling	1 (1.37)	1 (4.55)
Genital sore with growth	1 (1.37)	0 (0.00)
Asymptomatic genital sores	14 (19.17)	1 (4.55)
Painless genital sore with dysuria	1 (1.37)	0 (0.00)
Itching with dysuria	2 (2.74)	0 (0.00)
No complaints (partner examination)	1 (1.37)	1 (4.55)
Skin eruption over the genitals	7 (9.59)	0 (0.00)
Painful anal erosion	1 (1.37)	0 (0.00)
Total	73 (100)	22 (100)

Table 2: Distribution of the time of persistence of lesions upon presentation

Duration (days)	Male n (%)	Female n (%)
0–5	22 (30.14)	14 (63.63)
6–11	32 (43.83)	3 (13.64)
12–17	7 (9.59)	2 (9.09)
18–23	3 (4.11)	0 (0.00)
>23	9 (12.33)	3 (13.64)
Total	73 (100)	22 (100)
Prepuce, frenulum	1 (1.37)	
Prepuce, shaft, corona	1 (1.37)	
Shaft	2 (2.74)	
Periurethral area	2 (2.74)	
Perianal area	1 (1.37)	
Total	73 (100)	

The majority of patients had 1–3 ulcers, 57.53% of males and 40.91% of females (Fig. 2). Among males, more than 16 (21.92%) displayed a single ulcer, which was the most common presentation. The most common shape of ulcer was round (n = 29; 30.53%). Ulcers had well-defined margins in 58 (61.05%) patients, ill-defined in 36 (37.90%), and undermined in one (1.05%). Ninety-two (96.84%) patients had superficial ulcers, while only three (3.16%) had deep ulcers. A majority (n = 67; 70.53%) had clean ulcers. The surface was more erythematous in 29 (30.53%) patients than in the others. Tenderness was present in only 34 (35.79%) patients and induration in 13 (13.68%). Associated vesicles were found in 36 (37.89%) patients, associated discharge from the vagina in 9 (40.9%), and associated urethral discharge in one male (1.05%). Inguinal lymphadenopathy was present in 25 (26.32%) patients, 16 males and 9 females, among which tenderness was present in nine males and four females (Table 4a).

The KOH mount was positive in 26 (27.37%) patients, 19 males and 7 females. The Tzanck smear was positive in 31 (32.63%) patients, 19 males and 12 females. RPR was positive in four (4.21%) patients Table 4b. Gram stain showed mostly Gram-positive cocci and Gram-negative bacilli, besides Gram-positive bacilli (Table 5).

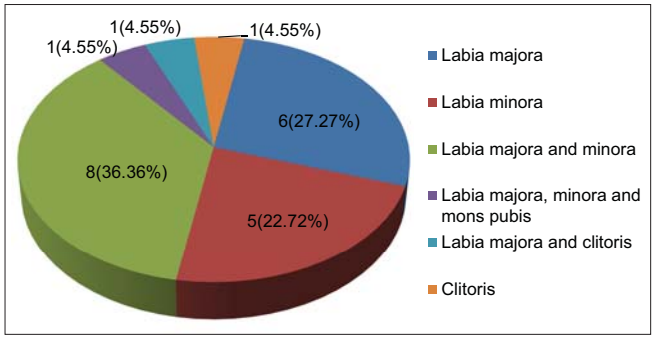

Figure 1: Distribution of ulcer sites in females.

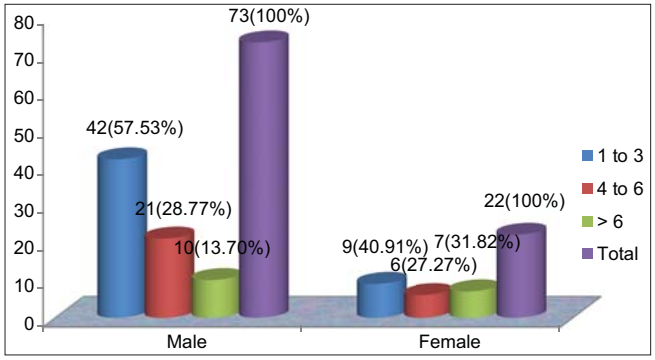

Figure 2: Distribution of the number of ulcers in both sexes.

There were no significant findings suggestive of microorganisms in 40 (42.10%) patients. HIV was positive in 11 (11.58%) patients; ten were positive and already on ART; one was recently diagnosed at the time of the study Table 4b. HCV antibody was positive in one HIV patient (1.05%) on ART, while there was not a single patient positive for HBsAg.

Table 3: Distribution of ulcer site in males

Ulcer site	Number (%)
Prepuce	16 (21.92)
Corona	3 (4.11)
Prepuce, corona	2 (2.74)
Glans	15 (20.55)
Glans, prepuce, corona	1 (1.37)
Glans, shaft	3 (4.11)
Glans, prepuce, shaft	1 (1.37)
Glans, prepuce	21 (28.76)
Glans, corona	3 (4.11)
Prepuce, scrotum	1 (1.37)

Table 4a: Other clinical characteristics of genital ulcers

Cutaneous examination	Male, n (%)	Female, n (%)	Total, n (%)
Ulcer margin			
Well-defined	40 (54.79)	18 (81.82)	58 (61.05)
Ill-defined	32 (43.84)	4 (18.18)	36 (37.90)
Undermined	1 (1.37)	0 (0)	1 (1.05)
	73 (100)	22 (100)	95 (100)
Surface			
Clean	53 (72.60)	14 (63.64)	67 (70.53)
Slough	18 (24.66)	8 (36.36)	26 (27.37)
Crusts	2 (2.74)	0 (0)	2 (2.10)
	73 (100)	22 (100)	95(100)
Depth			
Superficial	70 (95.89)	22 (100)	92 (96.84)
Deep	3 (4.11)	0 (0)	3 (3.16)
	73 (100)	22 (100)	95 (100)
Induration			
Present	8 (10.96)	5 (22.73)	13 (13.68)
Absent	65 (89.04)	17 (77.27)	82 (86.32)
	73 (100)	22 (100)	95 (100)
Tenderness			
Present	20 (27.40)	14 (63.64)	34 (35.79)
Absent	53 (72.60)	8 (36.36)	61 (64.21)
	73 (100)	22 (100)	95 (100)
Vesicles	22 (30.14)	14 (63.64)	36 (37.89)
Present	51 (69.86)	8 (36.36)	59 (62.11)
Absent	73 (100)	22 (100)	95 (100)
Inguinal lymph node			
Present	16 (21.92)	9 (40.90)	25 (26.32)
Absent	57 (78.08)	13 (59.10)	70 (73.68)
	73 (100)	22 (100)	95 (100)

Table 4b: Laboratory tests

Test	Male, n (%)	Female, n (%)	Total, n (%)
KOH			
Positive	19 (26.03)	7 (31.82)	26 (27.37)
Negative	54 (73.97)	15 (68.18)	69 (72.63)
	73 (100)	22 (100)	95 (100)
Tzanck smear			
Positive	19 (26.03)	12 (54.55)	31 (32.63)
Negative	54 (73.97)	10 (45.45)	64 (67.37)
	73 (100)	22 (100)	95 (100)
RPR			
Reactive	2 (2.74)	2 (9.09)	4 (4.21)
Nonreactive	71 (97.26)	20 (90.91)	91 (95.79)
	73 (100)	22 (100)	95 (100)
HIV antibody			
Reactive	6 (8.22)	5 (22.73)	11 (11.58)
Nonreactive	67 (91.78)	17 (77.27)	84 (88.42)
	73 (100)	22 (100)	95 (100)

Table 5: Gram stain findings (Gm+: Gram-positive; Gm-: Gram-negative)

Gram stain	Number (%)
Gm+ cocci singly	10 (10.53)
Gm+ cocci in pairs	6 (6.32)
Gm+ cocci in groups	6 (6.32)
Gm+ cocci in groups and pairs	3 (3.16)
Gm+ cocci in groups and chains	3 (3.16)
Gm+ cocci and Gm+ coccobacilli	1 (1.05)
Gm+ cocci in chains	1 (1.05)
Gm+ coccobacilli in groups (rail track appearance)	1 (1.05)
Gm- bacilli	8 (8.42)
Gm+ cocci and Gm- bacilli	8 (8.42)
Gm- bacilli and Gm- diplococci	3 (3.16)
Gm- diplococci	1 (1.05)
Clue cells	3 (3.16)
Polymorphs	1 (1.05)
No significant findings	40 (42.10)
Total	95 (100)

Herpes genitalis (n = 92; 96.84%) was the most common GUD, the second common being syphilis in 3 (3.16%) patients (Table 6).

Mixed STI infections, including those with HIV and HCV, comprised 39 (41.05%) patients. Among males, herpes genitalis was the most common GUD (n = 44). There were two cases of syphilis and one case per each of LGV and chancroid occurring as mixed infections with h. genitalis. In females, h. genitalis was the most common (n = 12) etiology of GUD, followed by h. genitalis with candidal vulvovaginitis (n = 7). However, there was no case of donovanosis (Table 6).

Table 6: Distribution of the diagnosis of the various GUDs

Diagnosis	Male n (%)	Female n (%)	Total n (%)
H. genitalis	44 (60.27)	12 (54.55)	56 (58.95)
Primary syphilis	1 (1.37)	0 (0)	1 (1.05)
Secondary syphilis	1 (1.37)	0 (0)	1 (1.05)
Secondary syphilis with candidal vulvovaginitis	0 (0)	1 (4.55)	1 (1.05)
Chancroid, h. genitalis	1 (1.37)	0 (0)	1 (1.05)
LGV with h. genitalis, HIV	1 (1.37)	0 (0)	1 (1.05)
H. genitalis with candidal balanoposthitis	16 (21.92)	0 (0)	16 (16.85)
H. genitalis, genital warts, BV, HIV	0 (0)	1 (4.55)	1 (1.05)
H. genitalis, BV	0 (0)	1 (4.55)	1 (1.05)
H. genitalis, genital warts	2 (2.74)	0 (0)	2 (2.11)
H. genitalis, NGU, candidal balanoposthitis	1 (1.37)	0 (0)	1 (1.05)
H. genitalis, candidal vulvovaginitis	0 (0)	3(13.62)	3 (3.16)
H. genitalis, candidal vulvovaginitis, HIV	0 (0)	4(18.18)	4 (4.21)
H. genitalis, NGU	1 (1.37)	0 (0)	1 (1.05)
H. genitalis, HCV, HIV	1 (1.37)	0 (0)	1 (1.05)
H. genitalis, HIV	2 (2.74)	0 (0)	2 (2.11)
H. genitalis, candidal balanoposthitis, genital warts, HIV	2 (2.74)	0 (0)	2(2.11)
Total	73 (100)	22 (100)	95 (100)

DISCUSSION

There are more than twenty pathogens transmissible through sexual intercourse but the exact magnitude of the burden of STIs is largely unknown due to the lack of in-depth studies, hindered by the stigma associated with STIs and by the lack of reinforcing clinical diagnosis with easy and quick diagnostic laboratory tests. In view of the rising prevalence of HIV/AIDS, proper control of STIs must be given due importance. It has been found that the presence of an untreated STI—ulcerative or nonulcerative—can increase risk of both the acquisition and transmission of HIV by a factor of ten [2]. A study by Desai et al. on the performance of STI syndromes against etiological diagnosis demonstrated that syndromic management based on genital ulcer syndrome (GUS) may miss around 85% of cases with active infection and lead to treatment of ulcers in 43% of cases in the absence of syphilis infection. Such a situation leads to the obvious financial burden of unindicated treatment while depriving the symptomatic cases of necessary care [3]. A study by Bailey et al. found that ulcers with bacterial or mixed etiologies were more likely to have detectable HIV-1 compared to those with HSV or with unknown etiologies, and concluded that

the presence of lesional HIV-1 in almost one-half of HIV-positive males underscores the importance of GUD in increasing HIV infectivity [4]. Choudhry et al. suggested that syndromic management of GUD is not very effective in identifying herpes genitalis and syphilis. They also found a high incidence of HIV seropositivity (10.3%) in their study population, suggesting a close association of STI with HIV [5]. A study by Coovadia, Kharsany, et al. conducted in Durban, South Africa, demonstrated that, because of the lack of laboratory facilities in most STD clinics, microbial diagnosis is based on clinical criteria alone; their findings indicate that clinical and epidemiological features alone are not reliable in diagnosing the etiology of genital ulcers. Multiple ulcers, which are said to be characteristic of chancroid, were also noted in 36% (16/44) of patients with syphilis and in only 60% (24/40) of those with chancroid. The presence of buboes and the length of the incubation period proved to be of some help in diagnosing chancroid [6]. In another study, the accuracy of a clinical diagnosis in men was 66% in lymphogranuloma venereum (LGV), 63% in donovanosis, 42% in chancroid, 39% in genital herpes, 32% in primary syphilis, and 8% in mixed infections. In women, it was 94% in secondary syphilis, 83% in donovanosis, 60% in genital herpes, 58% in primary syphilis, 57% in chancroid, 40% in LGV, and 14% in mixed infections. Differences between clinical and laboratory diagnostic accuracies may reflect the similarities between the clinical appearance of the various causes of GUD, the presence of mixed infections, atypical ulceration due to longstanding disease, and insensitive laboratory tests [7].

Although there are more than 500 STD clinics in India, only 42 are functioning properly and collecting adequate records of cases. With the advocacy of the syndromic approach to the treatment of GUD and discharge, cases are diagnosed on the basis of flow charts, without laboratory aid, and are treated accordingly. This results in the provision of less information on HIV-positive cases among unregistered patients, which becomes a considerable social issue because HIV-positive cases remain unrecorded and become sources further propagating infection [8]. A study by DiCarlo and Martin demonstrated that the results of reaching an accurate clinical diagnosis of GUD were dependent on the clinician's skills and are thus influenced by factors such as previous experience, knowledge of epidemiological risk factors, and disease prevalence, due to which the results may not be generalized. They found that comparing individual signs underlined statistically significant differences between ulcers in chancroid, genital herpes, and primary syphilis. Despite the statistical significance of these differences, however, there was a considerable overlap between the three groups [9].

Behets et al., in a study to determine the etiology of genital ulcers in Antananarivo, Madagascar, using a multiplex polymerase chain reaction (M-PCR) assay to detect DNA targets from *Haemophilus ducreyi*, *Treponema pallidum*, and herpes simplex virus in a single ulcer specimen and to assess the accuracy of clinical diagnosis and locally performed laboratory tests for comparison with the M-PCR results of 196 patients, found that syphilis and chancroid were clinically diagnosed in 42.9% of patients, syphilis in 36.7%, chancroid in 7.1%, LGV in 4.1%, syphilis and LGV in 4.1%, scabies in 4.1%, genital herpes in 0.5%, and multiple agents in 3.1% [10]. In HIV-infected patients, genital herpes can result in severe and atypical clinical presentations. Syphilis in an HIV patient appears to progress more rapidly through the clinical stages of syphilis and may often have an atypical clinical presentation or a refractory course after appropriate intramuscular penicillin, and lead to unusual serologic test results [11]. A study by Gopalkrishna et al. found that a majority of chlamydia-infected patients had syphilis (48%) besides other concomitant sexually transmitted infections, such as gonorrhea, genital herpes simplex type 2, condyloma acuminata, candidiasis, and bacterial vaginosis [12].

A study by Shaw et al. conducted in a rural Gambian community found that HSV2 positivity rose markedly with age in women while in men remained low in the younger age groups. In men, they found no association between HSV2 and the level of education or ethnicity [13]. In a study on rural Ugandans with genital ulcers, participants infected with HIV reported 26 episodes of genital ulcers per 100 person-years, compared with 7 per 100 person-years among those not infected [14]. A study by Sanchez et al. conducted in the Dominican Republic and Peru found that the clinical etiologic diagnosis of GUD was inaccurate and unsuitable as a basis for the management of genital ulcer lesions. Laboratory tests other than RPR are unavailable in many developing countries; even in industrialized countries, tests such as dark-field microscopy and *H. ducreyi* culture are troublesome to receive, and the latter is insensitive [15].

A study by Ahmed and Mbwana conducted in two Tanzanian cities found that HSV-2 was the most commonly identified agent in genital ulcer specimens with a high prevalence of HIV among STD patients. HSV-2 was detected at significantly higher rates among HIV-seropositive than HIV-seronegative patients with GUD [16]. A study by Renzi et al. on MSM (*men who have sex with men*) found a 1.7-fold increase in the risk of HIV acquisition among MSM who did not report herpes lesions or symptoms in the last twelve months and a low proportion of HSV-2-seropositive MSM who reported a history of genital herpes. Given the potential difficulty in recognizing reactivation of perianal herpes, they suggested that serological testing might be an important prevention strategy aimed at the identification of HSV-2-infected MSM [17].

One of the most critical drawbacks of diagnosing STIs through laboratory diagnostics is the need to send the specimens to a central reference laboratory for analysis, thus forcing the patient to return to receive the results. A significant number of patients do not return and are lost to follow up [18]. An STI study on a female Brazilian population by de Lima Soares et al. found that multiple infections were common and that 51% of women had at least one STI [19]. A study by Shepherd et al. conducted in Pune, India, found the cofactors in the susceptibility to HIV to include circumcision, urethritis, and genital ulceration [20]. Earlier, Zamzachin et al. conducted a study in the same setting and found the incidence of STI to be 3% of the total OPD visits for skin issues, while VDRL reactivity gave a median percentage of 8.49% and HIV prevalence among STI patients gave a median percentage of 8.12% [21]. A study by Shivaswamy, Thappa, et al. conducted in Mumbai found that, among patients with clinical evidence of genital herpes, 94.2% were positive for both HSV-1 and HSV-2. In cases of the first episode of herpes genitalis, 66% were positive for HSV-1 and HSV-2, whereas in recurrent genital herpes, 96.4% were positive for HSV-1 and HSV-2. 72.6% of patients with no history suggestive of genital herpes were seropositive for HSV-2 [22].

In India, the main strategy aimed at achieving effective management for people with established infections has been to integrate STD services into the existing health care system, with a special emphasis on integration at the primary health care (PHC) level. The National AIDS Control Organization (NACO) for case management at this level recommends syndromic management [23]. A study by Reynolds, Risbud, Shepherd, et al. found that the first six months following the estimated time of exposure to syphilis is the period characterized by the greatest risk of HIV-1 infection compared to individuals who either have never had syphilis or who have had syphilis but more than six months have passed since the estimated time of syphilis exposure [24].

An evaluation by Creegan, Bauer, et al. of the relative sensitivities of the VDRL and TP-PA tests found that the sensitivity of the diagnostic strategy of VDRL confirmed by TP-PA was 71%. Substituting RPR for VDRL in a subset of 51 patients produced the same sensitivity. The sensitivity of TP-PA as the first-line diagnostic was 86% [25]. In a study on genital ulcers in women by Gomes et al., the most frequent etiology was herpetic lesion followed by autoimmune ulcers. Histological diagnosis was conclusive in only 26.4% of patients. They found, therefore, that the etiologic diagnosis of herpetic ulcers is difficult to reach, even if a variety of diagnostic methods are applied [26].

The treatment of GUD is often based only on the patient's medical history, while physical examination is inaccurate. Tests specifically for the evaluation of genital ulcers include syphilis serology and either the DGI or DIF test for *Treponema pallidum*; the culture or antigen test for HSV; and the culture for *Haemophilus ducreyi*. Mandatory HIV testing should be performed on all patients with genital ulcers caused by *T. pallidum* or *H. ducreyi* and HSV. In most cases, health care providers based in developing countries must treat patients on the basis of clinical presentation and epidemiological circumstances since testing facilities are often unavailable [27]. A study by Richards, Krantz, et al. aimed to describe the healthcare-seeking behavior among patients with newly-acquired symptomatic genital herpes and found that the presence of exquisite tenderness as the chief complaint may impede the diagnosis in the absence of a careful genital examination, which underscores the need to use various laboratory methods, such as follow-up HSV serology, to confirm the diagnosis of HSV infection [28].

In studying the effects of genital ulcer disease and herpes simplex virus type 2 on the efficacy of male circumcision as HIV prevention, Gray, Serwadda, et al. suggested that ulcers prevented by circumcision are likely to be non-herpetic in origin. They also suggested that most of the reduction in the risk of HIV afforded by circumcision is attributable to the removal of vulnerable foreskin tissue that contains HIV target

cells [29]. Nath and Thappa showed the importance of Tzanck smear in the rapid diagnosis of genital herpes lesions by identifying multinucleate giant cells, although with less sensitivity than by viral cultures, and the feasibility of undertaking histopathology occasionally in cases such as a chronic herpes infection in HIV-infected individuals with atypical disease morphology and clinical course [30]. Since HIV shares numerous aspects with other STIs—including modes of transmission, behavioral and other cofactors, and potential control measures—HIV prevention can logically be situated within the larger encompassing domain of STI control [31]. In a study conducted in Brazil, Barbosa et al. verified the association between *C. trachomatis* infection and gonorrhea with urethral discharge, highlighting that STIs are often transmitted by the same route and treating them may reduce the incidence of HIV and other STIs, which would be an important step in prevention, planning, and care [32].

A prospective study of genital ulcer disease by Hope-Rapp et al. in Paris found primary syphilis to be the most common (35%) cause, followed by herpes genitalis (27%) and chancroid (3%). A high frequency of HIV infection (27%) was found particularly in patients with primary syphilis (33%). They stressed that no clinical characteristic is predictive of etiology, undermining the importance of performing a thorough microbiologic evaluation [33]. Not much data is available regarding the current status of STIs in India and how their epidemiological and clinical picture is being modified in the context of the ongoing HIV/AIDS epidemic. More care needs to be exercised in order to inculcate safe sex practices and, thereby, reduce the incidence of preventable STIs, since intercurrent STIs are known to hasten the progression of an HIV infection toward the stage of fully-developed AIDS [34].

In a study to determine the etiology of STIs in Maputo, Mozambique, Zimba et al. stressed that syndromic management (SM) guidelines need to be area-specific and based on the knowledge of the prevalence of etiological syndromes and their drug susceptibility. The overall prevalence of HIV-1 and HIV-2 infection was 35%. GUD was associated with a significantly higher HIV prevalence ($p < 0.001$) [35]. A prospective study by Bala et al. found that the frequency of biological false positive (BFP) reactions with the VDRL test was quite low (0.2%) and concluded that the TPHA test should be employed for the routine confirmation of a positive VDRL test irrespective of its titer, especially to accurately diagnose and confirm syphilis in cases with a titer less than 1:8. They further noted that some of the TPHA-positive cases with a VDRL result of less than 1:8 might have been treated cases of syphilis and, therefore, attempts should be made to differentiate between past and active infections [36].

The most common presentation among male patients was painful genital sores (n = 22; 30.14%), followed by asymptomatic genital sores (n = 14; 19.17%) and itching (n = 9; 12.33%). The healthcare-seeking behavior in female patients was mainly due to pain (n = 9; 40.90%), which were all herpetic cases, similarly to a study by Richards et al. [28]. Only one (1.37%) male patient with herpes genitalis produced clear urethral discharge. Internal dysuria was present in nine (9.47%) patients with herpes genitalis, out of which eight were males. Fourteen (19.17%) male patients, one patient with secondary syphilis and the others with herpes genitalis, and one (4.55%) female patient with herpes genitalis displayed asymptomatic GUD. Most (n = 32; 43.83%) of male patients presented themselves between day 6 and 11, most frequently on day 7 (n = 24; 32.88%), among which the majority (n = 23) were herpetic. This was in contrast to females, among which the majority (n = 14; 63.63%) reported earlier, between day 0 and 5 of the onset of the disease. The mean duration of disease was 11.88 ± 13.299 days (mean ± SD) in males and 11.14 ± 16.994 days in females with an overall mean of 11.71 ± 14.145 days, which is almost identical to a study by Hope-Rapp et al. [33]. Pain in herpes genitalis reaches its maximum intensity during day 7–11 [37].

The most common site in males was in the glans and prepuce (n = 21; 28.76%). In females, most ulcers appeared in both the labia majora and minora (n = 8; 36.36%), which may be due to the greater contact of these sites during sexual contact. A study by Gomes et al. found that a majority of female genital ulcers were in the midline near the clitoris or vaginal introitus [26].

Among male patients, more than 16 (21.92%) displayed a single ulcer, which is the most common presentation, similarly to what was observed by Hope-Rapp et al. [33]. Tenderness was present in only 34 (35.97%) patients, which may be due to the superficial nature of most of the ulcers. Associated vesicles, mostly minute, were found in 36 (37.89%) patients, almost identically to a study by Sanchez et al. [15], and associated discharge from the vagina in nine (40.90%) patients. Inguinal lymphadenopathy was present in 25 (26.32%) patients, which again mirrors other studies [10,15].

The KOH mount was positive in 26 (27.37%) patients, 19 males and 7 females, highlighting the importance of attending not only to the complaint at hand but also to the surrounding areas in order to rule out the possibility of other associated STIs. Multiple infections were also found in a study by de Lima Soares [19]. Tzanck smear was positive in only 31 (32.63%) cases, comparably to a study in Manaus, Brazilian Amazon, in which it was positive in 30.3% of GUD patients [38]; this, in turn, may be due to the fact that most of the patients presented themselves late, with a mean duration of 11.71 days. Besides, as described above, associated vesicles, mostly minute, were present in only 36 patients, which may likewise contribute to the lesser positivity of Tzanck smear. Indeed, Tzanck smear has a sensitivity of only 50% [39], may be negative in older lesions, and is inapplicable to dry lesions and crusts [40].

The RPR test was positive in four (4.21%) patients, among which TPHA was positive in three patients. One female patient with herpes genitalis, who was TPHA-negative, had a titer of as high as 1:64, which may be explained by the fact that acute biological false positive reactions are caused by herpes genitalis [41] and other viral infections [42]. The seroprevalence of syphilis in our study was 0.35%, which is quite low compared to the 3.5% of a study in Delhi [36]. This may be due to the widespread use of penicillin injection for all infections in this part of the country, which may have contributed to the relatively low prevalence of syphilis and other bacterial STIs as well. Histopathological examination was not deemed the gold standard for diagnosis in one study of female genital ulcers, where a low accuracy rate was found [26]. However, biopsies of genital ulcers might be helpful in identifying the cause of unusual ulcers or those that do not respond to initial therapy [43].

Herpes genitalis (n = 92; 96.84%) was the most common GUD in our study, similarly to other studies in different parts of the world [5,26,37,39,44,45]. The second most common cause was syphilis in three (3.15%) patients. In most countries around the world, syphilis ranks as the second most frequent cause of GUD, with a worldwide prevalence of 2–25% [16,39]. Hontelez et al. [46] opined that, since *T. pallidum* is susceptible to the commonly available antibiotics, increased antibiotic exposure would be expected to have a secondary effect on the prevalence of syphilis. In one study, primary syphilis was found to be the most frequent etiology of genital ulcerations in MSM [33]. There was only one (1.05%) case per each of chancroid and LGV, both as mixed infections with herpes genitalis. Mixed etiologies were also observed in other studies [19,32]. There was no case of donovanosis in our study, which may be due to its low prevalence in this region, whereas it is endemic along the east coast of Orissa, Andhra Pradesh, and Tamil Nadu [47]. The decrease in the prevalence of bacterial GUD, particularly chancroid, may be due to the improved bacterial STD management as well as the improved HSV-2 diagnostics, which may suggest a relative increase in the role of HSV-2 as a cause of GUD [16].

CONCLUSION

GUDs can have various modes of presentation with varied symptomatology, while atypical cases are a diagnostic dilemma. GUDs should never be presumed to be due to a single etiological agent, and all available laboratory facilities within reach should be utilized as far as practicable.

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

Classification and clinical evaluation of the types of angiokeratoma

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ABSTRACT

Background: Angiokeratoma is a group of benign vascular telangiectasias in the superficial dermis associated with hyperkeratosis of the epidermis. There are different types of angiokeratoma and the color of the lesions—pink, red, dusky red, blue-red—depends on their age. **Materials and Methods:** Twenty-four patients with different varieties of angiokeratoma were collected from April 2013 through March 2020 and classified according to well-defined types. Each patient gave their formal consent after the nature of the disease was explained to them. Full medical history taking and clinical examination were performed on all patients. Skin biopsies were taken from 12 cases and processed for histopathology with H&E stain. As for therapy, diathermy was used for the treatment of selected localized cases, especially those on the scrotum. **Results:** Twenty-four cases with different types of angiokeratoma were evaluated, 19 (79.16%) males and 5 (20.83%) females, with ages ranging from 13 to 25 years and a mean age of 19 years. The age of onset was most commonly around adolescence and early adulthood. The lesions were classified into the following: 11 (45.83%) cases of Fordyce, 5 (20.83%) cases solitary, 4 (16.66%) cases circumscriptum, 3 (12.5%) cases oral (on the tongue), and one (4.16%) corporis diffusum (Fabry disease). All patients displayed warty red, blue, or black papules, nodules, or plaques, with the exception of isolated angiokeratoma. Their histopathology revealed hyperkeratosis of the epidermis, which could have been mild or marked acanthosis, as seen in the form of pseudoepithelial hyperplasia with marked elongation of rete ridges. As a dermal change, markedly dilated blood vessels occupied the papillary and reticular dermis. Diathermy was an effective mode of therapy in selected patients with satisfactory cosmetic and therapeutic results. **Conclusion:** All types of angiokeratoma were recognized but the most common were angiokeratoma of Fordyce, mainly affecting male genitalia, followed by solitary angiokeratoma, affecting mainly the limbs, and angiokeratoma circumscriptum linearly along the limbs. Oral angiokeratoma of the tongue appeared in three patients. All these types have a characteristic presentation that is easy to recognize: warty dusky-red lesions.

Key words: Angiokeratoma; Classification; Papules; Histopathology

INTRODUCTION

Angiokeratomas are well-circumscribed vascular lesions characterized by superficial vascular ectasia and hyperkeratosis [1]. Five variants of angiokeratoma have to date been recognized.

1. Solitary or multiple angiokeratomas. This is the most common type and one that is frequent in males [2]. They are small, warty, black papules 2–10 mm in diameter on the lower limbs, but may be seen anywhere on the body. Trauma or chronic irritation of the walls of vessels in the superficial dermis can lead to the formation of new angiokeratomas [1].

2. Angiokeratoma of Fordyce. This type is located on the scrotum or vulva and is the second most common type of angiokeratoma [2]. Its prevalence in the general population is around 0.16% [3,4], accounting for 14% of all angiokeratomas [3]. As the age increases, its prevalence increases from 0.6% of males aged 16 years to 16.7% of males aged 70 years or above [5].

How to cite this article: Sharquie K, Jabbar RI. Classification and clinical evaluation of the types of angiokeratoma. Our Dermatol Online. 2021;12(2):130-134.

Submission: 11.07.2020; **Acceptance:** 02.10.2020

DOI: 10.7241/ourd.20212.5

Clinically, angiokeratoma of Fordyce appears as multiple well-circumscribed and dome-shaped papules, 2–5 mm in diameter, predominantly on the scrotum. In rare cases, the lesions may be located on the shaft of the penis, glans penis, inguinal areas, buttocks, abdomen, upper thighs in males, and vulva in females [5-7]. The lesions are red, blue, purple, or bluish-black [8]. In rare cases, they may be correlated with thrombophlebitis, inguinal hernias, or varicoceles. Vulvar lesions may be observed with vulvar varicosities, hemorrhoids, oral contraception, or elevated venous pressure during pregnancy [1].

3. Angiokeratoma corporis diffusum. This type is characterized by the evolution of numerous lesions, commonly in a bathing-trunk distribution, varying in number, and appearing mostly during late childhood and adolescence. X-linked recessive Fabry disease is the best-known entity with this clinical feature, which results from an insufficiency of the enzyme α-galactosidase A [1].

4. Angiokeratoma of Mibelli: This type is characterized by lesions appearing mainly between the ages of 10 and 15 years, most commonly located on the dorsal and lateral sides of the fingers and toes. They can appear on the dorsa of the hands and feet and, rarely, on the elbows and knees. Angiokeratoma of Mibelli may be associated with perniosis or acrocyanosis and shows an autosomal dominant inheritance pattern [1].

5. Angiokeratoma circumscriptum. In general, these lesions are solitary, although numerous lesions may appear in adulthood, and are commonly located on the lower limbs. They may appear anywhere on the skin, including the tongue, and may be multiple and disseminated, creating a band-like appearance. They are often asymptomatic but may become a concern if they turn excessively dark or black. The lesions may even be present at birth, since angiokeratoma circumscriptum can either be congenital or acquired. Generally, this type of angiokeratoma more commonly appears in childhood and early adulthood, and is predominant in females [9].

The pathology of angiokeratoma involves the dilation of vessels in the papillary dermis together with epidermal hyperkeratosis, acanthosis, and elongated rete ridges usually encircling dilated vessels [2,10].

Management

Because most cases are asymptomatic, there is no need for treatment except for cosmetic improvements and in the case of symptomatic lesions. Treatment includes shave excision, cryotherapy, electrocautery, and laser therapy. The choice between these different modalities depends on the size of the lesions [1].

MATERIALS AND METHODS

This was a descriptive clinical case-series study that collected twenty-four patients with different types of angiokeratoma from April 2013 through March 2020. These cases were classified according to well-defined types. Each patient gave their formal consent after the nature of the disease was explained to them.

A medical history was properly taken in each case, including the sex and age of the patient, the duration and age of onset of the disease, the associated symptoms and skin disorders, and a medical and drug history.

A complete clinical examination was conducted to identify the site, size, and color of each lesion, the associated signs, and the morphological distribution and patterns.

Skin biopsies were taken from 12 cases and processed for histopathology with H&E stain.

Pathological findings and clinical pictures were matched together for a clinicopathological relationship to classify all variants.

The diagnosis of Fabry disease was based on clinical pictures, laboratory results, and systemic manifestations.

As for therapy, diathermy was used for the treatment of selected localized cases, especially those on the scrotum.

RESULTS

Clinical Results

Twenty-four cases with different types of angiokeratoma were evaluated, 19 (79.16%) males and 5 (20.83%) females, with ages ranging from 13 to 25 years and a mean age of 19 years. The age of onset was most commonly in adolescence and early adulthood.

The lesions were classified into the following: 11 (45.83%) cases of Fordyce, 5 (20.83%) cases solitary, 4 (16.66%) cases circumscriptum, 3 (12.5%) cases oral (on the tongue), and one (4.16%) corporis diffusum

(Fabry disease) (Figs. 1 – 5) (Table 1). No cases of angiokeratoma of Mibelli were seen in our study.

The color of each lesion varied from pink to red to dusky red to blue-red to black depending on its age. Normally, most of the lesions were asymptomatic but occasional bleeding, mild pain, and mild itching were observed. All patients displayed warty red, blue, or black papules, nodules, or plaques.

With the exception of isolated angiokeratoma of the tongue seen in two sisters, no family history of angiokeratoma was recorded with the other types of angiokeratoma.

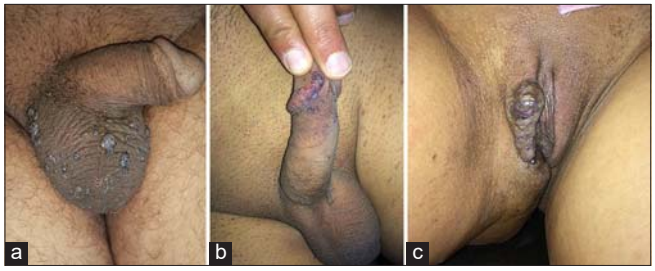

Figure 1: Angiokeratoma of Fordyce involving (a) the scrotum, (b) the shaft and glans penis, and (c) the vulva.

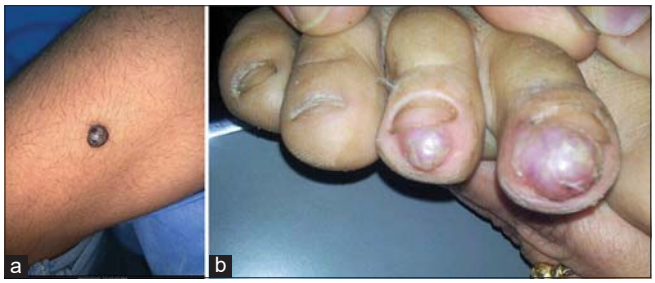

Figure 2: Solitary angiokeratoma affecting (a) the thigh and (b) toes.

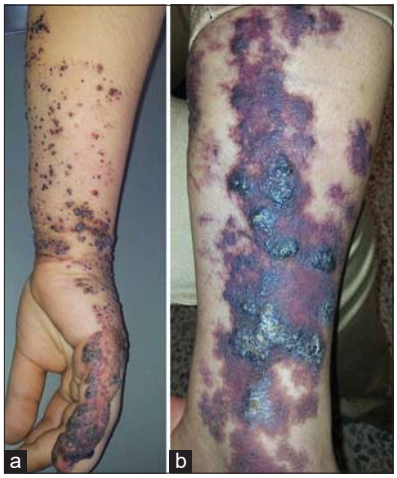

Figure 3: Angiokeratoma circumscriptum affecting (a) the upper limb in a 13-year-old male and (b) the left leg in a 22-year-old female.

Pathological Results

The epidermis showed hyperkeratosis, which could have been mild or marked acanthosis, as seen in the form of pseudoepithelial hyperplasia with marked elongation of rete ridges (Fig. 6). As a dermal change,

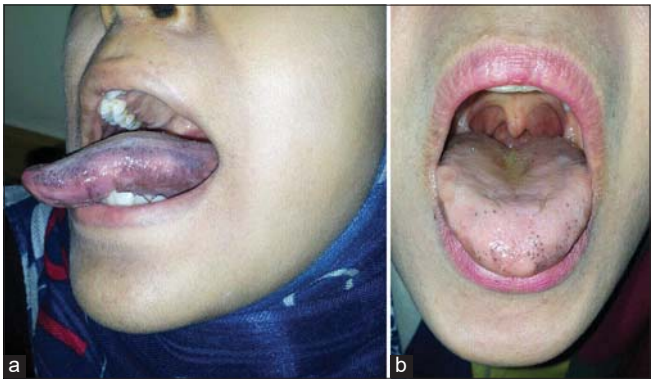

Figure 4: (a-b) Isolated angiokeratoma of the tongue in two adult sisters.

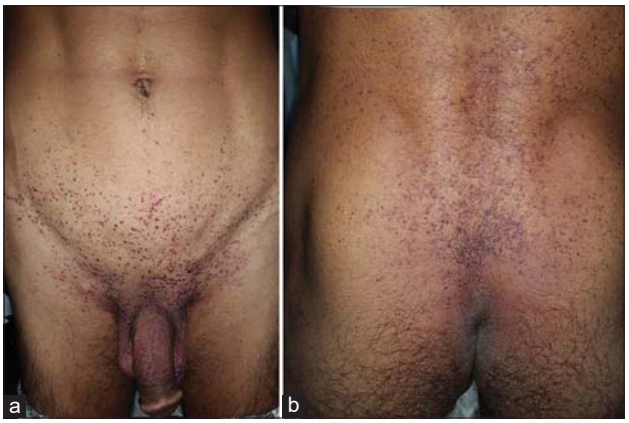

Figure 5: Angiokeratoma corporis diffusum (Fabry disease) in a 24-year-old male affecting (a) the lower abdomen, genital and inguinal regions, and inner thighs and (b) the lower back and gluteal region.

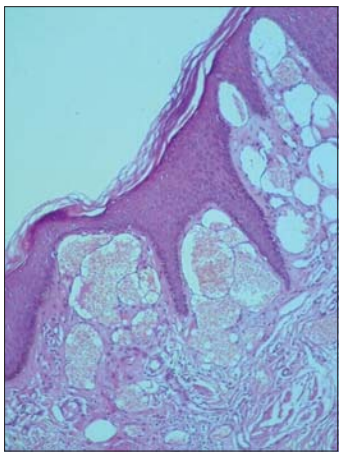

Figure 6: Angiokeratoma with hyperkeratosis, mild acanthosis, and elongated epidermal rete ridges encircling dilated superficial dermal vessels (H&E, 4×).

Table 1: Distribution of lesions in relation to type, site, and the sex of the patient

Type	No. of cases	Sex	Predominant sites	Frequency (%)
Fordyce	11	10 males 1 female	Scrotum and penis in males Vulva in females	45.83
Solitary	5	4 males 1 female	Lower limbs	20.83
Circumscriptum	4	3 males 1 female	Lower limbs (n = 3) Upper limbs (n = 1)	16.66
Isolated of the tongue	3	2 females 1 male	Tongue	12.5
Corporis diffusum	1	1 male	Lower abdomen Inguinal region Scrotum and penis Upper thigh Lower back Gluteal region	4.16

markedly dilated blood vessels occupied the papillary and reticular dermis (Fig. 7). Additionally, some of the vessels were located inside the epidermis.

Treatment

Diathermy was an effective mode of therapy in selected patients with satisfactory cosmetic and therapeutic results.

DISCUSSION

To the best of our knowledge, this is the first study of angiokeratoma in Iraq on a significant number of cases in which clinical and histopathological examination and classification of the different types of angiokeratoma were performed.

A clinicopathological study by Imperial et al. showed that, out of 116 cases with different types of angiokeratoma, 82% of them were males and 18% were females, while the age of onset was frequently in the second and third decades of life [2].

In our study, the age of onset was most commonly in adolescence and early adulthood; 79.16% of cases were males and 20,83% were females. These results are consistent with other studies [2,11].

The clinical features and morphological distribution of the lesions investigated in this study were similar to other publications [1-4,11].

As for the types of angiokeratoma, our study determined that angiokeratoma of Fordyce was the most common type, as seen in 45.83% of cases, followed by solitary angiokeratoma in 20.83% of cases. These results are unlike those in some other studies, in which solitary angiokeratoma was the most common, followed by angiokeratoma of Fordyce [2,11].

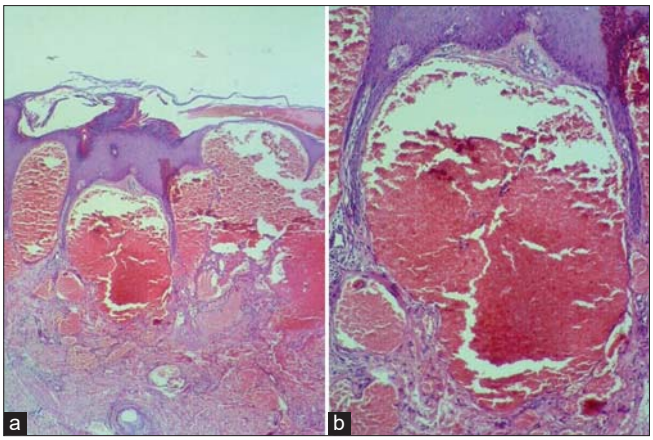

Figure 7: Angiokeratoma with hyperkeratosis, mild acanthosis, and elongated rete ridges in the epidermis with evident dilated blood vessels in the upper dermis (H&E; a: 4×, b: 10×).

The variability between the results of our study and other studies is difficult to explain but might be due to racial differences or individual concerns about the health and appearance of the genitalia.

Oral angiokeratoma is usually seen as a component of Fabry disease and is rarely observed with other types of angiokeratoma. Isolated angiokeratoma of the tongue is extremely rare and only 19 cases have been recorded by other studies [12]. In our study, there were 3 cases of isolated angiokeratoma of the tongue, two sister females and one male, and this is, to the best of our knowledge, the first piece of research to record three cases of isolated angiokeratoma of the tongue in one single study.

For reasons unknown to us, angiokeratoma of Mibelli was not seen in our study.

Most lesions were asymptomatic, but occasional bleeding, mild pain, and mild itching were observed, which aligns with other sources [2].

Histopathological manifestations included hyperkeratosis, mild acanthosis, and pseudoepithelial hyperplasia in the epidermis and dilated blood vessels in the papillary and reticular dermis. These results are similar to the pathologies of angiokeratoma reported by other studies [2,10].

The diagnosis of angiokeratoma should not generally be challenging, as it depends mainly on clinical pictures. However, histopathology might be necessary in some cases to confirm the diagnosis. Because a solitary angiokeratoma may be mistaken as a melanocytic nevus, wart, hemangioma, or even malignant melanoma [2], proper history taking and careful examination and pathological evaluation are highly recommended to reach a correct diagnosis, especially if doubts arise.

The treatment of angiokeratoma is difficult, especially in the case of extensive lesions, but diathermy may be used selectively for localized lesions, as in the scrotum. Pulsed dye laser (PDL), argon laser, neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, and CO_2 laser are alternatives forms of treatment [13-15].

CONCLUSION

Our study observed all types of angiokeratoma but the most common was angiokeratoma of Fordyce, mainly affecting male genitalia and even the vulva in females, followed by solitary angiokeratoma, affecting mainly the limbs, and angiokeratoma circumscriptum linearly along the limbs. Isolated angiokeratoma of the tongue was seen in three patients. All these types have a characteristic presentation that is easy to recognize: warty dusky-red lesions.

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

Advanced basal cell carcinomas of the face: A Moroccan series

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ABSTRACT

Background: Basal cell carcinoma (BCC) is the most common cutaneous skin malignancy. 85% of BCCs affect the face, a region particularly rich in noble organs. Although BCC progresses slowly, considerable local destruction and mutilation may be observed. **Material and Methods:** We performed a retrospective review of the database stored by our institution. All patients with histologically confirmed mutilating basal cell carcinoma of the face hospitalized at the dermatology department of the university hospital in Fez, Morocco, from 2015 through 2020 were evaluated. **Results:** Nine patients were included, with the tumors located in the lips, temporal region, orbital region, and cheeks, with sizes varying from 5 to 11 cm. **Conclusion:** In the series, we were able to highlight the high-risk character of the subpopulation living in rural areas and the role of smoking as a major risk factor.

Key words: Basal cell carcinoma; Locally advanced; Face; Dermoscopy

INTRODUCTION

Basal cell carcinoma (BCC) is the most common form of human cancer [1]. BCC affects mainly sun-exposed areas and, in around 80% of cases, it appears on the head [2]. The main etiological factor responsible for BCC is chronic UV exposure and its pathogenesis is linked to the interplay between environmental and patient-dependent characteristics [3]. With the increase in the incidence of BCC, and despite relatively low mortality, morbidity and treatment-related costs represent a significant burden to the health care system. Treatment options include medical and surgical modalities. The first therapy of choice is generally surgical excision with safe surgical margins [4]. Tumors of BCC exhibit a slow progression and metastases are found in only 0.5% of cases, but may result in considerable local destruction and disfigurement if treatment is neglected or inadequate [2]. In our study, we observed a series of nine cases with advanced BCC of the face. The aim is to describe the epidemiological, clinical, and histopathological features of this aggressive subtype of BCC and to evaluate its risk factors.

Patients and Methods

We performed a retrospective review of the database stored by our institution, with a wide acceptance of patients from the city of Fes and surrounding cities. All patients between January 2015 and September 2020 with advanced BCC of the face were evaluated.

The inclusion criteria were individuals over eighteen years of age with a BCC confirmed histologically, with the starting point and extension on the face and described as *giant*, which is defined according to the literature as a size greater than 5 cm [5] and *aggressive*, which is defined as an infiltrating and destructive tumor of soft tissues and the noble organs of the face [6].

We excluded from our work BCC in genodermatosis, mainly xeroderma pigmentosum, in order to be able to highlight the risk factors of this severe form independently of other particular cases.

The data collected included the patient's age, sex, household, profession, occupation, sun exposure,

How to cite this article: Elloudi S, Oulehri A, Baybay H, Douhi Z, Mernissi FZ. Advanced basal cell carcinomas of the face: A Moroccan series. Our Dermatol Online. 2021;12(2):135-139.

Submission: 17.12.2020; **Acceptance:** 11.03.2021

DOI: 10.7241/ourd.20212.6

history of irradiation, and known risk factors for BCC. For each patient, we also calculated the interval between the appearance of the lesion and the consultation to look for potential reasons for the delay.

Clinical examination allowed us to characterize the patient's phototype and the tumor's site, size, semiological description, and dermoscopic characteristics. We also collected data on the histological subtype, the patient's management, and the follow-up.

Ethics Statement

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

RESULTS

Nine patients were hospitalized at our department during the established period. The sex ratio (F:M) was 1.25: five females and four males. The patients' age ranged from 61 to 110 years, with an average age of 78.55 years. All patients were from rural areas. Three out of the four males (75%) were farmers; the fourth was a truck driver. All females worked in the fields. All patients were exposed to strong sunlight and never applied sunscreen. The only method of photoprotection was clothing: straw hats for males and covering clothes for females, who never wore hats.

Only one patient reported trauma prior to the development of the tumor in the temporal area. All males were smokers, with the number of cigarettes smoked per day varying between 10 and 30, with an average of 16.8, and with the duration of the smoking habit varying between 27 and 50 years, with an average of 36.75 years. 22.2% (2/9) of the patients were hypertensive and 11.1% (1/9) were diabetics. All patients recalled the beginning of the condition as a small lesion that gradually increased in size: as an erosion (55.6%), a papule (33.3%), or a nodule (11.1). The time between the appearance of the lesion and the consultation varied between 2 and 14 years, with an average of 5.4 years. The reasons found for this delay were a precarious social situation, a lack of financial means, remoteness of health services, and sometimes the asymptomatic character of recent lesions. Indeed, the majority of the patients consulted for pain, bleeding, or extension to a noble organ such as the eye or nose.

88.9% of the patients had phototype III according to the Fitzpatrick scale. Two tumors were located on the lips, with complete destruction of the lip and extension to the mucous membrane; two were in the temporal region; three were in the orbital region, two of which led to complete destruction of the orbit; and one had a deep cheek tumor. The size of the tumors varied between 5 and 11 cm, with an average of 6.7 cm. All BCCs were ulcerative budding tumors with pearly borders (Fig. 1) and only one case was clinically pigmented (Fig. 2).

In all cases, dermoscopy revealed polymorphic vascularization composed of irregular linear vessels and tree-trunk vessels, with grey-blue ovoid nests on the periphery of the tumor in 88.9% of the cases (Fig. 3).

No patient had locoregional adenopathies or distant metastases. All patients initially benefited from a biopsy, which confirmed the diagnosis of BCC. All patients exhibited an infiltrative histological subtype, which was associated in 66.7% of cases with a nodular contingent and in 11.1% with an adenoid contingent.

All patients' treatment records were discussed in multidisciplinary oncodermatology meetings attended by dermatologists, oncologists, radiotherapists, and surgeons.

Figure 1: Locally advanced basal cell carcinoma with the destruction of (a) the nasal septum and the upper lip, (b) the orbital region, and (c) the temporal region and the auricle.

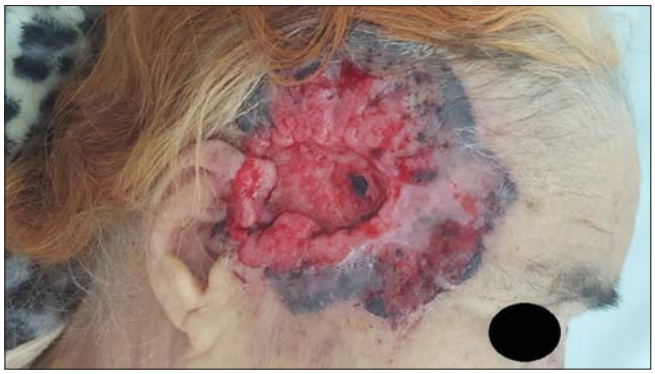

Figure 2: Pigmented locally advanced basal cell carcinoma of the temporal region and auricle.

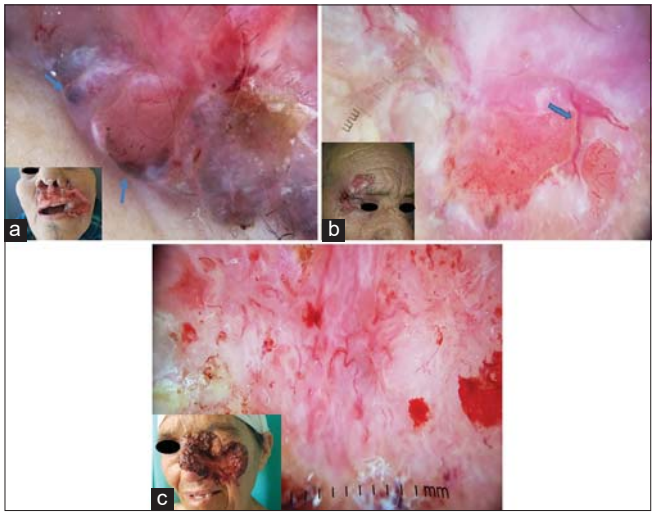

Figure 3: (a) Erythematous background, polymorphic vascularization, and blue-gray ovoid nests (blue arrows). (b) Erythematous background, polymorphic vascularization, and tree-trunk vessels (blue arrow). (c) Erythematous background, polymorphic vascularization, and shiny white structures.

Surgical management was indicated in eight patients and radiotherapy in one. Six patients underwent surgical excision with subsequent reconstruction. One patient died before any treatment (radiotherapy). One patient was lost to follow-up. During the follow-up period, we noted only one recurrence after a period of one year.

DISCUSSION

BCC most frequently occurs in the elderly [7] and is more common in males than females, with a male-to-female ratio of approx. 2:1 [8]. In our study sample, we noted a very advanced age on average, but the female sex was slightly predominant. Given the primary role of early and long-term sun exposure in BCC, outdoor workers, particularly farmers, are at much greater risk of developing BCC [9]. In addition, the data demonstrates that farmers develop the disease at a younger age and are more likely to suffer from a recurrence [10]. We were also surprised to see that all our patients came from rural communities and were almost exclusively farmers, which adds to the results from the literature on the increased risk of severe forms in this high-risk population. It is clear, however, that more targeted programs are needed for high-risk groups, such as farmers. Sun exposure was also the main risk factor in our study sample, in addition to fair skin and smoking in males. If lesions of BCC are left untreated for years, they become progressively *locally advanced* [7]. Our study confirms this data since all our patients' consultations were significantly deferred in time; however, metastases were not found in any patient.

In the process of research, we realized that there was no consensus on the denomination and criteria that would define aggressive and destructive cases of BCC. The different names found in the literature are *terebrant*, *giant*, *aggressive*, and *advanced*.

Although not clearly defined, the word *advanced* usually implies that 1) there is a long history of treatment avoidance or repeated failed treatments and recurrences, 2) there is extensive tissue destruction in the surrounding anatomical area, and 3) it has become difficult or impossible to cure the tumor through standard surgery procedures (unresectable) or radiotherapy [7,11].

The histological subtypes of BCC classified according to the risk of recurrence described by the current WHO classification [12] are 1) nodular, superficial, pigmented, infundibulocystic, and fibroepithelial (all low-risk) and 2) basosquamous or metatypical, sclerosing or morphoeic, infiltrating trabecular or micronodular, mixed-type, and with sarcomatoid differentiation (all high-risk). The adenoid type is a histological variant of BCC considered a subtype of the nodular subtype [13,14]. In our study, despite the presence of all clinical criteria of aggressiveness, we found no other high-risk histological types apart from the infiltrative type.

Peris et al. consider a more pragmatic and operational classification of BCC into easy-to-treat BCC, which involves the most common cases of BCC, and difficult-to-treat BCC [7].

There are two systemic medications, vismodegib and sonidegib, with a documented efficacy in locally advanced BCC (laBCC) [15]. Management should be

carefully planned by a skin cancer multidisciplinary team [16,17].

Chemotherapy may be considered for laBCC as the second- or third-line treatment in unresponsive patients or those who have progressed after vismodegib or sonidegib, often in combination with radiotherapy.

Radiotherapy may be considered the primary treatment if curative surgery is not possible or might be disfiguring or burdened by a poor aesthetic outcome, including BCCs located on the face (i.e., the eyelids, nose, lips) or large lesions on the ear, forehead, and scalp [18-20].

CONCLUSION

In this series, we wished to expose the dramatic aesthetic and functional repercussions of BCC of the face if treatment is delayed.

In addition to the known risk factors found in our patients, such as excessive sun exposure and a fair phototype, we were also able to highlight the high-risk character of the subpopulation living in rural areas, which is associated with excessive sun exposure, the absence of photoprotection measures, a precarious social situation, a lack of financial means, and sometimes the unavailability of health services. This implies that special and targeted attention must be directed toward this population.

Contrary to the literature, we were able to observe, in our series, that this serious form of BCC did not predominate among males but slightly among females. We were also able to highlight the detrimental role of smoking, found as a major risk factor in our series, which has rarely been described in the literature in this context.

The histological subtypes classified as aggressive were not found in our patients except for the infiltrative type.

Finally, despite the discussion of all our cases in a multidisciplinary oncodermatology team, the therapeutic options for these advanced forms were limited in the absence of targeted therapy (vismodegib or sonidegib) and immunotherapy (anti-PD-1). Our study emphasizes that these cases are not rare and that the introduction of such therapies would be beneficial for our population.

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

A study on the cutaneous manifestations of an internal malignancy in a tertiary care center in North India

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ABSTRACT

Introduction: Cutaneous metastases may precede a malignancy and, in other cases, herald the recurrence of a malignancy after surgery. **Aim:** To determine the significance of cutaneous manifestations in patients with an internal malignancy and to observe the various types of carcinomas in patients attending a dermatology OPD. **Methods:** This was a prospective hospital-based study undertaken to observe the cutaneous features in a dermatology OPD in patients coming from the oncology department of a medical college. **Results:** The commonest malignancy in males was a lung carcinoma, observed in 5.50% of the patients, followed by a prostate carcinoma, observed in 4.58% of the patients, an esophagus carcinoma, observed in 4.12% of the patients, and a penis carcinoma, observed in 2.29% of the patients. Specific cutaneous manifestations included cutaneous metastatic infiltrates, observed in 5.04% of the patients, and carcinoma erysipeloides, observed in 1.37% of the patients. **Discussion:** Skin metastases may herald the recurrence of a malignancy after treatment and usually indicate a poor prognosis.

Key words: Malignancy; Infiltrate; Cutaneous; Metastasis; Breast

INTRODUCTION

Internal malignancies involve various skin changes, among which some are related to the malignancy, such as malignant cutaneous infiltrates, some are treatment-related, mainly due to the toxic effect of the drugs taken, and some are non-specific [1]. Various internal malignancies give rise to cutaneous changes due to their immunological, metabolic, and metastatic consequences. The single most basic biologic process that characterizes a malignant tumor is the ability to produce secondary deposits (metastases) in distant sites. Generalized pruritis is one of the common cutaneous manifestations of a cutaneous metastasis. [2] The skin is an infrequent site for metastasis and was listed by one study as low as the eighteenth of the most common sites [3]. Cutaneous metastases may appear at any age. Considering, however, the increased incidence of malignant disease later in life, most cutaneous metastases occur during or after the fifth decade of life [4].

Cutaneous metastases are relatively uncommon but it is important to consider them. In some cases, they may precede a malignancy. Contiguous metastases are the most common in carcinoma of the breast and oral cavity and often herald the recurrence of a malignancy after surgery [1]. The trunk and the scalp are favored sites for distant metastases. The mortality rate is usually high with cutaneous metastases, although early recognition gives some chance of survival, especially in patients that present themselves with cutaneous metastases [5]. Cutaneous metastasis from an internal malignancy is relatively uncommon, with the incidence rate ranging from 0.7% to 10.4% as reported in various case series [6]. These metastatic deposits indicate a higher stage of malignant disease and, as in any other metastatic tumor deposits in a patient under treatment, signify a

How to cite this article: Puri N, Brar S, Brar BK. A study on the cutaneous manifestations of an internal malignancy in a tertiary care center in North India. Our Dermatol Online. 2021;12(2):140-144.

Submission: 10.11.2020; **Acceptance:** 11.01.2021

DOI: 10.7241/ourd.20212.7

lack of response of the malignancy to treatment. The common sites of skin metastasis from a lung cancer are the head, neck, chest, and abdomen [7]. As skin metastases may be suspected and detected earlier compared to metastases in other organs, the clinician should be cognizant of the various visual aspects of such lesions, and the pathologist should be aware of the various patterns of metastatic deposits in the skin. A biopsy evaluation of these deposits often yields clues as to the probable site of the primary tumor, based on the histological appearance of the deposits.

Aim

The study was aimed at determining the significance of cutaneous manifestations in patients with an internal malignancy and to observe the various types of carcinomas in patients attending a dermatology OPD.

MATERIALS AND METHODS

A prospective hospital-based study was undertaken in a dermatology OPD to observe the cutaneous features in patients coming from the oncology department of a medical college and lasted for a period of two years from April 2018 through April 2020. Detailed clinical and cutaneous examinations were performed for all patients. Relevant investigations were performed as the need arose. Specific investigations such as skin biopsies were performed for patients with specific features, such as cutaneous infiltrates. The relevant clinical data, including the duration and type of the malignancy and the cutaneous features, were recorded.

RESULTS

The data was collected and the results were analyzed. As for the age distribution of the patients, the highest number of patients was between 40–60 years old (46.78%), followed by 44.03% of the patients between 61–80 years old and 8.25% of the patients between 21–40 years old. There were only 0.91% of patients below the age of 20 years. The study comprised 138 males and 80 females and the male-to-female ratio was 1.7 to 1.

DISCUSSION

The age distribution (Table 1) in our study was somehow different from that by Puri et al. in which most (32.3%) patients were in the age group 60–69 years [8]. Only 0.8% of the patients were aged less than 10 years, and 2.6% were of age 80 years or older. Among the two patients below the age of 20 years, one was a six-year-old child with Wilms' tumor. The sex ratio in our study was different from a study by Hassan et al., in which 139 (55.6%) patients were males and 111 (44.4%) patients were females [9].

In our study, the most common malignancy (Table 2) in females was carcinoma of the breast, which was observed in 23.38% of the patients, followed by carcinoma of the cervix, observed in 9.17% of the patients, carcinoma of the ovary, observed in 4.12% of the patients, carcinoma of the endometrium, observed in 3.21% of the patients, and carcinoma of the vulva, observed in 0.45% of the patients. The most common malignancy in males was carcinoma of the lung, observed in 5.50% of the patients, followed by carcinoma of the prostate, observed in 4.58% of the patients, carcinoma of the esophagus, observed in 4.12% of the patients, and carcinoma of the penis, observed in 2.29% of the patients. This is in contrast to findings by Wani et al., which determined the esophagus and the gastrointestinal junction, followed by the lung and stomach, as the leading causes of malignancies [10]. Other malignancies observed both in males and females were leukemias, in 9.17% of the patients, lymphomas, in 8.71% of the patients, carcinoma of the tongue, in 5.04% of the patients, carcinoma of the larynx, in 3.66% of the patients, carcinoma of the colon, in 2.29% of the patients, carcinoma of the stomach, in 1.37% patients, carcinoma of the bladder, in 2.29% of the patients, carcinoma of the rectum, in 1.83% of the patients, carcinoma of the tonsil, in 1.37% of the patients, as well as carcinoma of the pancreas, hepatocellular carcinoma, carcinoma of the thyroid, brain tumor, renal cell carcinoma, and metastatic carcinomas, each in 0.91% of the patients. Wilms' tumor and nasopharyngeal carcinoma were observed each in 0.45% of the patients. 2.75% of the patients had a metastatic carcinoma with an unknown primary disease (Table 3). In our study, the most common cutaneous manifestation was generalized pruritis, observed in 17.88% of the patients, followed by acquired ichthyosis, observed in 11.46% of the patients, and herpes zoster (Fig. 1), observed in 12.38% of the patients. Other cutaneous features observed were pyodermas in 9.63% of the patients, dermatophytosis in 6.42% of the patients, candidal intertrigo and radiation dermatitis each in 4.12% of the patients, oral ulcers in 2.75% of the patients; scabies, eczemas, varicella zoster, and erythema multiforme each in 2.29% of the

patients; erythroderma and maculopapular drug rash each in 1.83% of the patients; urticaria, irritant contact dermatitis, seborrheic dermatitis, and paronychia each in 1.37% of the patients; nail pigmentation (Fig. 2), genital warts (Fig. 3), and photodermatitis each in 0.91% of the patients; geographic tongue, pseudoporphyria, papular urticaria, pediculosis, lupus erythematosus, genital molluscum contagiosum, SJS/TEN, and lichenoid drug eruption each in 0.45% of the patients. Specific skin manifestations included cutaneous metastatic infiltrates (Fig. 4) in 5.04% of the patients and carcinoma erysipeloides in 1.37% of the patients. In our study, vincristine caused bluish nail pigmentation, and generalized pruritus was the most common in patients with leukemia, lymphoma, hepatocellular carcinoma, and carcinoma of the stomach. Malignancies associated with herpes zoster were carcinoma of the breast, carcinoma of the cervix, carcinoma of the prostate, and carcinoma of the esophagus.

A cutaneous metastasis from an internal malignancy indicates a late stage of the disease. The skin is the eighteenth most common site for cutaneous infiltrates, which is rare. Some of the internal malignancies, such as carcinoma of the breast, have a tendency to produce cutaneous infiltrates. The incidence of a cutaneous metastasis in our study was 5.04%. Cutaneous infiltrates are mainly multiple. A cutaneous metastasis usually arises from carcinoma of the colon and lungs in males and from the colon, ovary, and breast in females. In our study, cutaneous infiltrates were the most common in the chest wall, followed by the abdomen, the face, and the extremities.

The skin often mirrors changes in the internal milieu, and skin metastases may herald the recurrence of a malignancy after treatment. A cutaneous metastasis may appear at any age, but most cutaneous metastases occur during or after the age of 55 years. The interval between the onset of the symptoms of the primary malignancy and the onset of the cutaneous metastasis

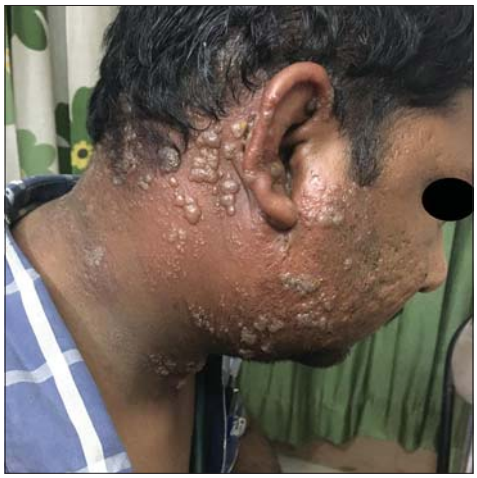

Figure 1: Herpes zoster in a 45-year-old male with carcinoma of the esophagus.

Figure 2: Nail pigmentation in a 48-year-old male secondary to vincristine.

Figure 3: Genital warts in a 46-year-old female with carcinoma of the ovary.

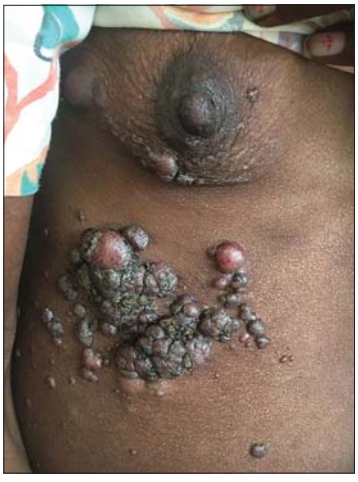

Figure 4: Nodular infiltrates in a 67-year-old female with carcinoma of the breast.

Table 1: Age distribution among the patients

	Age distribution (years)	No. of patients	Percentage
1	0–20	2	0.91
2	21–40	18	8.25
3	41–60	102	46.78
5	61–80	96	44.03
	Total	218	100

Table 2: Types of malignancies among the patients

	Type of malignancy	No. of patients	Percentage
1	Carcinoma of the breast	51	23.38
2	Carcinoma of the cervix	20	9.17
3	Lymphoma	19	8.71
4	Leukemia	20	9.17
5	Carcinoma of the bladder	5	2.29
6	Carcinoma of the penis	5	2.29
7	Carcinoma of the larynx	8	3.66
8	Carcinoma of the colon	5	2.29
9	Carcinoma of the stomach	3	1.37
10	Carcinoma of the prostate	10	4.58
11	Carcinoma of the lung	12	5.50
12	Carcinoma of the endometrium	7	3.21
13	Carcinoma of the ovary	9	4.12
14	Carcinoma of the rectum	4	1.83
15	Carcinoma of the pancreas	2	0.91
16	Carcinoma of the tongue	7	5.04
17	Carcinoma of the tonsil	3	1.37
18	Carcinoma of the nasopharynx	1	0.45
19	Hepatocellular carcinoma	2	0.91
20	Carcinoma of the ulva	1	0.45
21	Wilms' tumor / renal cell carcinoma	3	1.37
22	Carcinoma of the thyroid	2	0.91
23	Carcinoma of the esophagus	9	4.12
24	Metastatic carcinoma	2	0.91
25	Carcinoma with an unknown primary disease	6	2.75
26	Brain tumor	2	0.91
	Total	218	100

ranged from three months to six years. The shortest interval was three months in carcinoma of the lungs and the longest was six years in carcinoma of the breast.

The common malignancies that give rise to cutaneous metastases are carcinoma of the lung and colon in males and carcinoma of the colon and ovary in females. The incidence of cutaneous metastasis was the highest in the age group of 51 years and above (52%). In our study, the chest (Fig. 5) was the most common site for a cutaneous metastasis, followed by the abdomen. Metastasis to the skin gives a poor chance of survival and a hopeless outcome.

Cutaneous manifestations still prove to be an enigma in the diagnosis of dermatological disorders and internal malignancies. Cutaneous manifestations should not be neglected and must be recognized by the physician in time. Some life-threatening hypersensitivity reactions, such as Steven–Johnson syndrome, must be treated in an intensive care unit, as in treating a patient with burns to counter an electrolyte loss and restore the body to a state of equilibrium.

Table 3: Cutaneous manifestations among the patients

	Cutaneous manifestation	No. of patients	Percentage
1	Generalized pruritis	39	17.88
2	Scabies	25	11.46
3	Tinea	14	6.42
4	Pyodermas	21	9.63
5	Herpes zoster	27	12.38
6	Varicella zoster	5	2.29
7	Nail pigmentation	2	0.91
8	Urticaria	3	1.37
9	Geographic tongue	1	0.45
10	Radiation dermatitis	9	4.12
11	Pseudoporphyria	1	0.45
12	Cutaneous metastatic infiltrates	11	5.04
13	Scabies	5	2.29
14	Papular urticaria	1	0.45
15	Erythroderma	4	1.83
16	Carcinoma erysipeloides	3	1.37
17	Lupus erythematosus	1	0.45
18	Pediculosis	1	0.45
19	Seborrheic dermatitis	3	1.37
20	Irritant contact dermatitis	3	1.37
21	Candidal intertrigo	9	4.12
22	Erythema multiforme	5	2.29
23	Photodermatitis	2	0.91
24	Genital molluscum contagiosum	1	0.45
25	Paronychia	3	1.37
26	SJS/TEN	1	0.45
27	Lichenoid drug eruption	1	0.45
28	Maculopapular drug rash	4	1.83
29	Eczemas	5	2.29
30	Oral ulcers	6	2.75
31	Genital warts	2	0.91
	Totel	218	100

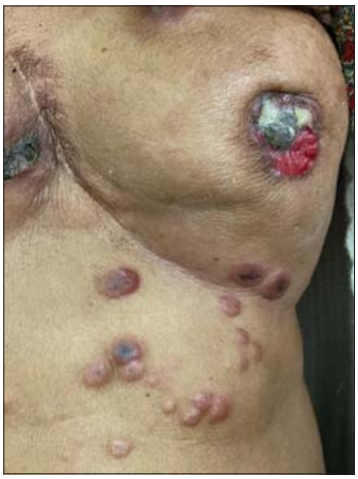

Figure 5: Cutaneous infiltrates on the chest wall in a 74-year-old female.

CONCLUSION

Cutaneous metastases indicating signs of recurrence as well as widespread metastases give poor prognosis and reduce the length of the survival period. A systemic response to any particular chemotherapeutic agent may be assessed by a visible regression of the skin metastasis. It is important to recognize a cutaneous metastasis in time as it may precede an internal visceral metastasis, especially because early recognition helps in prolonging the survival of the patient. The morphological features of the primary tumor are often reflected in the cutaneous metastatic deposits, and attempts to suggest a possible primary site during a skin biopsy evaluation help the clinician in narrowing down the primary tumor possibilities and in initiating specific radio-imaging and other relevant investigations for the patient's management as early as possible.

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

Nodular vasculitis or erythema induratum without cutaneous tuberculosis: An unusual presentation in an uncommon site

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ABSTRACT

Erythema induratum (EI) is a rare chronic disease, which occurs with cutaneous tuberculosis (TB). Nodular vasculitis, much rarer than erythema induratum, describes the same condition but without cutaneous TB, with lesions usually in the lower legs and rarely on the breasts. We report the case of a 46-year-old female with a history of crusted skin and necrotic lesions two years before, which, once self-limited, multiplied one month before and transferred to uncommon sites of the body, such as the breast. There was no evidence of other clinical presentations, and a chest X-ray gave no pathological findings. A biopsy was taken from the lesions, and the patient was diagnosed with erythema induratum without cutaneous tuberculosis, that is, nodular vasculitis. After treatment with calcineurin-inhibiting tacrolimus ointment, topical corticosteroids, and immunosuppressive oral azathioprine, the lesions improved.

Key words: Erythema induratum; Nodular vasculitis; Tuberculosis

INTRODUCTION

Nodular vasculitis (NV) is an uncommon, mostly lobar form of panniculitis [1], manifesting itself as erythematous nodules or plaques located preferentially on the calves, which may ulcerate and drain. NV has been thought of as a delayed hypersensitivity response to an antigenic stimulus, originally associated with tuberculosis. However, some cases have been associated with both nontuberculous infections, such as hepatitis B virus, hepatitis C virus, HIV, and streptococci, and noninfectious conditions [2], such as autoimmune diseases [3] and inflammatory bowel disease [1]. Chronic exposure to cold and drugs [4] have been reported. The term *nodular vasculitis* was coined by Montgomery to refer to cases of lesions similar to erythema induratum unassociated with tuberculosis [4]. These lesions are located on the anterior and/or posterior legs, including the calves, thighs, upper limbs, and trunk [5]. Erythema induratum (EI) has a chronic recurrent course and a female predominance, manifesting itself as persistent nodules or plaques usually on the lower third of the calf. Lesions may ulcerate and heal with a depressed scar. Histologically, a vasculitis affecting small and medium-sized vessels is seen producing a dermal granuloma with epithelioid and giant cells and fat atrophy [6].

CASE REPORT

We report the case of a 46-year-old female with a history of skin lesions two years before, which,

How to cite this article: Mofarrah R, Jallab N, Mofarrah R, Amiri KJ, Jallab N. Nodular vasculitis or erythema induratum without cutaneous tuberculosis: An unusual presentation in an uncommon site. Our Dermatol Online. 2021;12(2):145-147.

Submission: 07.04.2020; **Acceptance:** 31.07.2020

DOI: 10.7241/ourd.20212.8

once self-limited, multiplied one month before and transferred with uncertain etiology. These firm, brownish-red to red lesions were located on the right breast and the posterior side of the left calf (Figs. 1a and 1b). The patient reported pain and pruritus in the lesions but no constitutional symptoms. She had a history of diabetes mellitus for two years. The physical examination and laboratory results were unremarkable. A tuberculin test was negative and a chest X-ray showed no pathological findings. A biopsy was taken from the breast and leg to show small fragments of skin with epidermal acanthosis and mild hyperkeratosis. Perivascular infiltration of inflammatory cells, mainly lymphocytes, and extravasation of red blood cells were present in the superficial and deep dermis. Vesicular lesions and dense infiltration of inflammatory cells were absent.

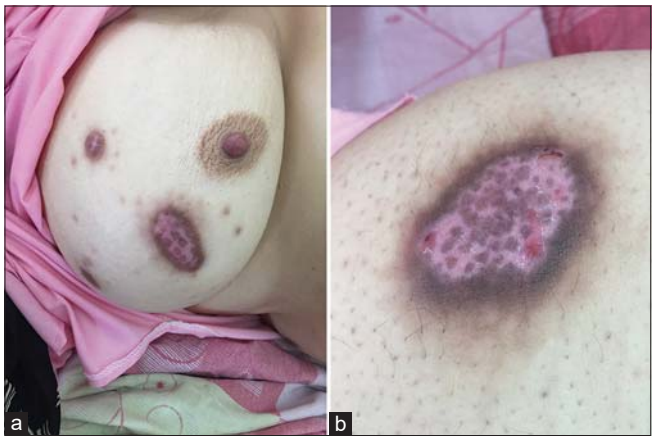

Figure 1: Hyperpigmented and erythematous ulcerated lesions on the left calve and right breast.

A granulomatous lesion with several multinucleated giant cells was also present in the deep dermis (Fig. 2). Based on these findings, a diagnosis of nodular vasculitis was reached. The patient was started on topical treatment with tacrolimus and clobetasol. After around two weeks, oral immunosuppression with azathioprine was started due to the lack of effectiveness of the previous treatment. This resulted in improvement of the lesions with no recurrence.

DISCUSSION

We report this case both because erythema induratum without TB is rare and because the breast is an uncommon site for this disease. Nodular vasculitis is a chronic relapsing lobular panniculitis with septal vasculitis. Its cause may be due to a hypersensitivity reaction to an antigenic stimulus [2]. Erythema induratum must be distinguished from erythema nodosum, nodular vasculitis, polyarteritis nodosa, tertiary syphilis, and other infectious and inflammatory panniculitides.

Erythema induratum was first identified in 1861 by Bazin as a nodular eruption on the posterior side of the lower legs in young women with tuberculosis [7]. In cases of erythema induratum with a negative tuberculin test, the cause is often unknown, but there have been case reports of an association of erythema induratum with infectious disorders caused by *Nocardia*, *Pseudomonas spp.*, *Fusarium spp.*, and the hepatitis C and B virus [3]. Erythema induratum,

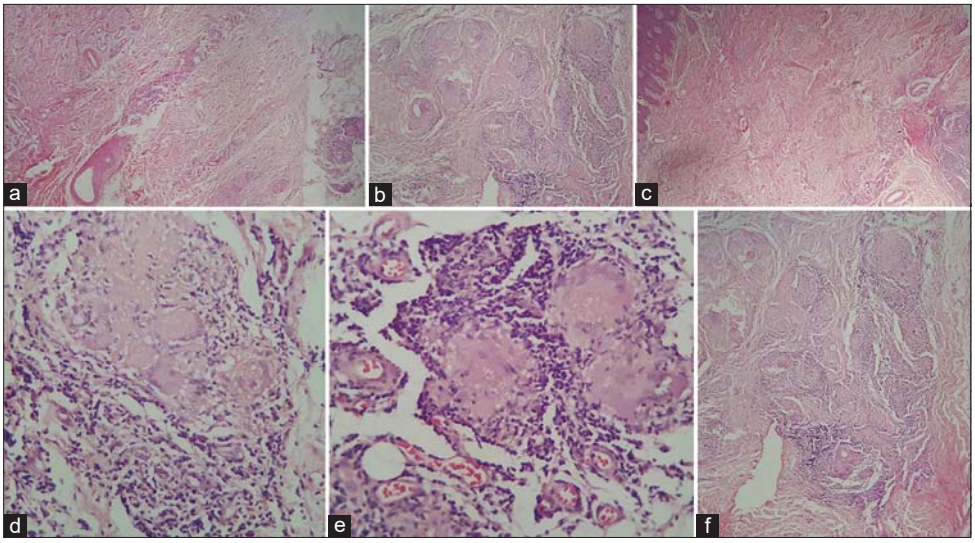

Figure 2: (a - f) Histological studies of biopsy specimens showing epidermal acanthosis and mild hyperkeratosis; perivascular infiltration of inflammatory cells, mainly lymphocytes, and extravasation of red blood cells seen in the superficial and deep dermis; vesicular lesions and dense infiltration of inflammatory cells absent; a granulomatous lesion with several multinucleated giant cells in the deep dermis.

one of the tuberculitides, affects males and females equally, although with a slight predominance among females in the age group of 20 to 40 years [8]. It manifests itself as tender, violaceous erythematous plaques or nodules characteristically on the bilateral pretibial areas. Lesions may also occur in other sites, such as the posterior and anterolateral pretibial sides of the lower legs as well as the trunk, buttocks, thighs, and arms [8,9]. Patients with erythema induratum have histories of tuberculosis and generally give significant results on the tuberculin test. Skin biopsies often show features of panniculitis with noncaseating granulomas. Tubercle bacilli are absent, although mycobacterial DNA is seen in up to 88% of erythema induratum cases. Although this condition is uncommon in developed countries, its incidence is still found to be high in countries such as India, Hong Kong, and South Africa [9]. It can occur in both sexes and at any age, but there is a female predominance usually seen through the second to fourth decade of life [8]. An examination of a skin biopsy from the lesional area revealed no tubercle bacilli, although mycobacterial DNA can be detected through the PCR in 56–88% of patients with cutaneous tuberculosis. Despite that, a rare presence of atypical mycobacteria in the lesions of erythema induratum has been reported [10].

CONCLUSION

In conclusion, erythema induratum without tuberculosis (TB), known as nodular vasculitis, is a rare disease found in middle-aged women, which usually manifests itself as subcutaneous erythematous nodules and plaques appearing on the posterior side of the lower extremities. Our case was especially rare and unique, being unassociated with tuberculosis and displaying lesions in unusual sites, such as the breast.

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

Lupus miliaris disseminatus faciei: A report with a new dermoscopy finding

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ABSTRACT

Lupus miliaris disseminatus faciei (LMDF) is a rare inflammatory disorder characterized by asymptomatic papular lesions mainly over the central part of the face, common in young adults and with a spontaneously resolving course. Its exact etiology remains unknown, its treatment is problematic, and there is a lack of controlled studies on LMDF. Histopathology shows dermal epithelioid granulomas with central necrosis and surrounding lymphocytic infiltrate with multinucleate giant cells. Dermoscopic findings published show discrete focal orangish structureless areas located around follicular openings with whitish keratotic plugs. Herein, we report a case of LMDF with dermoscopy showing stellate scar signs and structureless white areas.

Key words: Lupus miliaris; Dermoscopy; Acne agminata

INTRODUCTION

Lupus miliaris disseminatus faciei (LMDF), also known as acne agminata, is a rare chronic granulomatous disorder of unknown etiology first described by Fox in 1878 [1]. Its clinical features are asymptomatic bilaterally symmetric papules characteristically distributed over the central part of the face [2]. Histopathology shows epithelioid cell granulomas with central necrosis. Dermoscopic findings include discrete focal orangish structureless areas located around follicular openings with whitish keratotic plugs [3]. Although its classical clinical features and histopathology have been described, reports on the dermoscopic findings are scarce. Herein, we report a new case of LMDF with varied dermoscopic features not described before.

CASE REPORT

A previously healthy 21-year-old male consulted us about asymptomatic lesions over the face persistent for three months prior. There were no systemic complaints or concomitant systemic disorders. Upon examination, discrete erythematous papules were seen on the face. Several lesions had a pus top. The lesions were distributed symmetrically, more over the central part of the face, namely the nose, cheeks, perioral areas, and chin (Fig. 1). There were no telangiectasias. Other parts of the body—the mucosa, palms, soles—were uninvolved. The patient denied taking oral or topical medication prior to consultation.

Histopathology of the papule on the chin revealed a single large focus of tuberculoid granuloma involving the middle and deep layer of the reticular dermis, consisting of lymphocytes, epithelioid cells, Langhans giant cells, foreign-body giant cells, and plasma cells. The center of the granuloma showed a large focus of fibrinoid necrosis. The periphery showed abundant fibroplasia. The rest of the dermis showed moderately dense perivascular and periappendegeal inflammatory infiltrate (Figs. 2a and 2b). Staining for microorganisms with the periodic acid–Schiff stain, Grocott stain, and Ziehl–Neelsen stain was negative. A routine hemogram and biochemical investigations,

How to cite this article: Shashi Kumar BM, Savitha AS. Lupus miliaris disseminatus faciei: A report with a new dermoscopy finding. Our Dermatol Online. 2021;12(2):148-150.

Submission: 23.04.2020; **Acceptance:** 25.08.2020

DOI: 10.7241/ourd.20212.9

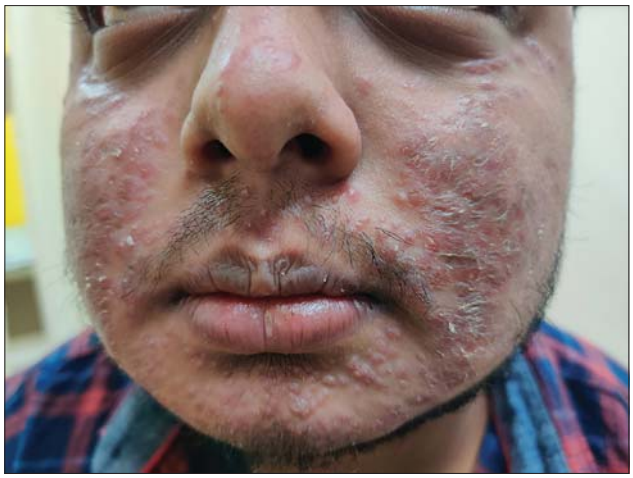

Figure 1: Erythematous papules on the central face, with scaling, several lesions, and a pus top.

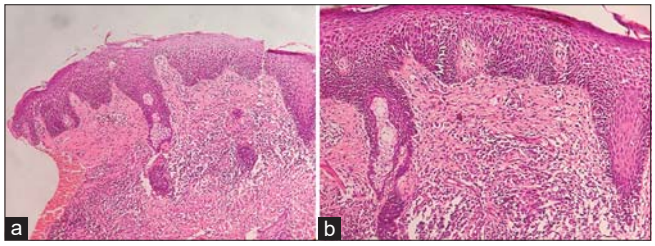

Figure 2: (a) A single large focus of tuberculoid granuloma involving the middle and deep layer of the reticular dermis, with the periphery showing abundant fibroplasia, and the rest of the dermis with moderately dense perivascular and periappendegeal inflammatory infiltrate; and an unremarkable epidermis (H&E, 10×). (b) A tuberculoid granuloma consisting of lymphocytes, epithelioid cells, Langhans giant cells, foreign-body giant cells, and plasma cells with a center demonstrating a large focus of fibrinoid necrosis (H&E, 40×).

including serum calcium and angiotensin-converting enzyme, were normal, and the Mantoux test was negative. A chest X-ray was normal. Basing on the clinical signs and histopathology, a diagnosis of LMDF was reached.

Dermoscopy showed white areas of the stellar scar sign, structureless white areas, follicular plugs, and brownish-red globules (Fig. 3). The patient was started on dapsone 100 mg OD. Lesions gradually decreased in number and size over a period of 4 months. The patient is still under observation for recurrence.

DISCUSSION

Lupus miliaris disseminatus faciei (LMDF) is an uncommon but very distinct chronic inflammatory dermatosis characterized by reddish-yellow or yellowish-brown papules on the central face, particularly on and around the eyelids [4]. The papules may occur alone

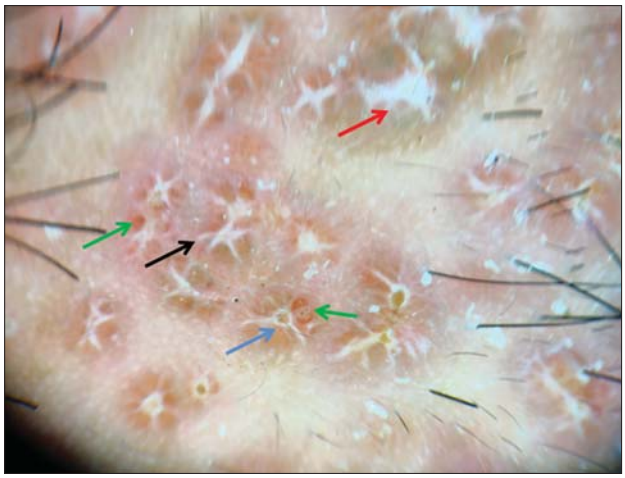

Figure 3: Dermoscopy of the facial lesion showing white areas of the stellate scar sign (black arrow), white structureless areas (red arrow), keratotic follicular plugs (blue arrow), and brownish-red globules (green arrow).

or in crops, may be follicular or non-follicular, and may sometimes have pustular tops [2].

Extrafacial lesions in the axillae, scalp, trunk, genitalia, neck, hands, and legs have been described [5]. LMDF usually affects young adults of both sexes between the second and fourth decade of life. Its exact etiopathogenesis remains unclear. Various hypotheses have believed it to be a form of cutaneous tuberculosis, tuberculid, sarcoidosis, and granulomatous rosacea, but research failed to support these associations [6]. LMDF is distinguished from granulomatous rosacea by the lack of erythema and telangiectasia and by the presence of caseating necrosis in the granulomas [5]. The disease heals spontaneously often over a chronic course of months to years, but treatment is required to prevent scarring. However, recurrences are not uncommon and may lead to more scarring [7].

According to Errichetti et al., the most characteristic dermatoscopic feature of LMDF is discrete (nonconfluent) focal orangish structureless areas located around follicular openings [3]. Such a pattern is due to the peculiar histological background of this kind of dermatosis, with perifollicular granulomatous infiltrate along with follicular hyperkeratosis. Ayhan et al. also described linear and hairpin vessels, targetoid flame-like follicular plugs, and ellipsoid keratotic follicular plugs upon dermoscopy [8]. Our case had white areas of the stellar scar sign, structureless white areas, keratotic follicular plugs, and brownish-red globules, previously unreported.

Due to the lack of a controlled trial standard, there is no recommended treatment for LMDF. Topical steroids

are ineffective. Several reports have been published on variably successful treatment with intralesional or systemic corticosteroids, topical tacrolimus, tetracyclines, metronidazole, erythromycin, dapsone, anti-tuberculous antibiotics, isotretinoin, chloroquine, and clofazimine. There have also been reports on successful laser therapy of lesions and scars with a 1,565 nm nonablative fractionated laser, a 1,450 nm diode laser, and a carbon dioxide laser [6].

CONCLUSION

Dermatoscopic findings help to aid the diagnosis of LMDF and differentiate it from other granulomatous conditions. Since LMDF is relatively uncommon, more dermatoscopic studies are required to establish its classical dermoscopic features.

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

Cutaneous lupus tumidus: An unusual unilateral presentation

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ABSTRACT

Lupus tumidus is a rare subtype of chronic cutaneous lupus erythematosus characterized by erythema and bright urticarial erythematous and violaceous lesions on sun-exposed areas that heal without leaving scars. Lupus tumidus follows a benign and intermittent clinical course and is rarely associated with systemic lupus erythematosus. Treatment involves photoprotection, topical corticosteroids, and antimalarials. We report the case of a 42-year-old patient with an atypical unilateral form of lupus tumidus successfully treated with the administration of hydroxychloroquine in combination with photoprotection and tacrolimus.

Keywords: Lupus erythematosus; Autoimmune diseases; Antimalarials

INTRODUCTION

Lupus erythematosus is a multisystemic autoimmune disease characterized by the production of autoantibodies against cellular constituents. The most affected organ is the skin, which may be involved in isolation or accompanied by systemic manifestations [1]. Cutaneous manifestations of lupus may be classified into the following: chronic cutaneous lupus erythematosus (CCLE), subacute cutaneous lupus erythematosus (SCLE), and acute cutaneous lupus erythematosus (ACLE). Lupus tumidus is considered a separate entity, showing a marked response to treatment with antimalarial drugs, extreme photosensitivity, and characteristic histopathologic findings [2].

CASE REPORT

A 52-year-old male with no history of comorbidity and medication presented himself with a slightly itchy lesion on the face persistent for twelve months. The lesion emerged as an erythematous macule, later evolving into an infiltrated erythematous lesion. There were no other systemic signs, such as photosensitivity or arthralgia. The patient reported a lack of improvement after the application of a topical corticosteroid. An examination of the face revealed a well-limited erythematous plaque roughly 4 cm in size on the left malar region (Fig. 1). A skin biopsy revealed deep perivascular and periadnexal lymphocytic infiltration of the skin (Fig. 2) and papillary edema with mucinous dispositions (Fig. 3), thus confirming the diagnosis of cutaneous lupus tumidus. The patient was started on antimalarials, photoprotection measures, and tacrolimus with great improvement.

DISCUSSION

The term *lupus erythematosus tumidus* (LET) was first used by Gougerot and Burnier in 1930 to describe infiltrated erythematous lesions with no clinical signs of desquamation or other superficial changes [3]. Lupus erythematosus tumidus may begin at any age, including childhood, but, according to one study, the mean age of onset is 36.4 years. The majority of patients with LET

How to cite this article: Mrabat S, Baybay H, Douhi Z, Elloudi S, Mernissi FZ, Rimani M. Cutaneous lupus tumidus: An unusual unilateral presentation. Our Dermatol Online. 2021;12(2):151-152.

Submission: 26.12.2020; **Acceptance:** 07.02.2021

DOI: 10.7241/ourd.20212.10

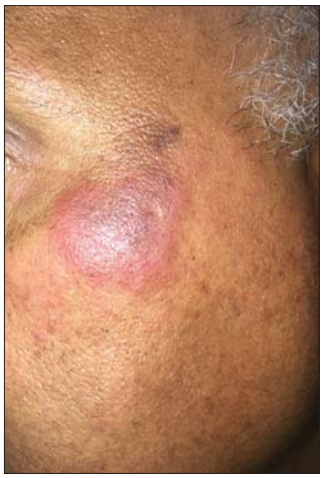

Figure 1: Well-limited erythematous plaque on the left malar region.

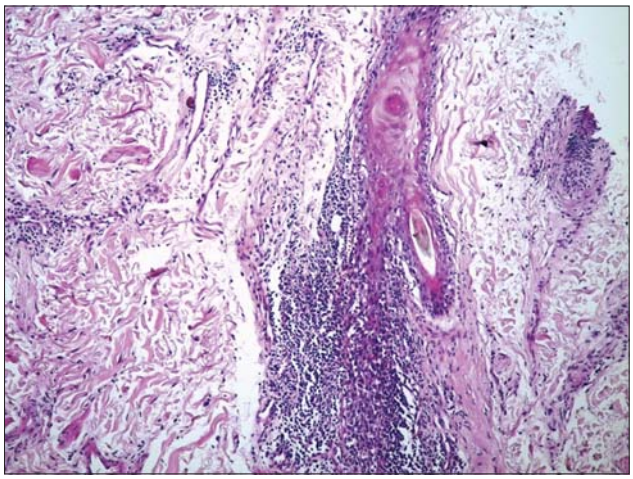

Figure 2: Periadnexal lichenoid infiltrate.

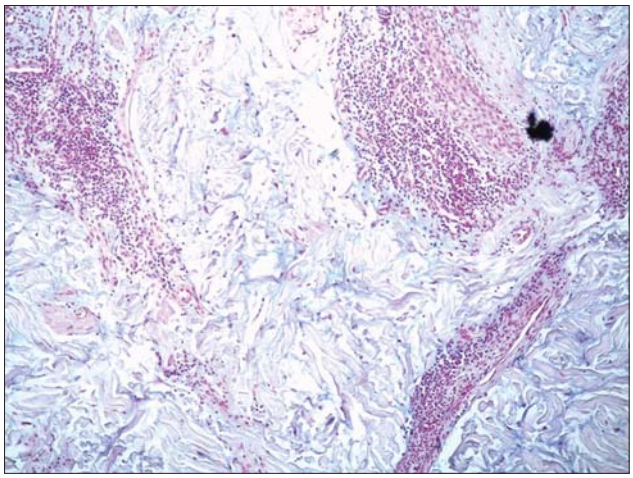

Figure 3: Moderate alkaliphilic mucinous deposits in the dermis.

are extremely photosensitive [4]. Lupus erythematosus tumidus may clinically mimic other skin disorders, such as polymorphous light eruption, pseudolymphoma, and Jessner lymphocytic infiltration. A histopathological examination of these skin lesions is, therefore, required to confirm the diagnosis. LET differs from the other conditions mainly by dermal mucin deposition and the lack of dermal edema [5]. Most patients with LET successfully respond to antimalarials and sunscreen. Other treatments, including topical or systemic corticosteroids and immunosuppressive agents, have been demonstrated to be effective [6].

CONCLUSION

Our case emphasizes the importance of detailed clinical examination as well as histopathological analysis in the diagnosis of this rare form of cutaneous lupus.

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

Pyoderma gangrenosum: An ulcerative variant developing at a paraincisional LSCS scar site

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ABSTRACT

Pyoderma gangrenosum (PG) is an uncommon entity based on a diagnosis of exclusion. It can manifest itself mimicking various ulcerative cutaneous conditions and nonhealing wounds. With its less known etiology and presentation, there is a danger of mistreatment. Herein, we present an interesting case of pyoderma gangrenosum in a young woman, developing around the area of a lower segment Cesarean scar, but not involving the scar tissue. The PG was not associated with any underlying systemic ailments and responded well to a tapering dose of oral corticosteroids. Prompt diagnosis and initiation of therapy lead to a good response and favorable prognosis. Recognizing the atypical clinical presentations of PG is pertinent. Treatment with immunosuppressive agents and a multidisciplinary approach are recommended.

Key words: Ulcer; Pyoderma gangrenosum; LSCS; Neutrophilic dermatosis

INTRODUCTION

Pyoderma gangrenosum (PG) is an inflammatory, noninfectious neutrophilic dermatosis usually characterized by rapidly developing ulcers, first described by Brunsting et al. [1]. PG is an uncommon entity, frequently associated with underlying conditions, such as inflammatory bowel disease, polyarthritis, and hematologic and hepatic disorders. One of its causes might be a dysregulation of the immune system. PG is rarely associated with pregnancy and surgical scar sites, and its appearance in areas around surgical scars, likewise, has not been reported in the literature.

CASE REPORT

A 25-year-old G_1P_1 woman with no history of underlying systemic ailments presented with painful, sudden-onset ulcerations, associated with swelling and induration. Twenty days prior, she underwent a lower segment Cesarean section (LSCS), which was seemingly uneventful. However, nine days after the operation, she developed painful reddish papules on the lower abdomen. Initially small and few, they increased in size rapidly over several days and started forming ulcers (Fig. 1). The patient was anxious and in visible distress due to the burning pain at the ulcer sites. Upon examination, the ulcers were multiple, tender, with undermined edges and mild violaceous changes at the borders. They were present on either side of the Cesarean wound. The surgical scar, however, had healed well with no signs of dehiscence. She was otherwise afebrile with stable vitals and no lymphadenopathy on palpation.

Routine blood investigations, including acute phase reactants (ESR and CRP), complete blood count, APLA and RA factor, were within normal limits. Viral markers were nonreactive. A pus culture was sterile.

A presumptive diagnosis of pyoderma gangrenosum was reached after excluding other infectious and autoinflammatory conditions.

A skin biopsy was taken from the margin of the ulcer, and histopathology showed neutrophilic infiltrate in the dermis and mild necrosis of the overlying epidermis,

How to cite this article: Pandey K, Shishak M, Yadav N. Pyoderma gangrenosum: An ulcerative variant developing at a paraincisional LSCS scar site. Our Dermatol Online. 2021;12(2):153-155.

Submission: 26.04.2020; **Acceptance:** 15.08.2020

DOI: 10.7241/ourd.20212.11

with acute and chronic inflammatory features. In the absence of other classical features suggestive of vasculitis and granuloma, a diagnosis of pyoderma gangrenosum was established

She was counseled and started on oral prednisolone (1 mg per kg of body weight), an oral antibiotic course of doxycycline 100 mg twice daily, and anti-inflammatory agents twice daily. The patient was advised to do wound care. Topical tacrolimus and mupirocin application to the ulcers were prescribed. Within a month of initiating treatment, the ulcers reduced in size by 50% along with a decrease in pain and discomfort. After a three-month course of tapering steroids, there was a significant and dramatic improvement (Fig. 2). All ulcers healed with scarring and the patient reported an excellent general health condition.

DISCUSSION

Pyoderma gangrenosum commonly occurs in the lower extremities, displays a male predominance, and has rarely been reported to complicate Cesarean sections [2]. Its exact etiology is yet unknown but resembles class II Schwartzman-like hypersensitivity reactions. Initially a single pustular lesion, it is known to progress rapidly, causing painful ulcerated nodules or plaques with undermined, dusky, and violaceous borders that heal with cribriform scarring [3]. Though commonly associated with other inflammatory, infectious, and malignant pathologies, it may at times be idiopathic with no relevant causative factors [4]. While, in adults, it is found in up to 74% cases, in children, it is less common, with only a handful of reported cases (50% of cases) [5]. The underlying systemic predisposing factors include ulcerative colitis, Crohn's disease, arthritis, hematological malignancies, HIV, and lupus.

Figure 1: Ulcerations with indurated, inflammatory, and violaceous margins.

Figure 2: Clean and well-healed scars after three months of therapy.

The chances of developing PG during pregnancy and postpartum, albeit rare, may occur due to immunosuppression. Alterations of immune function in pregnant women could play a role in the development of PG during pregnancy due to IL-2 and IL-1 inhibition and depressed polymorphonuclear leukocyte (PMN) chemotaxis and adherence functions. An increase in granulocyte-macrophage colony-stimulating factor, a known attractant of neutrophilic inflammation, and an increase in band neutrophils could possibly magnify the risk of neutrophil-driven PG [6]. Histology is nonspecific, which makes PG predominantly a clinical diagnosis of exclusion. Histopathology shows dermal neutrophilic infiltrate in 50% of cases [7].

There have been few reports of cases of post-surgery pyoderma gangrenosum, leading to delay in diagnosis. Additionally, post-surgical cases wherein lesions develop at the site of the suture wound itself are attributed to the pathergy reaction [8].

Our patient, however, had no underlying medical conditions and no history suggestive of an autoimmune diathesis or an immunosuppressive state. However, the patient met enough criteria—five out of eight—to be diagnosed with PG: 1) exclusion of infection; 2) a history of papules, pustules, or vesicles ulcerating within four days of appearing; 3) peripheral erythema, an undermining border, and tenderness at the ulceration site; 4) a cribriform or "wrinkled-paper" scar at healed ulcer sites; and 5) a decrease in the size of the ulcer within a month of initiating the immunosuppressive medication of corticosteroids [9].

What is special in this case is the development of lesions only *around* the scar site, but not affecting the

scar tissue itself, which is unlike the existing cases in the literature. To the best of our knowledge, such a case has not been documented in the literature. The question remains whether this was a coincidental occurrence or whether there is a possibility of development in a paraincisional area without trauma, in which case the inciting cause cannot be determined exactly.

CONCLUSION

Pyoderma gangrenosum is a rare entity, especially in the setting of pregnancy and surgery. It is likely to be misdiagnosed as a case of complicated wound healing, leading to a poor response to wound care, such as antibiotics. Prompt and high-index clinical suspicion is needed, followed by quick treatment with immunosuppressive agents. A multidisciplinary approach is recommended for a smooth treatment and alleviation of the patient's symptoms.

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

An atypical case of eosinophil-rich Sweet's syndrome

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ABSTRACT

Sweet's syndrome is an inflammatory disease that occurs mainly in young adults. Its clinical and histological aspects are usually characteristic. Its diagnostic criteria were proposed by von den Driesch. Two major and at least two minor criteria are required to establish the diagnosis. Sweet's syndrome is classically associated with neutrophilic infiltrate. A few cases of Sweet's syndrome with dense eosinophil infiltrate have been described. Here, we report a new case of eosinophil-rich Sweet's syndrome in a young woman without underlying pathology.

Key words: Sweet's syndrome; Eosinophils; Neutrophils

INTRODUCTION

Sweet's syndrome is an inflammatory disease that occurs mainly in young adults. Its clinical and histological aspects are usually characteristic. Sweet's syndrome is classically associated with neutrophilic infiltrate [1]. A few cases of Sweet's syndrome with dense eosinophil infiltrate have been described. Here, we report a new case of eosinophil-rich Sweet's syndrome in a young woman without underlying pathology.

CASE REPORT

A previously healthy 30-year-old woman presented with an abrupt onset of inflammatory erythematous plaques associated with polyarthralgia and fever evolving for the past week. No new drug intake or insect bites were noted. A physical examination revealed inflammatory and infiltrated plaques and nodules on the upper limbs. On the lower limbs, large pseudo-urticarial inflammatory plaques with centrifugal extension and purplish borders were noted (Fig. 1). The rest of the examination did not reveal further abnormalities. A biological assessment showed an accelerated sedimentation rate, CRP at 45 mg/L, and hyperleukocytosis at 11,000 cells/mm^3 with a predominance of polynuclear neutrophilic leukocytes. Cutaneous biopsies from the forearm and thigh showed an edematous dermis with perivascular inflammatory infiltrate rich in neutrophils (Fig. 2) and eosinophilic polynuclear cells, with leukocytoclasia and collagen necrobiosis (Fig. 3). A thoracoabdominopelvic scan was without abnormalities, and an immunological assessment was negative. The patient was treated with corticosteroid therapy at a dose of 1 mg/kg/day with a marked improvement.

DISCUSSION

Sweet's syndrome (SS) is an inflammatory disease that occurs mainly in young adults with a predominance in females. Its diagnostic criteria were proposed by von den Driesch [2]. The presence of two major and at least two minor criteria establishes the diagnosis of SS. The major criteria are (1) an abrupt onset of painful erythematous plaques or nodules and (2) a predominantly neutrophilic infiltration of the dermis without leukocytoclastic vasculitis. The minor criteria are (1) association with a respiratory or gastrointestinal tract infection, vaccination, inflammatory disease, malignancy, or pregnancy, (2) fever, (3) abnormal

How to cite this article: Soua Y, Ben Rjeb M, Moussa A, Dadaa S, Laouel I, Belhadjali H, Youssef M, Zili J. An atypical case of eosinophil-rich Sweet's syndrome. Our Dermatol Online. 2021;12(2):156-158.

Submission: 14.06.2020; **Acceptance:** 13.09.2020

DOI: 10.7241/ourd.20212.12

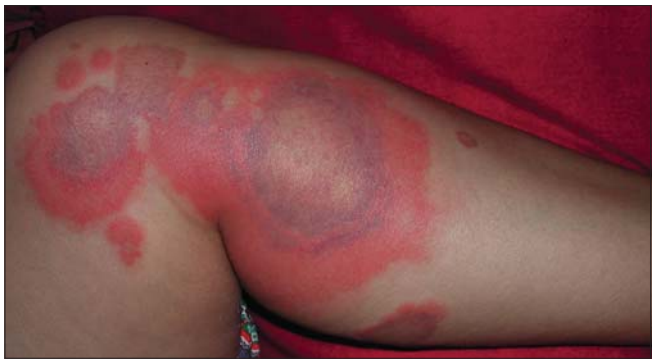

Figure 1: A large plaque with a centrifugal extension, purplish center, and inflammatory borders.

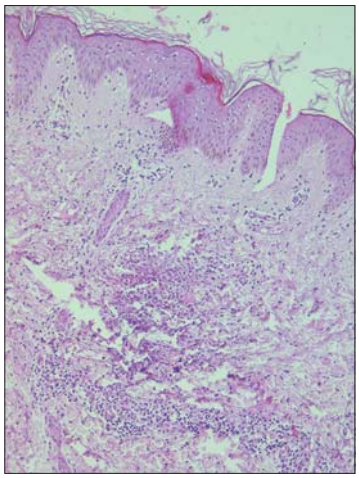

Figure 2: An edematous dermis with perivascular inflammatory infiltrate rich in neutrophils and eosinophilic polynuclear cells (H&E, ×40).

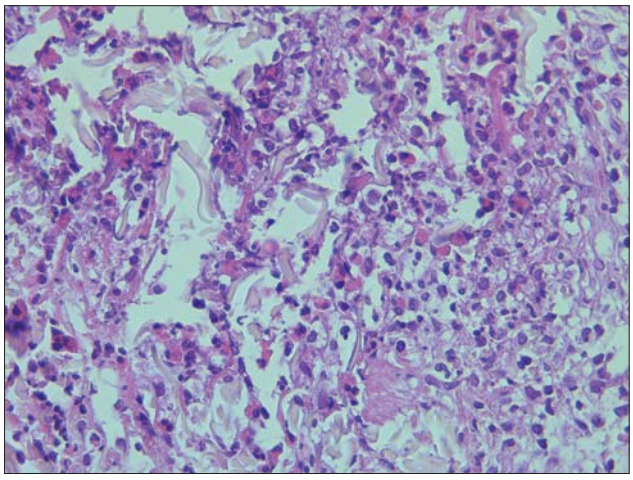

Figure 3: Dermal inflammatory infiltrate rich in neutrophils and eosinophilic polynuclear cells with collagen necrobiosis (H&E, ×400).

laboratory values—erythrocyte sedimentation rate (ESR) at 20 mm/h, a raised level of C-reactive protein, leukocytosis at 8000 cells/mL, 70% neutrophils in peripheral blood (3 out of 4 abnormal laboratory values required for the diagnosis)—and (4) excellent response to treatment with systemic corticosteroids or potassium iodide. Our patient fulfilled the two major criteria and two minor criteria of SS. In our patient, the minor criteria were blood neutrophilia and excellent response to systemic corticosteroids [1]. The diagnosis of Sweet's syndrome was upheld, but it was particular by its histology. Sweet's syndrome is classically associated with neutrophilic infiltrate. Additional features of leukocytoclastic vasculitis may be present [1]. Unusual histopathologic variants of Sweet's syndrome, including histiocytoid Sweet's syndrome, have been reported [3]. The presence of eosinophils in the neutrophilic infiltrates of acute febrile neutrophilic dermatosis has also been reported in the literature. In a histopathological review of 73 cases, eosinophilic infiltration was present in up to 40% of the lesions and associated, in some cases, with eosinophilia in peripheral blood [4]. The pathogenesis of eosinophil infiltrate in this syndrome has not been well understood. Cases with dense eosinophilic infiltrates are much rarer. To the best of our knowledge, four cases of eosinophils-rich Sweet's syndrome have been reported [5]. Among these, a patient with a B-cell lymphoma developed Wells' syndrome, following eosinophil-rich Sweet's syndrome [6]. Another patient, with a subsequent appearance of Wells' syndrome, Sweet's syndrome, and leukocytoclastic vasculitis, developed a ganglial lymphoma for several months [7]. Other underlying processes of SS may include inflammatory bowel disease, infection, pregnancy, or medication. Neoplastic diseases are associated with approximately 20% of cases [8]. Clinical manifestations can precede the diagnosis of a neoplasm in patients. Although etiological investigations were negative in our patient, monitoring should be continued to detect a later association of pathology.

CONCLUSION

We report here the case of a particular form of Sweet's syndrome rich in eosinophils.

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

Neutrophilic dermatosis of the dorsal hands: A new case report associated with Basedow's disease

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ABSTRACT

Neutrophilic dermatosis of the dorsal hands (NDDH) is a newly described and poorly known disease, a topographic variant of Sweet's syndrome, most often clinically misdiagnosed as an infectious process, which, as a result, delays treatment. In addition, its association with underlying systemic and neoplastic disorders increases the need for accurate and early diagnosis. Interestingly, our case had an additional lesion located on one leg. Our patient also presented bacterial conjunctivitis, which may have either been part of the clinical presentation or the trigger of this entity and which was an association with Basedow's disease never described before.

Key words: Neutrophilic dermatosis; Dorsal hands; Basedow's disease

INTRODUCTION

Sweet's syndrome, originally described by Dr. Robert Douglas Sweet in 1964, is characterized by an acute onset of fever, leukocytosis, and tender erythematous plaques infiltrated by mature neutrophils. The lesions usually involve the face and extremities and show an excellent response to corticosteroids [1]. Recently, several new variants have been described, including neutrophilic dermatosis of the dorsal hands (NDDH). NDDH is characterized by tender erythematous plaques, pustules, bullae, and/or ulcers usually limited to the dorsa of the hands. Both Sweet's syndrome and its dorsal hand variant have been reported in association with malignancies, inflammatory bowel diseases, and drugs [2]. We report a case associated with Basedow's disease in a 61-year-old female.

CASE REPORT

A 61-year-old female was admitted to our hospital with a painful eruption on the hands. She had been followed since ten years of age for Basedow's disease with exophthalmos, for which she had been taking carbimazole, and had, besides, no notable medical history. Five days prior to the consultation, the patient presented herself with flu-like syndrome manifesting fever, arthralgia, myalgia, rhinorrhea, and pharyngitis, for which the patient took emergency-prescribed antibiotics and paracetamol. Subsequently, the patient developed redness of the eyes observed by an ophthalmologist who diagnosed bacterial conjunctivitis without further eye damage and treated it locally. Several days later, the patient felt painful tension in both hands, which gradually swelled. A physical examination revealed tense erythematous edema of both hands with the presence of multiple deep-seated pustules and purplish papules on the backs of the hands (Fig. 1). An examination of the rest of the skin found one purplish patch on the right leg (Fig. 2). The rest of the examination was normal, except for exophthalmos and bacterial conjunctivitis (Fig. 3). Laboratory tests on admission showed a total leukocyte count of 12.4 × 109/L with 75% neutrophils. C-reactive protein was 50 mg/L (0–6 mg/L). Urine analysis, serum electrolytes, and

How to cite this article: Oulehri A, Elloudi S, Baybay H, Douhi Z, Rimani M, Mernissi FZ. Neutrophilic dermatosis of the dorsal hands: A new case report associated with Basedow's disease. Our Dermatol Online. 2021;12(2):159-162.

Submission: 11.09.2020; **Acceptance:** 14.11.2020

DOI: 10.7241/ourd.20212.13

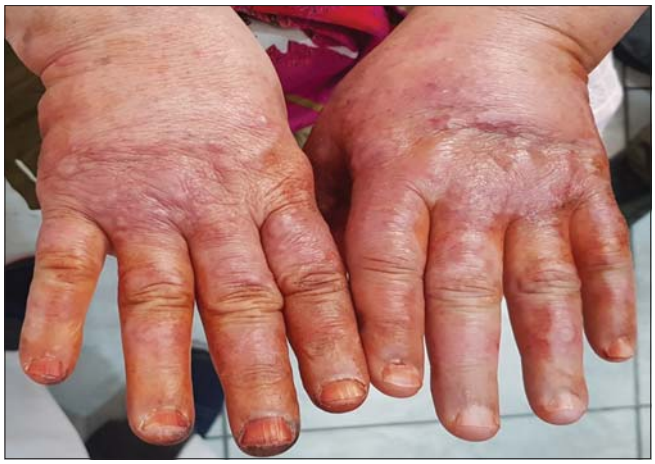

Figure 1: Tense and painful edema with multiple deep-seated pustules and purplish papules on the back of the hands (exogenous orange coloration due to henna).

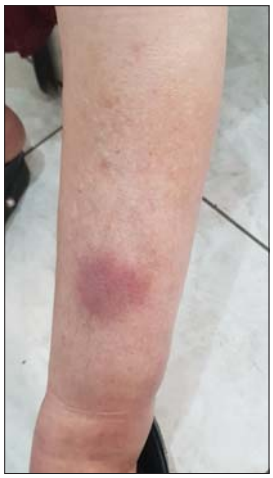

Figure 2: An additional isolated purplish patch on the right leg.

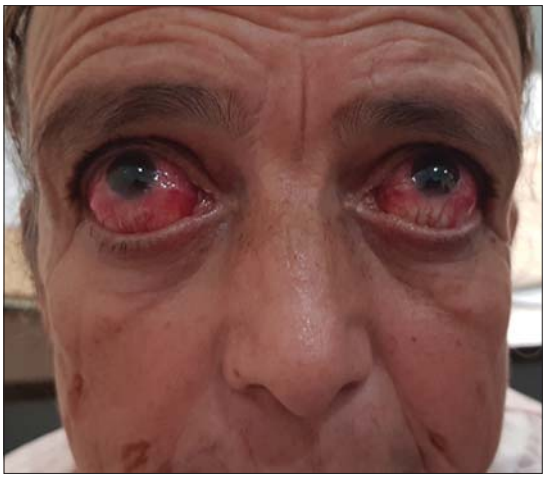

Figure 3: Chronic exophthalmos with bacterial conjunctivitis.

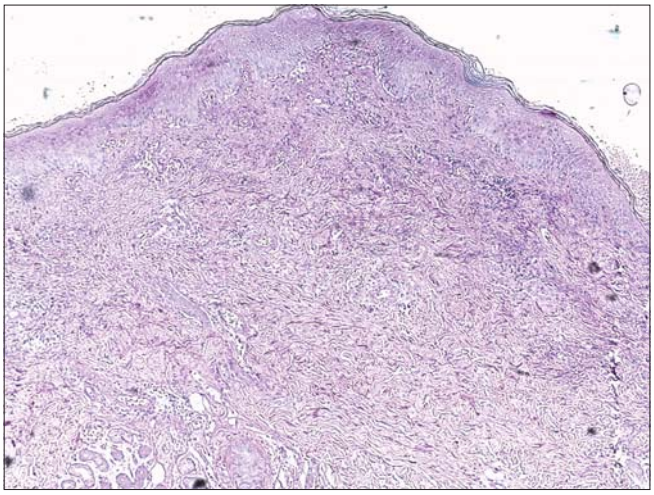

Figure 4: A dense dermal infiltrate of neutrophils restricted to the papillary and superficial reticular dermis with associated dermal edema.

liver and renal function were normal. Electrophoresed proteins had an inflammatory profile. No abnormality was detected on a chest X-ray. A histopathologic examination revealed a dense dermal infiltrate of neutrophils restricted to the papillary and superficial reticular dermis with associated dermal edema (Fig. 4). There was no leukocytoclastic vasculitis. In the light of the patient's history, the physical examination, and the histopathologic features found, the diagnosis of neutrophilic dermatosis of the dorsal hands (NDDH) was reached. Treatment with indomethacin at an initial daily dose of 150 mg for one week, and reduced to 100 mg daily for the next two weeks, was initiated with remarkable improvement observed over the next week. The bacterial conjunctivitis completely regressed under the treatment. Complete resolution of all lesions was observed over the next two weeks. No recurrence was noted six months after the initial episode.

DISCUSSION

Pustular vasculitis of the hands was first described by Strutton et al. in 1995 as a rash on the dorsal hands resembling Sweet's syndrome with histological leukocytoclastic vasculitis [3]. Subsequently, clinically similar cases were reported but without vasculitis [4,5]. *Neutrophil dermatosis of the dorsal hands* (*NDDH*), a term proposed by Galaria et al. in 2000, is now a widely accepted name for this clinicopathological condition [6].

Today, NDDH most commonly represents a "distributional or localized variant" of Sweet's syndrome, which belongs to the spectrum of neutrophilic dermatoses, rather than a primary vasculitis, with any vasculitis observed histologically being a secondary phenomenon. The different timings of the biopsies

taken during the evolutionary phases of the lesions are likely to result in different findings with regard to the presence or absence of vasculitis [7].

The number of report cases of this entity remains limited [8-11]. A total of 123 cases were collected in a recent literature review [2].

Epidemiologically, there is a slight predominance in females, with a mean age of occurrence of 62.1 years [2], which is in accordance with our patient. These statistics are significantly different compared to those of Sweet's syndrome, which shows a female-to-male ratio of 4:1 and tends to occur in middle-aged females, often aged 30 to 50 years [12].

Clinically, the lesions are very similar to classic Sweet's syndrome with painful erythematous and purplish papules and plaques. Nodules, pustules, and hemorrhagic bullae that become ulcerated have also been described. The most common sites of eruption are the dorsal surfaces of both hands. The backs of the fingers or wrists may also be affected, with rare involvement of the palms. Both hands were affected in the majority of cases but unilateral involvement was also described and in 30.9% of cases [2]. There may be simultaneous or subsequent lesions elsewhere, such as on the back, lips, legs, and forehead [9,11,13], as in our patient, who developed an isolated lesion on the right leg. The most common clinical differential diagnosis is an infection, for which the patient receives antibiotics but with no success.

Pathologically, NDDH is considered a variant of Sweet's syndrome with identical histological findings. Histologically, there is prominent papillary dermal edema, superficial and deep perivascular, and diffuse infiltrate of neutrophils with leukocytoclasia, extravasated erythrocytes, and no vasculitis. Admixed lymphocytes and occasional eosinophils may also be seen. It appears that any vasculitis observed is of secondary type rather than a primary phenomenon, similarly to PG or Sweet's syndrome [7,11]. Is usually only identified in early lesions and this phenomenon most likely represents a reaction to endothelial damage [14].

Hematological and serological investigations may, in NDDH, reveal neutrophilic leukocytosis and raised levels of CRP, although these are less frequently identified than in classical Sweet's syndrome and in keeping with a more localized variant of the disease [2]. Indeed, our patient manifested slight hyperleukocytosis at PNN and a moderate CRP level at 50.

Associations have been reported with a variety of diseases, while the majority of the comorbid conditions were diagnosed prior to the NDDH; several were diagnosed concomitantly to or shortly after a diagnosis of NDDH [2]. The most common are hematologic disorders, such as myelodysplastic syndrome, acute leukemia, and lymphoma [11,15]. In addition, solid neoplasms may be seen, such as cancers of the breast, kidney, colon, stomach, lung, and hypopharynx. Associated non-neoplastic disorders include inflammatory bowel diseases such as ulcerative colitis and Crohn's disease [7] and recent infections, by far the most common of which have been respiratory tract infections [2,7,11]. According to our knowledge, this is the first case associated with a thyroid pathology such as Basedow's disease. These findings highlight the importance of a thorough systematic inquiry in patients with NDDH. This may reveal a history of recent infection or guide the clinician to further investigation of inflammatory bowel diseases or solid organ tumors. Given the fact that hematological disorders have been reported in almost 15% of cases, a full blood count and serum protein electrophoresis would be sensible in all patients [2].

Multiple therapies have been used for NDDH with different rates of success and relapse. The treatment options for NDDH are similar to those for Sweet's syndrome. Corticosteroids are commonly used as first-line therapy; the majority of cases usually respond well to moderate doses of systemic corticosteroids. Dapsone has also been used either alone or in combination with systemic corticosteroids [13].

Several alternative therapies have been proposed, including cyclosporine, methotrexate, and Salazopyrin. Successful treatment with indomethacin, intravenous immunoglobulin, colchicine, minocycline, azathioprine, intralesional triamcinolone, topical steroids, and topical tacrolimus has also been reported [16,17].

According to the latest review on the subject [2], and given that all treatment modalities were successful in yielding improvement within several weeks, we suggest it to be worth considering topical steroid monotherapy or non-steroid systemic agents guided by the patient's comorbidities and by the side-effect

profile of the respective agent. Indeed, a topical steroid and/or an oral steroid-sparing agent appear to be as effective as systemic corticosteroids and may have a better side-effect profile. This was the same approach that we used with our patient, who received indometacin alone with complete remission after two weeks and no relapse. The current follow-up is at six months.

CONCLUSION

Although NDDH is an infrequent entity, the increase in cases reported in the literature proves that NDDH is not as rare as it may seem and that it is likely to be underdiagnosed, as it is mostly unrecognized.

A correct diagnosis would avoid unnecessary antibiotic treatments and potentially aggressive management strategies, such as surgical debridement, and will prompt search to exclude any possible association, particularly hematological malignancy, but also an occult solid organ, an inflammatory bowel disease, or infection, based on a history and examination.

Consent

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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

Hemorrhagic plaques in the oral cavity: A clue to diagnosing thrombocytopenia

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ABSTRACT

Idiopathic thrombocytopenic purpura is a disorder with a myriad of possible clinical presentations. The mechanism of thrombocytopenia involves both increased platelet destruction and impaired platelet production. The patient can manifest a wide range of symptoms: from asymptomatic or minimal gingival bleeding to profuse bleeding from any site. The disease may first present itself to the dermatologist in cutaneous findings such as petechiae, purpura, and mucosal manifestations in the form of gingival bleeding and hemorrhagic bullae. The diagnosis of idiopathic thrombocytopenic purpura is mostly done by exclusion. In this report, we present two cases with characteristic oral manifestations, who were diagnosed, on investigation, with idiopathic thrombocytopenic purpura. The patients were successfully treated with immunosuppressive therapy. The report aims to raise awareness that would help in enabling prompt referral to the appropriate specialty, especially because of the rarity of this presentation.

Key words: Thrombocytopenia; Purpura; Oral cavity

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is a disorder characterized by a low platelet count (thrombocytopenia), usually of no known cause (idiopathic). As most causes appear to be related to antibodies against platelets, it is also known as immune thrombocytopenic purpura. Although most cases are asymptomatic, a significantly low platelet count can lead to bleeding diathesis and purpura. A platelet count below 50,000 mm^3 increases risk of dangerous bleeding from trauma [1].

CASE REPORT

A 52-year-old female presented herself to the dermatology department with asymptomatic oral ulcers for fifteen days prior. On further probing, the patient admitted to having noticed multiple asymptomatic flat and red lesions over both legs for ten days prior. She also had associated low-grade fever, constitutional symptoms, and reduced appetite and sleep for two weeks prior. There was no history of prior drug intake or associated gingival bleeding, headaches, blurring of vision, seizures, abdominal pain, nasal bleeding, hematuria, hematochezia, or melena. The family history was insignificant. She was a known case of hypothyroidism and hypertension under treatment. A general physical examination revealed no abnormality except for pallor. A systemic examination was normal. A dermatological examination revealed multiple non-palpable, non-blanchable purpura over the bilateral lower limbs till the lower third, a few scattered lesions over the upper left half and abdomen, and an isolated ecchymotic patch over the left shoulder (Figs. 1 and 2). An examination of the oral cavity revealed multiple ulcers with surrounding hemorrhagic plaques over the buccal mucosa (Fig. 3). The patient was promptly referred to a physician for further evaluation. Laboratory investigations showed hemoglobin at 13.9 g/dL and the

How to cite this article: Raj A, Asfiya A, Pinto M, Shenoy MM, Hegde SP, Bejai V, Razak AA. Hemorrhagic plaques in the oral cavity: A clue to diagnosing thrombocytopenia. Our Dermatol Online. 2021;12(2):163-166.

Submission: 01.07.2020; **Acceptance:** 01.10.2020

DOI: 10.7241/ourd.20212.14

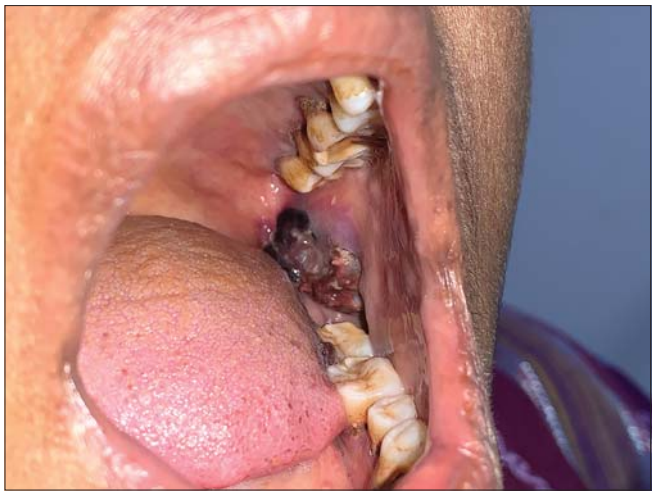

Figure 1: Hemorrhagic plaque on the left side of the buccal mucosa.

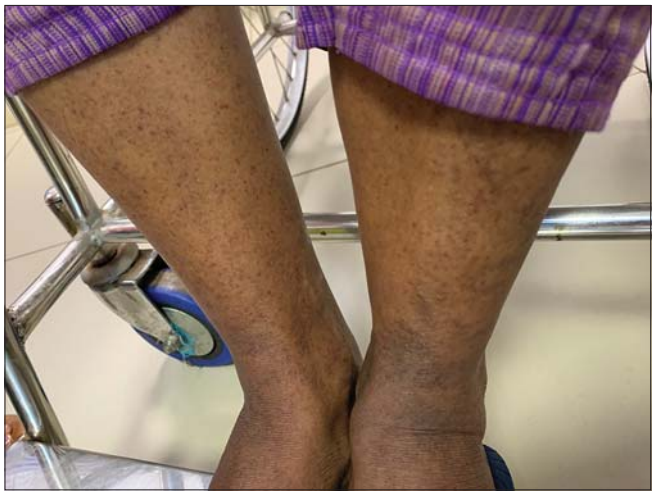

Figure 2: Purpura over the bilateral legs.

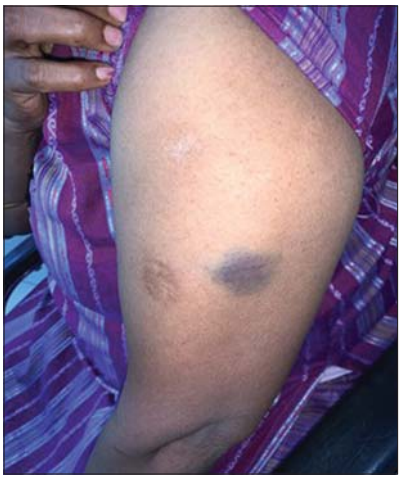

Figure 3: Ecchymosis over the left arm.

platelet count at 6000/μL. The coagulation profile was normal. Tests for malaria and dengue were negative. Peripheral smear showed severe thrombocytopenia. The patient was, thus, diagnosed with ITP and initiated on antibiotics and steroids. However, due to a minimal response, hematologist opinion was sought and the patient as started on azathioprine 50 mg BD along with a tapering dose of steroids. Following this, the platelet count increased and the cutaneous lesions improved.

The second patient was a 36-year-old male who presented himself with an asymptomatic dark lesion in the oral cavity and the right side of the tongue for fifteen days prior. There were no red lesions anywhere else on the body. No history of fever, weight loss, drug intake, joint pain was present, as well as no history suggestive of bleeding manifestations. No history of headache, blurring of vision, seizures, or other comorbidities was present either. An examination revealed normal vitals. An examination of the oral cavity revealed a hemorrhagic plaque over the posterior part of the right buccal mucosa and a smaller plaque over the right lateral border of the tongue (Figs. 4 and 5). The patient's general condition as well as a systemic examination were normal. A laboratory investigation revealed hemoglobin at 12.8 g/dL, the platelet count at 23000/μL, the total count at 8200/μL, and ESR at 9 mm/h. The coagulation profile was normal. Peripheral smear showed thrombocytopenia. The patient was started on oral prednisolone in tapering doses, considering a diagnosis of ITP. Over a period of two weeks, improvement in the platelet count was noted with a resolution of oral lesions.

DISCUSSION

ITP, also known as Werlhof's disease, is caused by antibody and cell-mediated platelet destruction and suppression of platelet production, which may occur without any predisposing factor (primary ITP) or secondary due to other conditions, including autoimmune disorders, neoplasms, congenital immune deficiencies, drugs, and infections. There are two clinical subtypes of primary ITP: acute primary ITP (present for less than 6 months), a self-limited form commonly seen in children subsequent to viral infections, and chronic primary ITP (present for more than 6 months), more commonly seen in young adult females between 20 to 40 years of age. Chronic ITP is characterized by antiplatelet antibodies directed against platelet membrane glycoproteins IIb/IIIa or Ib/IX complexes. The diagnostic criteria of ITP, outlined by an international working group, include either a confirmed platelet count of $\geq 50 \times 10^9$/L and $< 100 \times 10^9$/L on two or more consecutive occasions

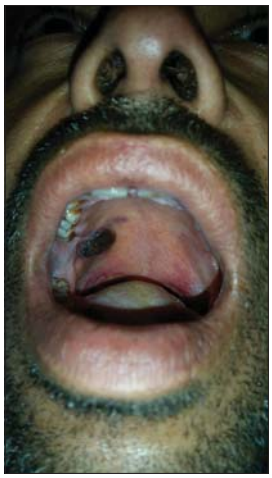

Figure 4: Hemorrhagic plaque over the posterior part of the oral cavity.

Figure 5: Hemorrhagic plaque over the right lateral side of the tongue.

over a period of one month or a confirmed platelet count of $<50 \times 10^9$/L on two or more consecutive occasions over any period of time; with normal hemoglobin, a normal white blood cell (WBC) count, no splenomegaly, normal peripheral smear, except for a low platelet count, and no evidence of an alternative nonautoimmune etiology of thrombocytopenia [2].

The first sign of thrombocytopenia is usually spontaneous bleeding or bleeding on minor trauma, as during brushing or flossing. Common sites involved are the lateral border of the tongue, the buccal mucosa, and the junction between the hard and soft palate. Clinical features include petechiae, purpura, ecchymosis, hematoma, and multiple hemorrhagic blisters [3]. The characteristic clinical indicators of ITP include easy bruising of the skin, mucocutaneous lesions such as petechiae and ecchymosis, epistaxis, gingival bleeding, and hemorrhagic bullae in the mouth [4]. Other symptoms may include hematemesis, menorrhagia, conjunctival hemorrhages, and melena. Symptomatic bleeding is uncommon unless the ITP is severe (platelet count of less than 30,000/μL). A platelet count below 10,000/μL is increases risk of internal bleed [5]. The disease is usually self-limiting, mostly occurring after a viral infection or immunization. Recovery is generally observed within six months. Some patients will develop chronic thrombocytopenia and usually die from cerebral hemorrhage. A similar case was reported by Sugiura T et al. in which a 79-year-old female presented herself with a sudden onset of gingival bleeding and hemorrhagic bullae on the buccal mucosa, with a platelet count of 2000/μL [5]. Another report describes a patient with multiple comorbidities who presented themself with bleeding from the gingiva in the lower anterior region with purpuric spots over the neck, forearms, right arm, dorsum of the tongue, hard palate, and maxillary tuberosity region with a platelet count of 6000/μL [1]. Our patient had no evidence of gingival bleeding, in contrast to most previously reported cases, making it important to examine the entire oral cavity for hemorrhagic lesions as this may sometimes be the only manifestation of the disease. Dermatologists should be aware of this unusual clinical finding to promptly institute treatment and prevention of any serious complications that may arise if the disease is left untreated.

CONCLUSION

ITP presenting itself as hemorrhagic bullae in the oral cavity is a rare finding. Very few cases have been reported in the medical literature with oral hemorrhage as the first symptom of ITP. Hence, it is imperative that dermatologists exercise a pragmatic approach to oral hemorrhage and consider ITP as a differential diagnosis in such cases. Prompt referral and treatment of these cases have the potential to lead to a significant reduction in mortality.

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

Sclerosis and blisters: An uncommon association revealing a new case of bullous morphea

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ABSTRACT

Bullous morphea is a rare variant of localized scleroderma (morphea) characterized by subepidermal bullae developed over sclerotic plaques. The pathogenesis of bullae formation has been the subject of several debates, which arrived at the conclusion of a multifactorial mechanism. We report the case of a 67-year-old patient with bullous morphea of the trunk and thighs, who showed a good response to PUVA therapy combined with topical steroids. Our case report supports the efficiency of PUVA therapy associated with topical steroids as a safe regimen compared to other therapeutic approaches.

Key words: Bullous Morphea; Sclerosis; Bullae

INTRODUCTION

Bullous morphea is a rare variant of localized scleroderma (morphea) that presents a diversified semiology, with tense bullae overlying plaque-type, linear, or deep sclerotic lesions. Histologically, it is associated with epidermal atrophy, subepidermal blistering, and prominent thick bundles of hyalinized collagen that destroy the adnexal structures. The pathogenesis of bullae formation has been the subject of several debates, which arrived at the conclusion of a multifactorial mechanism. Numerous treatments have been proposed, but the therapeutic strategy is still poorly codified.

We report the case of a 67-year-old patient with bullous morphea of the trunk and thighs.

CASE REPORT

A 67-year-old female with a history of diabetes and high blood pressure presented herself at our dermatology department with pruritic lesions on the abdomen evolving one month prior to the visit.

A physical examination revealed multiple sclerotic and dyschromic plaques localized symmetrically on the lower side of the breasts, abdomen, and thigh roots. The plaques were bordered by tense and serous bullae, arranged in an annular pattern, with generalized scaling, and covering 30% of the body surface (Fig. 1).

A skin biopsy was performed on a bullous lesion and histopathology revealed sclerodermiform dermal fibrosis with subepidermal blistering housing punctuate serum spots, red blood cells, and mature lymphocytes, as well as telangiectasias of the papillary dermis (Fig. 2). An autoimmunity assessment was negative.

The patient received 27 PUVA therapy sessions combined with daily topical steroids, and reported total disappearance of the bullous lesions and noticeable softening of the sclerotic areas, with regression of the sclerotic skin surface to 4% at the end of the treatment.

DISCUSSION

Morphea may appear on different aspects, and the bullous form is its rarest variant. Its first case was

How to cite this article: Aouali S, Sefraoui S, Sof K, Dikhaye S, Zizi N. Sclerosis and blisters: An uncommon association revealing a new case of bullous morphea. Our Dermatol Online. 2021;12(2):167-168.

Submission: 21.09.2020; **Acceptance:** 04.01.2021

DOI: 10.7241/ourd.20212.15

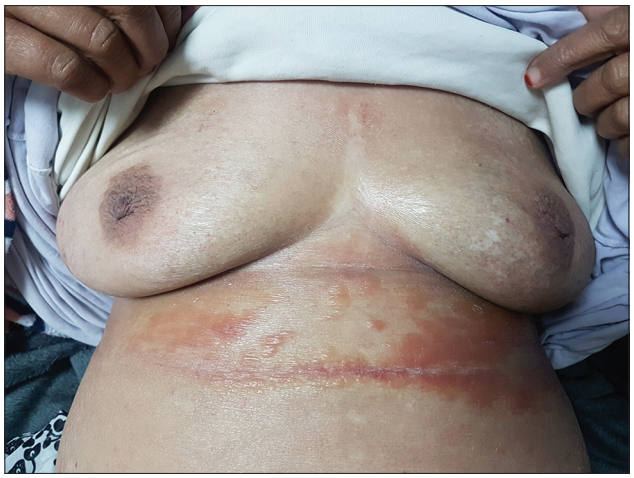

Figure 1: Clinical photo showing sclerotic plaques bordered by tense bullae.

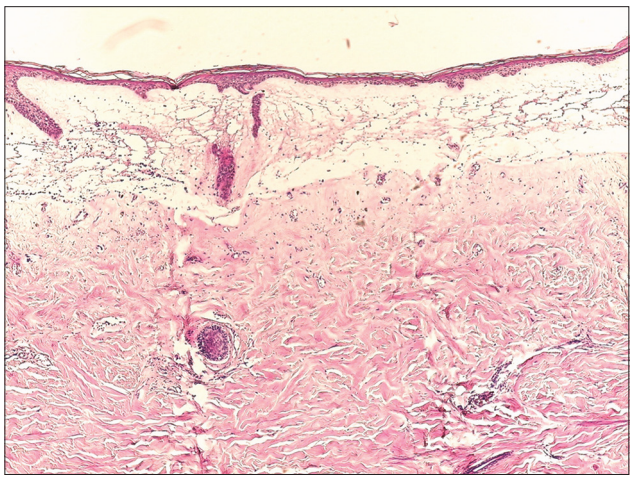

Figure 2: Histopathological image showing sclerodermiform dermal fibrosis with subepidermal blistering.

described by Morrow in 1896 [1]. Since then, it has been described in several anecdotal reports and small series.

An eight-year retrospective American study identified 53 cases of scleroderma, with only four cases of bullous morphea (7.5%) [2].

A more recent study, including 137 cases of localized scleroderma over a period of eleven years, showed a lower frequency of the bullous form, which was observed in two cases (1.4%) [3].

The pathogenesis of bullae formation has been the subject of several debates. Indeed, the blistering mechanism may be multifactorial, resulting from subepidermal edema induced by lymphangiectasias secondary to cutaneous sclerosis, excessive skin trauma, or friction to an area of low resistance [4].

The therapeutic approach is similar to the treatment regimens for non-bullous morphea and is based on topical treatments (topical steroids, vitamin D analogs) or phototherapy in first intention and the use of synthetic antimalarials, immunosuppressants, colchicine, or systemic retinoids in severe cases [5].

CONCLUSION

Bullous morphea is a rare pathology and its diagnosis is based on clinical and histological findings. The pathophysiology of bullae formation is multifactorial and its management is essentially based on topical steroids, phototherapy, and immunosuppressants in resistant forms. Our case report supports the efficiency of PUVA therapy combined with topical steroids in bullous morphea.

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

Papillomatosis cutis lymphostatica: a sign of chronic edema

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ABSTRACT

An obese 53-year-old male presented himself to our department with lymphedema of the left leg and ulcerated lesions evolving for two weeks prior. His medical history included epilepsy since childhood, mental retardation, chronic venous insufficiency, and chronic lymphedema complicated by recurrent ulceration and cellulitis. Over the previous four years, he had developed verrucous and papillomatous lesions on the left leg. A physical examination revealed an edematous leg with multiple painless coalescent verrucous skin-colored papules with a smooth or hyperkeratotic surface on the left lower leg surrounding the ulceration. The lesions were associated with oozing. A skin biopsy revealed hyperkeratosis, verrucoid acanthosis, and papillomatosis of the epidermis with moderate perivascular inflammatory infiltration of the dermis. A diagnosis of papillomatosis cutis lymphostatica (PCL) was reached based on histopathological and clinical findings. Our patient received lymphatic drainage and locally 5% salicylic acid.

Key words: Chronic lymphedema; Papillomatosis cutis lymphostatica; Elephantiasis nostras verrucosa

INTRODUCTION

Papillomatosis cutis lymphostatica (PCL), or elephantiasis nostras verrucosa, is a rare, benign, and asymptomatic condition affecting usually the lower legs and resulting from chronic lymphedema [1]. Herein, we report a new sporadic case of PCL.

CASE REPORT

An obese 53-year-old male presented himself to our department with lymphedema of the left leg and ulcerated lesions evolving for two weeks prior. His medical history included epilepsy since childhood, mental retardation, chronic venous insufficiency, and chronic lymphedema complicated by recurrent ulceration and cellulitis. Over the previous four years, he had developed verrucous and papillomatous lesions on the left leg. A physical examination revealed an edematous leg with multiple painless coalescent verrucous skin-colored papules with a smooth or hyperkeratotic surface on the left lower leg surrounding an ulceration 10 × 5 cm in size (Fig. 1). The lesions were associated with oozing. A skin biopsy revealed hyperkeratosis, verrucoid acanthosis, and papillomatosis of the epidermis with moderate perivascular inflammatory infiltration of the dermis (Fig. 2). A diagnosis of PCL was reached based on histopathological and clinical findings. The patient received lymphatic drainage and locally 5% salicylic acid.

DISCUSSION

Normally, PCL results from primary or secondary lymphedema or from damage to lymphatic vessels by metabolic diseases, chronic infections, or venous insufficiency [1]. Obstruction of lymphatic drainage causes an excess of protein in the affected regions, inducing fibroblast proliferation and increasing

How to cite this article: Daldoul M, Aounallah A, Mokni S, Tlili T, Sriha B, Belajouza C, Denguezli M. Papillomatosis cutis lymphostatica: a sign of chronic edema. Our Dermatol Online. 2021;12(2):169-170.

Submission: 27.05.2020; **Acceptance:** 01.08.2020

DOI: 10.7241/ourd.20212.16

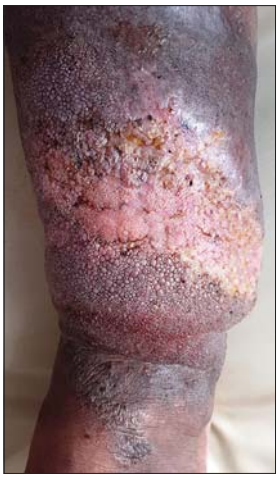

Figure 1: A papillomatous skin-colored lesion on the left leg.

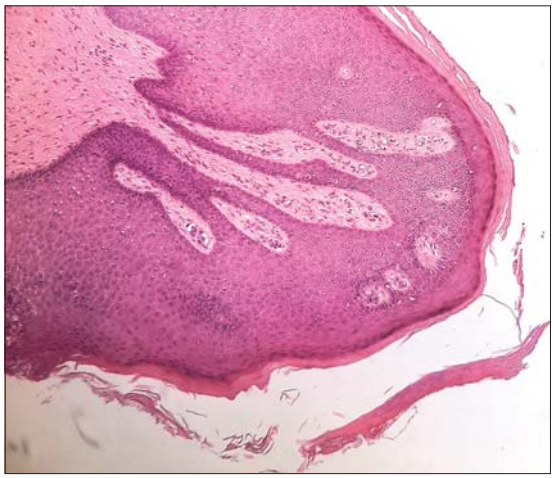

Figure 2: A biopsy of the papillomatous lesion showing hyperkeratosis, verrucoid acanthosis, and papillomatosis of the epidermis.

the recurrence of infections [2]. Also, alteration of the lymph flow leads to the formation of dilated and congested dermal collaterals. The most typical locations are the legs, feet, toes, and around venous ulcers.

The use of compression stockings is the cornerstone of conservative management. Topical and oral retinoids have shown therapeutic efficacy in many cases reported by interfering with epidermal proliferation and inflammation [3-5].

Topical keratolytic agents can be an option. Surgical interventions and CO_2 laser excision might be performed if other treatments fail.

CONCLUSION

As far as we know, few cases of PCL have been reported, and PCL remains a vulnerable area in the occurrence of infection and neoplasia. We insist on the importance of its early recognition to prevent complications.

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

The initial impact of low-level laser therapy on a traumatic leg ulcer

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ABSTRACT

Low-level laser therapy (LLLT) has been used as an effective, safe, and noninvasive treatment for wound healing. This paper reports the case of a 78-year-old female who had suffered trauma to the anterior tibial region of the leg. The injury continued to worsen for a month, along with an increase in pain, even with medical treatment involving antibiotics and conventional bandaging. An examination revealed a hyperemic injury with secretions, and LLLT was proposed, with red laser at 3 J and 660 mW and for a 25 s exposure time. The patient returned after four days reporting a substantial improvement in both the pain and the wound. Low-level laser therapy (LLLT) proved effective at controlling pain and improving the healing of a traumatic ulcer that had been worsening with conventional treatment.

Key words: Low-level laser therapy; Traumatic leg ulcer; Treatment

INTRODUCTION

Low-level laser therapy (LLLT) has been used as an effective, safe, and noninvasive treatment for wound healing. This therapeutic modality accelerates the healing process by stimulating microcirculation, the proliferation of fibroblasts, the formation of granulation tissue, the synthesis of collagen, and the modulation of the immune system [1,2].

According to a review study, a variety of light sources, such as LEDs and lasers, have been used, each with specific advantages and limitations. However, there is no consensus on treatment parameters, such as wavelength and dose, and different results are reported in the studies reviewed [3]. One study reports a significant reduction in pain in ulcers treated with LLLT [4]. Another study, on the other hand, states that this treatment modality is not an efficient method for the treatment of venous ulcers on the legs [5].

LLLT is considered an effective complementary treatment, especially for inflammation and wounds from skin injuries [6]. Positive effects include acceleration of the tissue repair process, an increase in the formation of granulation tissue, contraction of the wound, modulation of the inflammation, and a reduction in pain [7]. The aim of this study was to report the change in the evolution of a traumatic leg ulcer with the administration of low-level laser therapy.

CASE REPORT

This paper reports the case of a 78-year-old female who had suffered trauma to the anterior tibial region of the leg. The injury continued to worsen for a month, along

How to cite this article: Pereira de Godoy JM, Pereira de Godoy LM, Pacheco EF, Guerreiro Godoy Mde F. The initial impact of low-level laser therapy on a traumatic leg ulcer. Our Dermatol Online. 2021;12(2):171-173.

Submission: 02.09.2020; **Acceptance:** 05.12.2020

DOI: 10.7241/ourd.20212.17

with an increase in pain, even with medical treatment involving antibiotics and conventional bandaging. The patient consulted us on February 27. An examination revealed a hyperemic injury with secretions (Fig. 1), and LLLT (Eco Reability / Ecco Fibras) was proposed, with red laser at 3 J and 660 mW and a 25 s exposure time (Table 1). Besides the laser, conventional bandaging was maintained. The patient returned after four days, on March 3, reporting a substantial improvement in both the pain and the wound (Fig. 2). A substantial improvement was noted in the hyperemia, along with a reduction in the size of the ulcer and the formation of a fibrin film on the wound. Another session of LLLT was performed and the patient was instructed to leave the wound uncovered, allowing the fibrin film to serve as a biological bandage. After seven days, on March 9, the patient returned without pain and with a substantial improvement in the wound (Fig. 3). The patient returned again on March 16 with the wound healed almost completely (Fig. 4). This study was approved by the Ethics and Research Committee of Faculdade de Medicina de São José do Rio Preto (FAMERP), Brazil (#4.027.569).

DISCUSSION

This study observed a remarkable change in the evolution of a traumatic ulcer in the tibial region. There is no consensus, in the literature, on the laser treatment for ulcers, and a wide range of parameters are reported, which may compromise the results. Some effects of LLLT are well-reported, such as improvement in pain, as in our case. The patient was taking an analgesic three times a day, but only needed to take it once in the four days after the first laser therapy session. The mechanism of the reduction in pain that was proposed is a hormonal or opioid response dependent on the wavelength and dose.

We standardized the wavelength parameter to enable better evaluation of the results and to identify the

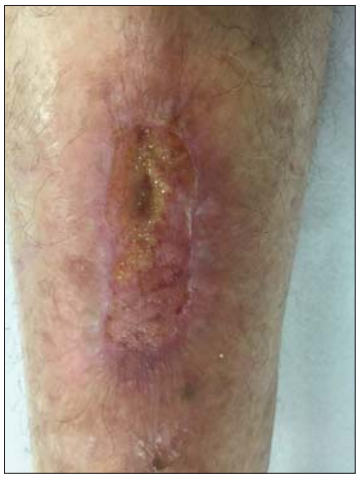

Figure 1: The first examination revealed a hyperemic injury with secretions.

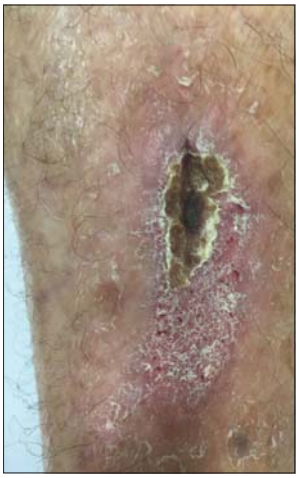

Figure 3: A substantial improvement of the wound.

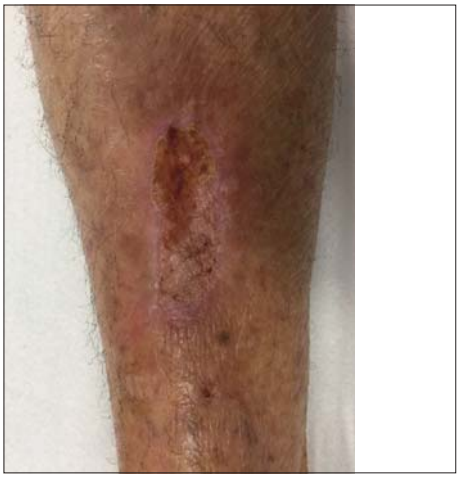

Figure 2: A substantial improvement in both the pain and the wound.

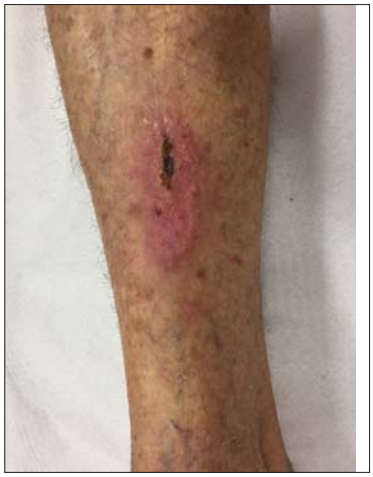

Figure 4: The wound healed almost completely.

Table 1: Laser parameters.

Apparatus	Eco Reability (Ecco Fibras)
Wavelength	660 nm
Form of application	Punctual
Power	3 × 100 mW
Energy	3 J by point
Total energy on the emitter surface	9 J (3 emitters, 3 J each)
Emitter surface	9 cm^2 (1,5 × 3 cm)

best option for each ulcerated injury. Another striking aspect of this case was the change in the evolution of the wound, which had been worsening steadily prior to LLLT and improved abruptly with this therapeutic modality (Figs. 1 – 4). The only change to the original treatment was the addition of LLLT. On the patient's first return to the clinic, she reported a reduction in pain and there was a substantial improvement in the wound, along with the formation of a fibrin film on the entire ulcer. Thus, the decision was made not to continue bandaging.

The improvement in hyperemia suggests that LLLT modulated the inflammatory process. The injury had no venous components and was located in the proximity of the tibia, which explains the difficulty in healing with conventional bandaging. These findings suggest that LLLT may be a complementary therapy for such patients.

The literature offers conflicting results regarding the efficacy of LLLT. Moreover, there is a fundamental need to standardize the parameters of LLLT. This was one of our objectives, and more studies are being undertaken to improve our understanding of laser therapy.

CONCLUSION

Low-level laser therapy proved effective at controlling pain and improving the healing of a traumatic ulcer that had been worsening with conventional 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 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 corporis diffusum universale: A rare case report from Nepal

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ABSTRACT

Angiokeratoma corporis diffusum universale, a clinical variant of angiokeratoma, is a generalized vascular ectasia that is associated with overlying epidermal changes rather than a true vascular neoplasm. It is the cutaneous hallmark of several rare inherited lysosomal diseases associated with specific enzyme deficiencies in the metabolism of glycoproteins. Herein, we present possibly the first case report from Nepal of angiokeratoma corporis diffusum universale in a 14-year-old female from consanguineous parents who presented herself with characteristic clinical and laboratory features of angiokeratoma corporis diffusum with progressive mental and motor developmental delay along with seizures, dystonia, and recurrent chest infections. Resource constraints limited confirmation with an enzyme assay and electron microscopy. We report this unusual case with the intention of re-emphasizing the importance of clinical evaluation in reaching a diagnosis in a resource-deficient setting.

Key words: Angiokeratoma corporis diffusum; Fabry's disease; Fucosidosis; Nepal; Vascular ectasia

INTRODUCTION

Angiokeratomas are rare vascular ectasias with epidermal changes rather than true vascular neoplasms. These malformations clinically present themselves as single or multiple dark red to black papules, nodules, or plaques and histologically by superficial ectatic vessels with epidermal proliferation. Angiokeratoma corporis diffusum (ACD) is its diffuse involvement, typically on the lower trunk, buttocks, and thighs, usually associated with an enzyme deficiency in the metabolism of glycoproteins. For years, the term has been used interchangeably with Fabry's disease, a systemic X-linked disease caused by a deficiency in the enzyme α-galactosidase A [1]. Angiokeratoma corporis diffusum, known to occur in several enzyme deficiency diseases involved in the metabolism of glycoproteins, such as fucosidosis, sialidosis, mannosidosis, gangliosidosis, and Kanzaki disease, is a multisystem disorder [2].

CASE REPORT

We report the case of a 14-year-old female from consanguineous parents who presented herself with recurrent episodes of fever and chest infections along with severe neurodevelopmental delay. According to the parents, the patient had had development regression since two years of age and delayed milestones in all domains. Besides, no language skills were present and vocal sounds lacked meaning. She was also showing features of seizures and myoclonic jerks. She was bedbound for six years with plasticity and generalized dystonia. A cutaneous examination revealed diffuse multiple erythematous papules and plaques of angiokeratoma over the lower back, abdomen, genitalia, and extremities (Figs. 1a and 1b). She also had coarse facies, a pigeon chest, a widened wrist elbow, and knee and ankle contractures. There was no similar family history. The clinical pictures of angiokeratoma corporis diffusum, neuroregression, spasticity, dystonia, coarse facies, dysostosis multiplex, and hepatomegaly, were

How to cite this article: Paudel V, Chudal D. Angiokeratoma corporis diffusum universale: A rare case report from Nepal. Our Dermatol Online. 2021;12(2):174-176.
Submission: 26.06.2020; **Acceptance:** 01.10.2020
DOI: 10.7241/ourd.20212.18

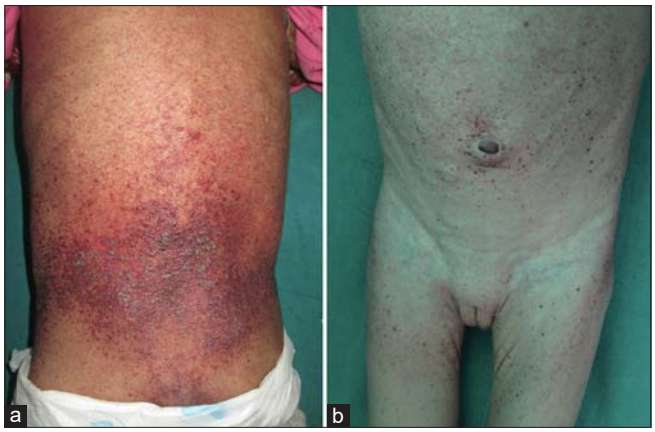

Figure 1: (a) The posterior trunk showing diffuse involvement of pink papules and plaques. (b) The anterior trunk showing multiple but spare dark dome-shaped papules.

suggestive of fucosidosis. Lab parameters revealed severe anemia with hemoglobin at 4.8 g/dL and a high erythrocyte sedimentation rate at 45 mm/h with normal liver, kidney, and thyroid function. Enzyme levels could not be tested because of economic constraints. Histology showed vascular ectasia with marked dilatation of papillary dermal vessels, which formed large cavernous channels, and a superficial hyperkeratotic epidermis enclosing vascular channels (Fig. 2).

DISCUSSION

The term *angiokeratoma* describes variably-sized hyperkeratotic papules that range in color from deep red to bluish-black. Histopathologic alterations include ectasia of the upper dermal vessels with overlying epidermal hyperkeratosis [3]. Angiokeratoma corporis diffusum universale is a generalized variant of angiokeratoma, usually associated with an enzyme deficiency in the metabolism of glycoproteins [1]. Since the original independent descriptions by Anderson and Fabry in 1898, it has been recognized as a systemic disease rather than a dermatological curiosity. It is commonly seen in Fabry's disease, fucosidosis, sialidosis, mannosidosis, gangliosidosis, or without an enzyme deficiency. Fabry's disease is X-linked recessive, whereas the others are autosomal recessive disorders [4]. In fucosidosis, defects lead to intracellular accumulation of fucose-containing glycolipids and glycoproteins in various organs, leading to progressive mental and motor deterioration, coarse facies, recurrent infections, dysostosis multiplex, angiokeratoma corporis diffusum, visceromegaly, and seizures [5]. In our case, the typical clinical features of angiokeratoma corporis diffusum with consanguinity and neuroregression, spasticity, dystonia,

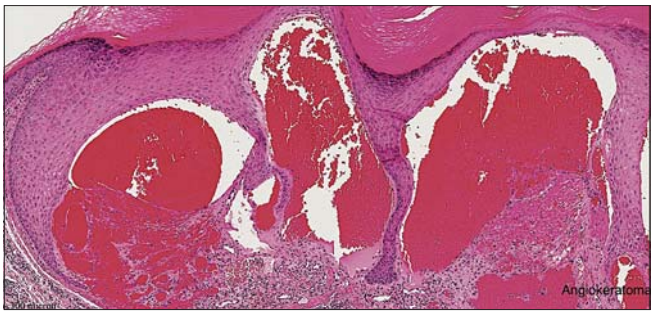

Figure 2: Histology of angiokeratoma showing ectasia of the upper dermal vessels with overlying epidermal hyperkeratosis.

coarse facies, dysostosis multiplex, and hepatomegaly were suggestive of fucosidosis. The complexity of Fabry's disease demands a multidisciplinary therapeutic approach. There have been case reports unaided by electromicroscopic or biochemical analysis intended to re-emphasize the importance of clinical evaluation in reaching a diagnosis in a resource-deficient setting [6,7]. The role of dermoscopy has also been recently regarded as a noninvasive technique of diagnosis of angiokeratoma [8]. Ours could be the first reported case of angiokeratoma corporis diffusum from Nepal accompanied by various morbidities and systemic manifestations.

CONCLUSION

Angiokeratomas are hyperkeratotic vascular ectatic lesions that may either be localized or diffuse. There has been only a handful of reports on angiokeratoma corporis diffusum in the dermatologic literature. Thus, if a diffuse form of angiokeratoma is encountered, efforts should be made to search for systemic involvement together with a multidisciplinary approach employed.

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

An axillary granular cell tumor: A rare neoplasm at an unusual site

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ABSTRACT

A granular cell tumor (GCT) is a rare neoplasm occurring usually in submucosal and subcutaneous tissues anywhere in the body, affecting mainly the head and neck. GCTs at unusual anatomic sites, such as the breast or the axillary extension, could be taken for invasive carcinoma. We report the case of a 30-year-old male who presented himself with an axillary nodule. A physical examination revealed a firm and painless subcutaneous tumor on ulcerated skin. Lymphoma and lymph node metastasis were suspected. An imaging survey was negative outside the axillary nodule. The tumor was surgically removed. A microscopic examination showed the typical features of a benign GCT. Surgical margins were negative. No recurrence has been observed within a 6-month follow-up period. A GCT can mimic a malignancy since it presents itself as an axillary nodule, and requires complete surgical resection with clear margins.

Key words: Granular cell tumor; Abrikossoff; Axillary; Malignancy

INTRODUCTION

Granular cell tumors (GCTs) are rare [1-6], first described by Abrikossoff in 1926 [7]. Immunohistochemical and ultrastructural studies have demonstrated their Schwannian differentiation [8]. A slight female to male and black to white predominance exists [1,3,6,9,10]. GCTs occur in adults between the fourth and sixth decade of life [3,7,10,11]. They develop mainly in the head and neck. As for the oral cavity, the tongue is most affected in up to 65% of cases [1,3,6,9,10,12,13]. Cases of GCTs of the digestive tract, back, and vulva have been reported as well [1,3,4,11,14-16]. The pathogenesis of the GCT has not yet been elucidated [1,6,12]. GCTs may also develop at unusual anatomic sites and can, therefore, be taken for other tumors, essentially malignant. The breast and axillary extension are unusual sites also affected by GCTs in almost 5–8% of cases [5,6,13,17,18]. Such a tumor can clinically and/or radiographically mimic an invasive carcinoma.

Herein, we report a new case of an axillary GCT in a young male patient.

CASE REPORT

A 30-year-old male patient without a particular medical history presented himself to the department of dermatology with an axillary nodule. A physical examination revealed a firm painless axillary subcutaneous tumor on ulcerated skin, initially presumed to be a lymphoma or a metastatic lymph node. An imaging survey and laboratory tests were within normal limits. The nodule was surgically removed. Upon gross examination, it was a mass 1 cm in diameter. A microscopic examination revealed a well-circumscribed proliferation occupying the dermis. The overlying epidermis showed pseudoepitheliomatous hyperplasia and was focally ulcerated. Large and polygonal tumor cells had abundant eosinophilic and granular cytoplasm with small nuclei in a central position (Fig. 1). There was no nuclear pleomorphism or tumor necrosis. The tumor cells stained positively for S100 (Fig. 2). Surgical margins were clear. No recurrence has been observed within a 6-month follow-up period.

How to cite this article: Msakni I, Khemir A, Gargouri F, Mansouri N, Tlili K, Laabidi B. An axillary granular cell tumor: A rare neoplasm at an unusual site. Our Dermatol Online. 2021;12(2):177-179.

Submission: 22.05.2020; **Acceptance:** 25.08.2020

DOI: 10.7241/ourd.20212.19

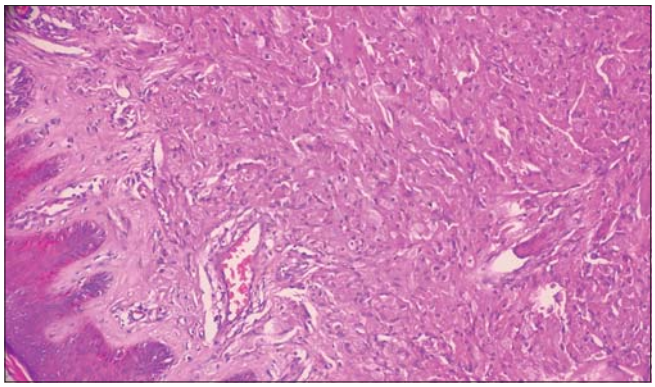

Figure 1: A benign tumor occupying the dermis, made of medium-sized cells with abundant and granular cytoplasm and regular nuclei (insert x 400) (H&E, 100×).

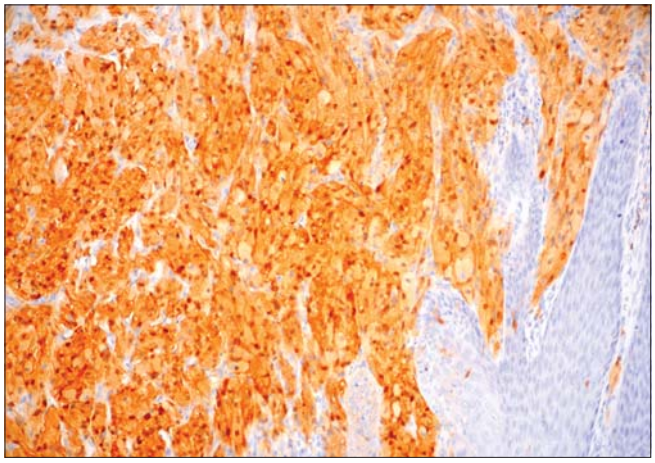

Figure 2: The diffuse positivity of tumor cells for S100 immunostaining (H&E, 100×).

DISCUSSION

GCTs are rare nonmelanocytic tumors with Schwannian differentiation [1-6], usually reported as benign slow-growing tumors [1,3,5,12]. They affect the breast and axillary extension in almost 5–8% of cases. Clinically, GCTs present themselves as asymptomatic isolated nodules less than 4 cm in diameter, as in our case. However, around 5% of patients may show multiple nodules [1,4,9]. Most of them are sporadic [3,6]. Other symptoms, such as pruritus and pain, have been reported [11,16]. Malignancy is suspected in cases at unusual anatomic sites, rapidly growing masses more than 5 cm in diameter, and skin ulcerations [1,5,6,10,12]. In our case, the clinical presentation was challenging because the isolated axillary nodule with ulcerated skin mimicked a malignancy. Such diagnostic pitfalls have been reported in many cases of GCTs of the breast and axillary extension. The GCT mimicked an invasive carcinoma clinically and radiographically [2,5,6].

Histologic diagnosis of GCTs is usually unchallenging. These tumors present themselves as well-circumscribed or infiltrative proliferations polygonal in shape with abundant and granular cytoplasm. Their nuclei are small and have a central position. GCTs are usually separated by thin bands of connective tissue [1,4-6,9,10,12], and, although they are usually reported as benign, malignant forms exist, even if rare, accounting for less than 3% of all cases of GCTs reported in the literature [7,9,10,12]. Most cases of GCTs in the breast and axillary region were histologically diagnosed as malignant GCTs [8,18,19]. The unique criteria confirming malignancy is the presence of metastasis [7]. However, some classification systems have been established to predict the malignant potential of GCTs. Fanburg-Smith et al. were the first to establish a classification system of six items defining three categories of GCTs: benign, malignant, and atypical [7,10,12]. In order to refine this classification, Nasser et al. reviewed 48 cases of GCTs, concluding that necrosis and mitotic activity were most correlated with malignancies. They also showed that Ki67 may be helpful in cases difficult to classify [7]. Conventional GCT cells stain positively for S100, CD68, and neuron-specific enolase [1,6,10,11]. Immunohistochemistry is of great help to rule out differentials and mimickers of GCTs, such as atypical fibroxanthoma, rhabdomyoma, dermatofibroma, and hibernoma [7]. Benign GCTs require surgical removal with negative margins to prevent recurrence [1,2,5,7]. Malignant forms with metastases complicate survival and increase mortality rates, which may reach 40% [4,7,12]. The benefits of adjuvant therapies after surgical excision have not been proven so far [12].

To conclude, the clinical presentation observed in our case eventually confirmed the diagnosis of malignancy. The negative results of the imaging survey and laboratory tests prompted surgical removal of the tumor mass. A diagnosis of a benign GCT with negative margins was reached and spared our patient from overtreatment.

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

Temporal primary cutaneous carcinosarcoma in the ear: A case report

Issam Msakni[1,3], Aya Khemir[1,3], Nada Mansouri[1,3], Karima Tlili[1,3], Faten Gargouri[1,3], Ghassen Chebbi[2,3], Besma Laabidi[1,3]

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ABSTRACT

Carcinosarcoma is a rare biphasic tumor made of two malignant components—the epithelial component and the stromal component—that can develop anywhere on the body, but mainly in sun-exposed areas. We report the case of a 78-year-old male who presented himself with a right temporal tumor in the ear 10 cm in diameter. A biopsy suggested a sarcoma. The patient underwent an extensive surgical resection of the temporal mass and the ipsilateral ear. A microscopic examination of the tumor revealed two intermixed malignant contingents. The epithelial component was made of atypical basaloid cells arranged in nests with peripheral palisading and expressing cytokeratin. The stromal component was made of atypical spindle cells expressing smooth muscle actin (SMA). A diagnosis of primary cutaneous carcinosarcoma with clear margins was reached. The patient is alive and without recurrence after twelve months of a follow-up period.

Key words: Cutaneous carcinosarcoma; Metaplastic carcinoma; Prognosis

INTRODUCTION

Carcinosarcoma is a rare biphasic tumor made of two malignant components—the epithelial component and the stromal component [1-5]—also referred to as metaplastic carcinoma [6,7], with a male-to-female predominance. Carcinosarcoma affects elderly patients, appearing anywhere on the body [1,4-7]. The first case of cutaneous carcinosarcoma (CC) was described in 1972 [8]. CC occurs in the head and neck, but mainly in the face, scalp [1], forearms, and all other sun-exposed areas of the body [7]. The tumor can grow slowly or increase rapidly in size [5]. The current recommended treatment of CC is complete surgical excision [1,9]. Its prognosis is poorly defined given its rarity: only 120 cases of CC have been reported in the literature [7]. We report a new case of a primary CC in a 78-year-old male patient.

CASE REPORT

A 78-year-old male presented himself with a right temporal tumor mass. A physical examination revealed an ulcerative and infiltrative tumor mass, large and extensive, eroding the right ear below. The physical examination was otherwise normal and there was no notable lymphadenomegaly. An imaging survey was normal outside the temporal tumor. Laboratory tests were within normal limits as well. The tumor mass was biopsied. A pathological examination led to the diagnosis of sarcoma. Therefrom, the patient underwent extensive surgical excision of the tumor and the right ear. A gross examination showed an ulcerative tumor, 10 cm in diameter, infiltrating the underlying skin layers. The right ear was eroded by the tumor in its upper portion. A large sampling was made, and a microscopic examination revealed a biphasic malignant proliferation. The tumor was made of two components: an epithelial and a mesenchymal. The epithelial component was made of nests of atypical basaloid cells with peripheral palisading (Fig. 1), reminiscent of the features of basal cell carcinoma. The nests were intermixed with the sarcomatous component, which was made of atypical spindle cells organized in a storiform pattern (Fig. 2). Immunohistochemical

How to cite this article: Msakni I, Khemir A, Mansouri N, Tlili K, Gargouri F, Chebbi G, Laabidi B. Temporal primary cutaneous carcinosarcoma in the ear: A case report. Our Dermatol Online. 2021;12(2):180-182.

Submission: 22.05.2020; **Acceptance:** 16.08.2020

DOI: 10.7241/ourd.20212.20

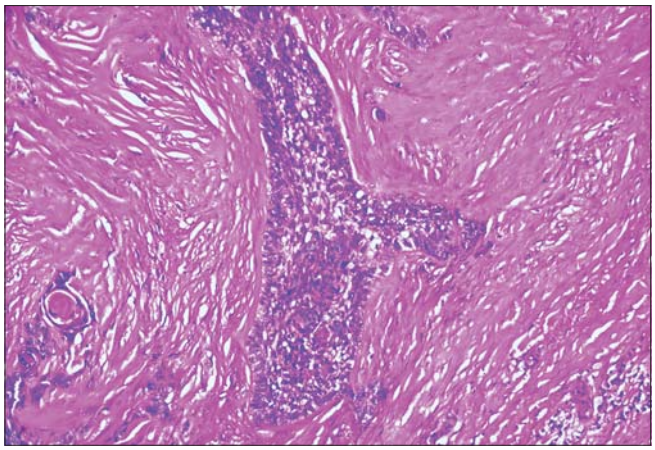

Figure 1: Atypical basaloid cells in the epithelial contingent arranged in cords, showing peripheral palisading reminiscent of the features of basal cell carcinoma (H&E, 10×).

staining showed a positivity of the tumor cells in the epithelial contingent for cytokeratin and a negativity for epithelial membrane antigen (EMA) and smooth muscle actin (SMA). The mesenchymal contingent showed a diffuse positivity for SMA and cytokeratin (Fig. 3) and a negativity for EMA.

The diagnosis of primary cutaneous basal cell carcinosarcoma was upheld. Surgical margins were clear. The patient is alive without recurrence after a 12-month follow-up period.

DISCUSSION

Carcinosarcoma is a rare biphasic tumor [1-5]. The term *carcinosarcoma* was first proposed in 1864 [10]. Carcinoma affects elderly patients [1,5-7] and may develop anywhere on the body: in the skin, uterus, lung, or digestive tract [1,4,5]. The first case of CC was described in 1972 [8]. As far as we know, only 120 cases of CC have been reported in the literature [1]. CC occurs in the head and neck, but mainly in the face and scalp, as in our case [1], as well as in the forearms and other sun-exposed area of the body [7]. The tumor can grow slowly or increase rapidly in size [5]. Its development in sun-exposed areas explains the existence of squamous dysplasia in areas adjacent to the carcinosarcoma, reminiscent, thus, of sun-induced skin damage [1]. The presence of such lesions may help if a metastatic origin is suspected. CC can be secondary to a carcinosarcoma of the gastrointestinal tract or bones. The skin is an infrequent site for gastrointestinal or bone cancer metastases but makes prognosis difficult if affected.

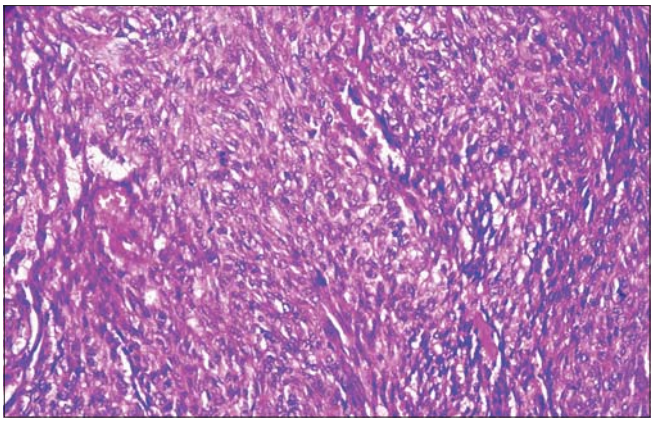

Figure 2: Atypical spindle cells in the stromal contingent arranged in a storiform pattern (H&E, 10×).

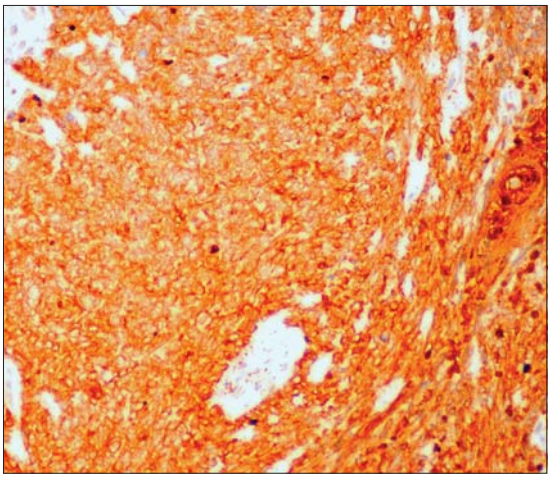

Figure 3: Tumor cells in the stromal component with a marked diffuse positivity for cytokeratin antibody (H&E, 10×).

Morphologically, the tumor is biphasic and made of two adjacent or intermixed malignant components: the epithelial component and the heterologous stromal component [1]. Due to its heterogeneity, such a tumor necessitates large sampling not to misdiagnose it simply as a carcinoma or sarcoma. Cases of CC misdiagnosed as the spindle cell variant of squamous cell carcinoma or atypical fibroxanthoma due to insufficient sampling have been reported. Besides, it can be confused with differentials such as leiomyosarcoma, fibrosarcoma, and other mesenchymal malignancies, especially if the stromal component is predominant, as in the case of our patient [1].

The pathogenesis of carcinosarcoma has not yet been well understood [2]. The same chromosomal changes have been identified in both the stromal and epithelial components [7]. A study by Kwak et al. reviewed 11 cases of carcinosarcoma in Korean patients. The epithelial component stained positively for epithelial markers in

all cases. The stromal component stained positively for epithelial markers in 63% of cases, as in our study, where the stromal contingent stained positively for cytokeratin [1]. These results were in favor of the dated hypothesis suggesting that the stromal component is a divergence of the epithelial component [7].

Surgical excision is the current recommended treatment for CC, but there are no well-defined sufficient surgical margins reported in the literature [1,9]. Excised tumors recur often [3].

Given the rarity of CC, its prognosis is poorly known [7]. However, a relatively better prognosis for the group of basal cell carcinosarcomas has been reported [3]. A study by Tran compared two groups of patients diagnosed with CC. The subdivision into groups was according to the histological type derivation of the epithelial component. In the first group, the epithelial component was of the epidermal type (squamous or basal malignant component). In the second group, the epithelial component was of the adnexal type (including spiradenocarcinoma and porocarcinoma). The conclusion was that the patients from the first group were older and had a better prognosis. In contrast, the patients from the second group were younger but a had poorer prognosis [5,6].

CC is a rare and aggressive malignancy that develops in sun-exposed areas of the body, affecting elderly male patients. Cases of CC reported in the literature appeared mostly in the head and neck. Its pathological diagnosis is challenging because of its rarity. It can easily be misdiagnosed as a sarcoma or carcinoma especially due to insufficient sampling. In some cases, and despite large sampling, the diagnosis of CC remains challenging because one of the two malignant contingents—either epithelial or stromal—may be predominant and conceal the other, for which immunohistochemical staining may be of great help. Surgical excision with negative margins is recommended to prevent recurrences. The prognosis is not yet well-defined, given the limited number of cases studied in the literature so far.

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

Primary essential cutis verticis gyrata: A case report

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ABSTRACT

Cutis verticis gyrata (CVG) is a rare condition of the scalp characterized by convoluted folds and furrows produced by the excessive growth of the skin of the scalp and resembling the cerebral gyri. CVG can be identified as primary—essential or nonessential—or secondary. Herein, we report the case of a 20-year-old female with primary essential CVG, who presented herself with thickened and convoluted skin folds over the vertex and parietal region of the scalp persistent for one year prior without other symptoms. CVG is a rare congenital or acquired disease distinguished by redundancy of the scalp skin that resembles the cerebral gyri. The management of primary essential CVG can be symptomatic or surgical depending on the patient's aesthetic expectations.

Key words: Cutis verticis gyrata; Scalp dermatoses; Rare

INTRODUCTION

Cutis verticis gyrata (CVG) is a rare disease characterized by the excessive growth of the skin of the scalp, resulting in furrows and folds that resemble the gyri of the brain cortex [1,2]. Depending on its form, CVG can be identified as primary—essential or nonessential—or secondary [2]. Primary nonessential CVG is associated with neurological and ophthalmological manifestations while primary essential CVG is not. The secondary form of CVG is much more frequent and accompanies other pathologies [3]. There have been around 28 cases of primary essential CVG described in the literature. We report a case of primary essential CVG in a young female.

CASE REPORT

A 20-year-old female presented herself with a history of thickened and prominent skin folds over the vertex and parietal region of the scalp persistent for one year prior (Fig. 1). No other symptoms were reported. A physical examination revealed enlargement of the skin folds of the scalp arranged in a vertical position.

There was no history of comorbidity, no family history of similar lesions, and no history of consanguinity. The patient reported no neurological or ophthalmological symptoms. Neurological, psychiatric, ophthalmological, and endocrine consultations were obtained and, to exclude secondary causes, a complete blood count, a thyroid function test, and syphilis screening were done and the levels of growth hormone, follicle-stimulating hormone, luteinizing hormone, and serum cortisol were checked, all of which reported normal values. MRI of the brain revealed a thickened scalp with marked ridges and furrows of a gyriform appearance in the parietooccipital region, suggestive of cutis verticis gyrata with no underlying defects. As the clinical picture was pathognomonic of CVG, a skin biopsy and histopathology were deemed unnecessary.

DISCUSSION

Cutis verticis gyrata (CVG), also known as cutis sulcata, cutis capitus strata, cutis verticis plicata, or the "bulldog scalp," was first described in 1837 by Jean-Louis-Marc Alibert, and the term *cutis verticis gyrata* was proposed by Unna in 1907 [1,4]. Depending on its form, CVG can be identified as primary or secondary (Fig. 2) [3].

Primary CVG refers to cases with no underlying cause [4], beginning after puberty, usually before

How to cite this article: Mainali P, Joshi S. Primary essential cutis verticis gyrata: A case report. Our Dermatol Online. 2021;12(2):183-185.
Submission: 22.05.2020; **Acceptance:** 13.08.2020
DOI: 10.7241/ourd.20212.21

the age of thirty, and occurring predominantly in males, with a male-to-female ratio of 5:1. Primary CVG is divided further into two types: essential and nonessential (Fig. 2) [4,5].

The essential form, exhibited by our patient, is a rare disorder characterized by the thickening of the scalp, where the excess skin folds are symmetrical and take the shape of the cerebral gyri. There is no underlying neurological or ophthalmological association [1].

The nonessential form is associated with neurological (epilepsy, intellectual disability, microcephaly), psychiatric (schizophrenia), and ophthalmic (cataract, strabismus, blindness, retinitis pigmentosa) disorders [1,4].

Secondary CVG is more common than primary CVG, can occur at any age, and displays no gender predilection. Secondary CVG has a number of underlying causes [5]. Several sources explain that the secondary form may develop after inflammatory dermatosis, endocrine and genetic disorders, and internal malignancies as paraneoplastic syndrome (Table 1) [1,6].

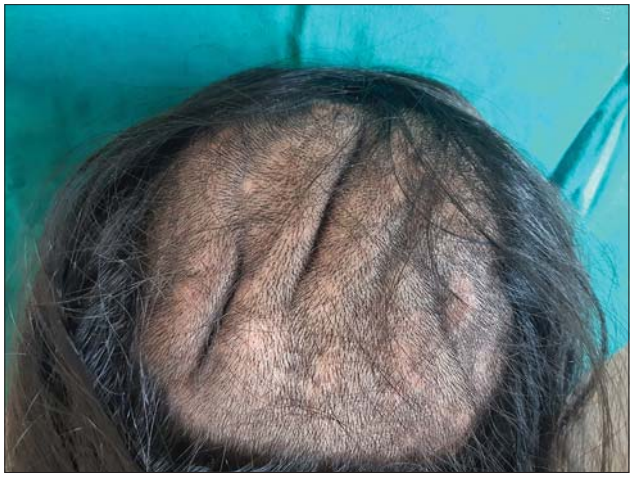

Figure 1: Scalp hypertrophy with anteroposterior folds in the vertex and occipital region of the head.

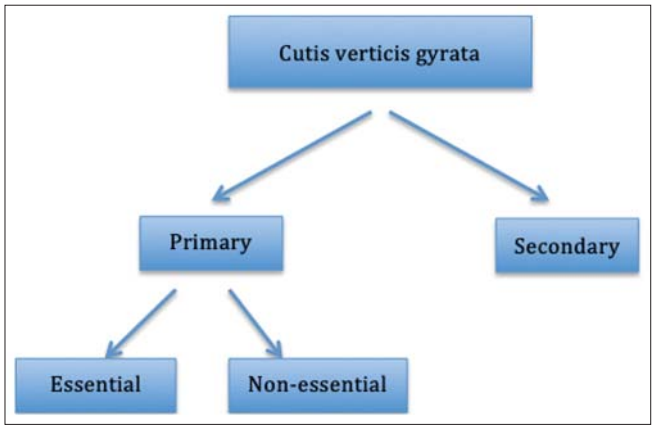

Figure 2: The classification of cutis verticis gyrata (CVG).

CVG usually affects the vertex and the occipital scalp, and may sometimes involve the entire scalp. Generally, the folds are arranged in an anteroposterior direction but may be transverse on the occiput [5]. CVG is usually asymptomatic but the patient may sometimes complain of pruritus, a burning sensation, malodor, and thinning of the hair in the folded areas due to aggregation of debris and skin secretions in the folds [7].

The diagnosis of CVG is based on clinical findings but investigations are necessary to distinguish between primary and secondary CVG [5].

The treatment of primary essential CVG depends on the patient's aesthetic expectations, since no organic function

Table 1: Diseases associated with CVG

Type of CVG	Associated conditions
Primary [1,6]	
Essential	No associated abnormalities
Nonessential	Mental deficiency, cerebral palsy, seizures, microcephaly, ophthalmological abnormalities (cataract, optic atrophy, strabismus, blindness, retinitis pigmentosa)
Secondary [1,4,6,7]	
(local underling process, usually asymmetric, onset at any age)	
Infectious diseases	Folliculitis, erysipelas, impetigo, syphilis
Inflammatory disorders	Eczema, scalp psoriasis, keloidal acne
Inherited diseases	Klinefelter syndrome Turner syndrome Noonan syndrome Ehlers–Danlos syndrome Michelin tire baby syndrome Fragile X syndrome Beare–Stevenson syndrome Tuberous sclerosis
Tumors	Neurofibromatosis Cylindroma Lymphangioma Leukemia Pituitary tumor Intracerebral aneurysm Dermatofibroma
Nevi	Melanocytic nevus Lipomatous nevus Sebaceous nevus Cerebral intradermal nevus
Endocrine	Acromegaly Myxedema Diabetes mellitus type 2
Miscellaneous	Drugs (anabolic steroids) Chronic traction Acanthosis nigricans Trauma Acne conglobata Pachydermoperiostosis Amyloidosis Mucinosis

needs to be corrected. Local hygiene is important to prevent the accumulation of secretions with an unpleasant odor [8]. Surgical treatment may be considered to remove excess skin folds with the aim to achieve a more aesthetically satisfying appearance of the scalp. In our case, CVG was easily concealed by the patient's long hair. She was counseled regarding the benign nature of her condition and informed about the possibility of secondary infection due to the trapping of debris in the depressions. Explained to her was also the importance of local hygiene and attending regular follow-ups.

CONCLUSION

Primary essential CVG is an extremely rare condition, with around 253 cases of CVG and 28 cases of primary essential CVG reported in the literature. Because it is a rare condition, our case appears as a valuable educational opportunity. A dermatologist finding cases such as ours should take a proper medical history and perform careful examinations and complementary investigations to reach a definitive 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 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

Solitary nodule on the forearm

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ABSTRACT

Herein, we report the case of a 58-year-old male who presented himself with a single, slowly progressive, asymptomatic lesion on the right forearm persistent for the last three years. Clinical evaluation revealed a single firm reddish nodule. Histopathological findings from a complete excision revealed a lipidized dermatofibroma, which was characterized by the accumulation of numerous foamy cells dissected by distinctive hyalinized wiry collagen fibers and the presence of foamy macrophages. Lipidized dermatofibroma—a rare variant of dermatofibroma—must be considered in the differential diagnosis of fibrohistiocytic lesions.

Key words: Lipidized dermatofibroma; Touton-type giant cells; Fibrous hystiocytoma; Ankle-type

INTRODUCTION

Dermatofibroma (DF), also known as benign fibrous histiocytoma, is a soft-tissue tumor usually occurring in middle-aged adults and showing a slight female predominance. The typical dermatofibroma generally occurs as a single or multiple skin-colored to reddish-brown or dark-brown firm nodule located most commonly on the lower legs [1]. While its diagnosis poses little trouble in the presence of classical clinicopathological features, a dermatofibroma may show a wide variety of clinicopathological variants and, therefore, its diagnosis may become difficult. The lipidized dermatofibroma represents a rare variant of dermatofibroma. Herein, we report a typical case of this type of tumor.

CASE REPORT

A 58-year-old male presented himself with a single, slowly progressive, asymptomatic lesion on the right forearm persistent for the last three years. Past medical and family history was unremarkable. A clinical examination revealed a well-circumscribed erythematous nodule 15 mm in diameter (Fig. 1). The lesion, which was tender and firm on palpation, was excised under local anesthesia. Histological evaluation revealed mild epidermal acanthosis and basal pigmentation. The dermis showed a cellular proliferation of foam cells and histiocytes surrounded by hyalinized collagen bundles. Touton giant cells were also observed in some parts of the tumor (Fig. 2). These histopathologic findings led to the diagnosis of lipidized fibrous histiocytoma—one of the rare subtypes of DF.

DISCUSSION

Dermatofibroma (DF) is one of the most common types of cutaneous soft-tissue lesions [1]. The typical dermatofibroma generally occurs as a single or multiple firm reddish-brown nodule. It usually occurs on the lower extremities of young to middle-aged females [1]. Apart from its classical features, different variants have been described. Lipidized fibrous histiocytoma is a rare variant of dermatofibroma that represents approximately 2.1% of all dermatofibromas [2]. Lipidized DF was described by Iwata as ankle-type fibrous histiocytoma (dermatofibroma) due to its characteristic location on the ankles [3]. Subsequent evaluation by Wagamon demonstrated no significant difference in location between lipidized and non-lipidized dermatofibromas.

How to cite this article: Soukaina M, Yosra S, Nouha A, Jameleddine Z. Solitary nodule on the forearm. Our Dermatol Online. 2021;12(2):186-187.

Submission: 19.05.2020; **Acceptance:** 07.09.2020

DOI: 10.7241/ourd.20212.22

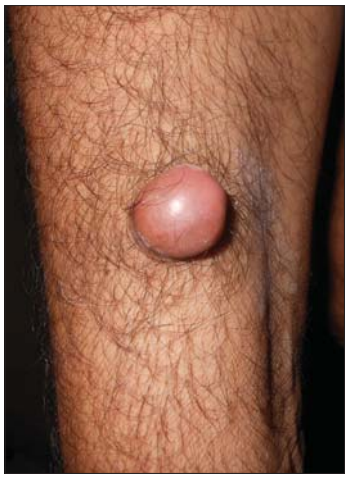

Figure 1: A solitary nodule on the forearm.

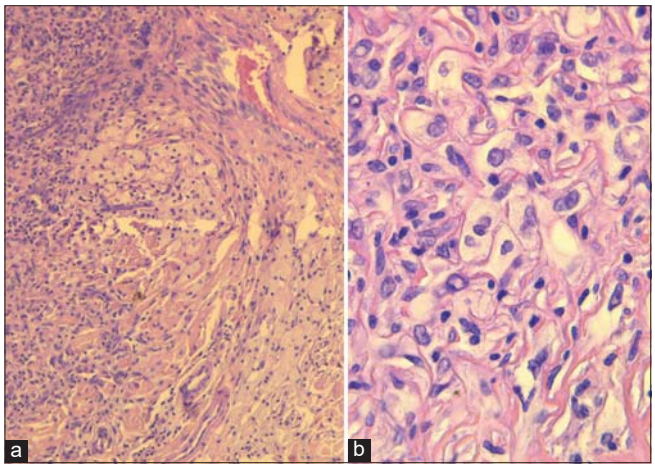

Figure 2: (a) Lipidized fibrous histiocytoma characterized by the predominance of xanthoma cells (H&E, 40×). (b) A hyper-power view of the foamy histiocytes (H&E, 100×).

Compared to ordinary dermatofibromas, patients with lipidized dermatofibromas tend to be older, most commonly in the fifth and sixth decades of life, and predominantly male [3]. Clinically, it manifests itself as a solitary exophytic yellow nodule usually larger than the common variant [1,3,4]. Apparently, it is not associated with hyperlipidemia [4]. It is frequently confused with other nodular tumors such as dermatofibrosarcoma protuberans, epidermoid carcinoma, sarcoma, and cutaneous leiomyoma [5].

Lipidized fibrous histiocytoma is defined by histological features. Its lesions are histologically characterized by the accumulation of numerous foamy cells dissected by distinctive hyalinized wiry collagen fibers. Foamy cells can be round, polygonal, or stellate in shape. These characteristic features in combination with the typical features of common dermatofibromas fulfill the criteria for the diagnosis of a lipidized dermatofibroma [3,4]. Touton giant cells are also frequently present [4]. The differential diagnosis includes eruptive xanthoma, granular cell tumors, tuberous xanthoma, and xanthogranuloma, but the presence of unique features such as distinctive stromal hyalinization are clues to the correct diagnosis of lipidized dermatofibroma [3].

CONCLUSION

Lipidized dermatofibroma is a rare histological variant of dermatofibroma that should be distinguished from other cutaneous foamy histiocytic lesions, which may impact patient management.

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:** None declared.

Our Dermatology Online

Review Article

Drug reactions with the involvement of the periungual folds

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ABSTRACT

Drug reaction in hospitalized patients has an incidence rate of 2–3% and can affect any organ of the body, including the skin and its appendages. Each of the components of the nail apparatus can be affected, and the clinical manifestation to be observed will depend on the condition of each component. When it comes to the periungual folds, fixed drug eruptions, Stevens–Johnson syndrome, and Lyell's syndrome are the associated skin drug reactions. Periungual lesions can manifest themselves as a condition per se or arise from a drug reaction. Erythema, hemorrhage, necrosis, painful desquamation, edema, vesicles, and dyschromia are among the lesions that can develop. Other possible reactions include paronychia and the formation of pyogenic granulomas caused by drugs. Therefore, it is important to assess the periungual folds should any drug reaction occur.

Key words: Periungual fold; Drug reactions; Drugs, Paronychia; Pyogenic granuloma

INTRODUCTION

According to the World Health Organization, a drug reaction is defined as an "unintended effect that occurs at drug doses normally used in patients for the prophylaxis, diagnosis or treatment of their diseases." Drug reactions can involve various organs and systems of the body, and the skin is the most frequently involved, sometimes accompanied by the involvement of its appendages, such as the nail apparatus, hair, and mucosa. As for the nail apparatus, all its components may be affected, but we will focus on the lesions that can be evidenced at the level of the nail folds caused by drug reactions or pharmacodermas, which have similarly been observed [1-4].

The proximal nail fold is crucial because it gives rise to the formation of the nail plate through the dorsal matrix in the segment below its ventral portion and because, together with the lateral folds, it adheres to the dorsal surface of the nail plate and acts as a waterproof barrier that protects the nail matrix from injury and provides support and protection to the nail plate [1,5].

Pharmacodermas that may compromise the periungual folds include pigmented fixed erythema (Figs. 1 and 2), minor multiform erythema, Stevens–Johnson syndrome (Figs. 3a -3c), and Lyell's syndrome (Fig. 4) [1,2].

The skin manifestations that are due to the different drug reactions already mentioned can lead to injuries such as erythema, bleeding, necrosis, desquamation, purpuric lesions, vesicular bullous lesions, epidermal exfoliation, and dyschromia (Fig. 5) (Table 1).

Numerous case reports have been published with periungual tissues affected by drugs or components of drugs, such as capecitabine, which has been approved for the treatment of metastatic colorectal cancer and advanced breast cancer, and brings about adverse events that can affect the nail matrix, the nail bed, and the nail folds. These can manifest themselves as subungual hyperkeratosis, onycholysis, onychomadesis, acute paronychia, secretion of nail exudate, and vascular lesions in the nail folds. In the treatment of psoriasis with adalimumab, the

How to cite this article: Chang P, Mancilla Gudiel PM. Drug reactions with the involvement of the periungual folds. Our Dermatol Online. 2021;12(2):188-194.
Submission: 07.04.2020; **Acceptance:** 10.08.2020
DOI: 10.7241/ourd.20212.23

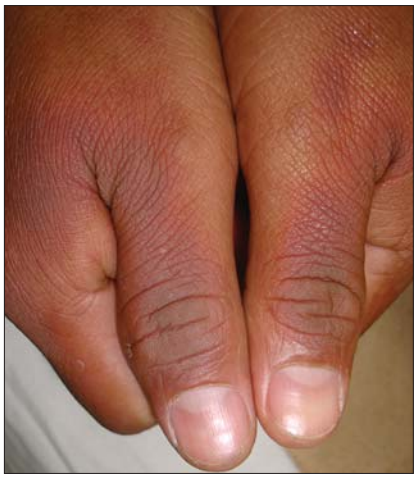

Figure 1: Fixed drug eruption from metamizole.

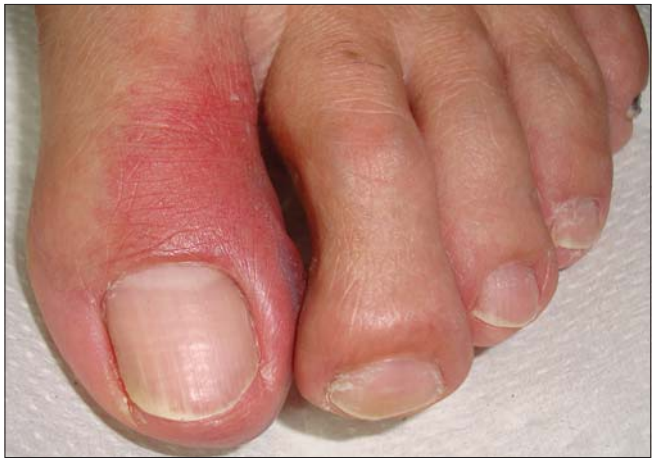

Figure 2: Spotted and blistered fixed drug eruption from levofloxacin.

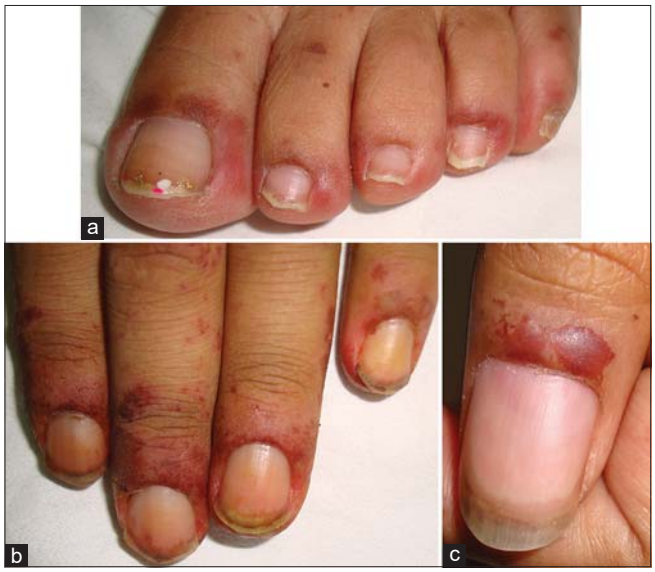

Figure 3: (a) A close-up of a condition of the periungual folds from Stevens–Johnson syndrome caused by allopurinol and AIDS. (b) A condition of the left-hand periungual folds in a patient with AIDS and Stevens–Johnson syndrome. (c) A condition of the proximal folds from diclofenac in a patient with Stevens–Johnson syndrome.

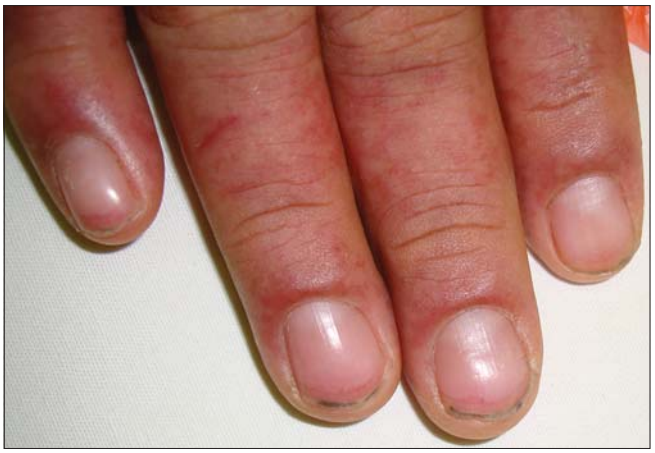

Figure 4: A condition of the proximal folds of the hands from quinolones in a patient with Lyell's syndrome.

Table 1: Injuries to the periungual folds due to drug reactions

Fixed pigmented erythema	dyschromia (purplish, brown, or blackish pigmentation), vesicles, blisters
Erythema multiforme minor	vesicles, blisters (bull's-eye lesions)
Stevens–Johnson syndrome	purpuric lesions, vesicles, blisters
Lyell's syndrome	vesicles, blisters, skin exfoliation

paradoxical development of *de novo* psoriasis has appeared in some cases, especially the form called palmoplantar pustulosis. In another case report, nail changes occurred in all of the twenty nails, and the surrounding tissues were affected, displaying erythema, edema, scales, and inflammation of the proximal nail fold. In contrast, bleomycin as such produces no adverse events at the level of the nail folds; however, vascular changes may develop with the use of bleomycin near or around the periungual area. These changes can appear as Raynaud's phenomenon or sclerodermiform changes, which can be acute and lead to gangrene and necrosis of the toes, requiring immediate cessation of treatment and its conclusive abandonment [1,2,6-10].

Drug-induced nail abnormalities are usually temporary and reversible once the causative agent is removed, and are rarely life-threatening. They frequently appear as paronychia and pyogenic granulomas (Table 2) [2,11-14].

Paronychia and Pyogenic Granuloma

Paronychia is an inflammation of one or more periungual folds that involves erythema, edema, and tenderness. In addition, it can be exceptionally painful and can restrict fine motor activity. It can be acute, or chronic if the inflammation persists for more than 6 weeks. Drug-induced paronychia mainly affects the

Table 2: Drugs that most frequently induce paronychia and/or pyogenic granulomas

Retinoids	Isotretinoin
	Etretinate
	Acitretin
	Tretinoin
	Tazarotene
Antivirals	Ledipasvir and sofosbuvir
Antiretrovirals	Indinavir
EGFR inhibitors	Cetuximab
Taxanes	Paclitaxel
	Docetaxel
MEK inhibitors	Selumetinib
mTOR inhibitors	Everolimus
	Temsirolimus
Others	Methotrexate
	Cyclophosphamide
	Vincristine
	5-fluorouracil
	Capecitabine
	Cephalexin
	Topical cyclosporine
	Ibrutinib
	Mitoxantrone
	Bevacizumab
	Rituximab
	Vemurafenib

thumbs and the first toe, and occurs shortly after starting treatment [7,11,15-17].

Paronychia can progress to form friable granulation tissue in the periungual folds and pyogenic granuloma lesions that later mimic onychocryptosis [10,13,18].

An important feature of drug-induced pyogenic granulomas is that they affect multiple fingers and/or toenails, but the location in the feet is more prevalent, possibly due to chronic footwear friction [3,7,19].

Generally, these lesions resolve with drug discontinuation, although this is often not a viable option since it may be secondary to the use of antineoplastic drugs. Some other therapeutic measures will be presented later in case drug discontinuation is not possible [20,21].

Retinoids

Retinoids can cause paronychia and pyogenic periungual granulomas approx. 3 months after starting treatment. These lesions are a known, although rare, adverse event of systemic retinoids, especially isotretinoin and etretinate. Chronic paronychia and granulation tissue formation in the lateral nail folds are most often seen with the use of etretinate and are less common with acitretin. Pyogenic granulomas may also appear at the site of topical retinoid application, as with tretinoin and tazarotene [7,8,20,22,23].

Retinoids have been postulated to induce these lesions as a result of weak bonding between keratinocytes, inducing nail fragility and leading to the penetration of nail plate fragments into the surrounding tissues. This, in turn, creates an inflammatory reaction against a foreign body. Furthermore, retinoids have angiogenic properties and inhibit collagenases and gelatinases *in vitro* [7,8,21].

Topical treatment with steroids and antimicrobials is recommended; a 2–3 week regimen of 2% topical mupirocin cream can be administered in the morning and 0.05% clobetasol propionate ointment in the evening. For lesions that persist despite retinoid removal or that show no response to topical treatment, a biopsy should be performed to exclude malignancy before using more aggressive treatment modalities, such as excision or destruction of the lesion [7,8,20,24].

Antivirals and antiretrovirals

Ledipasvir and sofosbuvir are a new class of direct-acting antivirals against the hepatitis C virus (HCV), and paronychia has currently been reported as a side effect of this treatment [21].

Antiretroviral therapy causes pyogenic granulomas in approx. 6% of patients, and the onset time is 2 months to 1 year from the start of treatment. Indinavir, a protease inhibitor, is the most common cause of chronic paronychia in patients infected with the human immunodeficiency virus (HIV). Protease inhibitors are believed to have a retinoid-like effect due to homologous portions of the amino acid sequences of cellular retinoic acid-binding protein 1 (CRABP1) and the catalytic site of HIV-1 protease. Therefore, retinoid receptors can be occupied and activated by an antiretroviral drug, thus increasing the activity of vitamin A and its analogs [7,8,16,21].

The treatment of periungual lesions induced by these drugs is similar to that of retinoids, involving topical and antimicrobial steroids. In the case of antiretrovirals, substitution with an alternate antiretroviral agent should be made whenever possible, since it frequently leads to the resolution of the condition. Should no response occur, an effective combination therapy of an ointment steroid and chemical phenol matrixectomy is recommended [8,15,16,21].

Epidermal growth factor receptor (EGFR) inhibitors

EGFR inhibitors, a form of targeted cancer therapy, offer a new possibility for the treatment of multiple

types of advanced cancer, including metastatic non-small cell lung cancer and colorectal, breast, head, neck, and pancreatic cancer. Two classes of EGFR inhibitors are currently employed: monoclonal antibodies (cetuximab, panitumumab, and matuzumab), which target the extracellular binding domain; and small molecules that inhibit the activity of tyrosine kinase (gefitinib, erlotinib, lapatinib, and afatinib), which target the intracellular domain [7,12,25,26].

Despite the promising treatment efficacy of EGFR inhibitors as an antineoplastic drug and their better safety profile than conventional chemotherapy, their use is accompanied by numerous adverse skin events, leading to poor adherence to treatment, decreased dosage, or complete discontinuation of such treatment, in addition to the patient's psychosocial discomfort. This is because EGFRs are crucial for the sound development and physiology of the skin, since they are expressed in the keratinocytes of the basal and suprabasal layers of the epidermis and the outer root sheaths of hair follicles. Inhibition of EGFR-dependent pathways leads to changes in epidermal cell differentiation and migration, in addition to inhibited keratinocyte proliferation and decreased cell survival through induction of apoptosis [8,10,12,18,25,27].

Cutaneous manifestations appearing in targeted therapies are found in more than 50% of patients under treatment, and are enumerated by the acronymic name of PRIDE syndrome: papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness. The earliest and most common adverse event is papulopustular or acneiform eruption observed in 50% to 100% of these patients. Periungual lesions occur less frequently. A 2012 meta-analysis estimated them at 17.2% with a relative risk of 76.94%. Even though dermatological symptoms can lead to a reduction in the quality of life of patients, it has been observed that the presence and severity of this toxicity have a positive correlation with the patient's chance of survival and are considered a marker of tumor response [12,13,25,26,28].

Paronychia and pyogenic granulomas occur in 10% to 15% of patients under treatment. Paronychia develops approx. 1 to 2 months after starting EGFR inhibitors, but its pathogenesis remains unsettled. The epidermis is believed to thin and subsequently perforate the periungual tissue along the edges of the nail plate and induce an inflammatory foreign body reaction. Cetuximab is the most frequent targeted anticancer treatment causing paronychia (Fig. 6), corresponding to 10% to 20% of cases. As for the development of pyogenic granulomas, these are dose-dependent and usually show after six weeks of therapy. Resolution of this type of lesion occurs 1 to 2 months after drug withdrawal [7,8,10,11,14].

In the treatment of paronychia, the use of systemic tetracycline antibiotics, such as doxycycline, the combined application of powerful steroids and topical antiseptics, the management of secondary infections with antibiotics, and surgical intervention in patients with lateral matrixectomy, with phenolization in the nails affected, are described. Topical application of 0.1% adapalene gel daily has also been reported; the mechanism of action by which this topical retinoid alleviates the symptoms of paronychia involves its ability to increase the levels of EGF-type growth factor, which binds to heparin (HB-EGF; heparin-binding epidermal growth factor-like growth factor) and amphiregulin, which, in turn, reactivates the EGFR

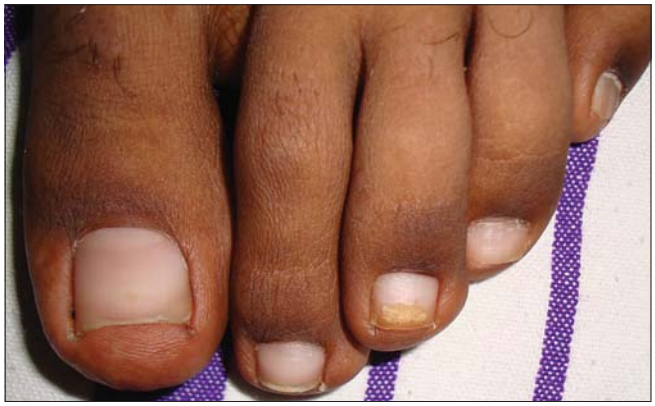

Figure 5: Acute and chronic paronychia from cetuximab in a patient undergoing treatment for head and neck cancer (primary unknown).

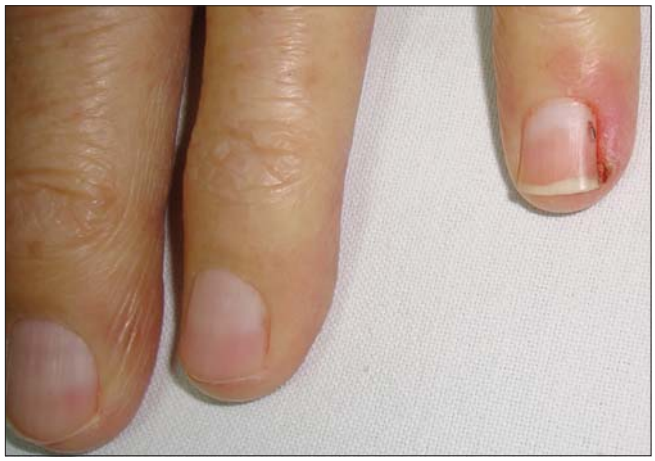

Figure 6: Proximal fold dyschromia in a patient undergoing treatment for seminoma.

pathways in the epidermis and reduces periungual inflammation [7,8,16,26,29].

It has been mentioned that, in tyrosine-kinase-inhibitor–induced paronychia, a dose reduction can lead to some lesion improvement. However, a study that quantified the concentrations of these inhibitors on a paronychia site found no relationship with the degree of toxicity or the severity of the injury. One recommendation, hence, is to educate the patient on the measures to avoid finger compression, since it is a more effective approach to managing this adverse event than reducing the dose or discontinuing tyrosine-kinase-inhibitor anticancer drugs [18].

The management of pyogenic granulomas is more difficult than that of paronychia, and liquid nitrogen, topical or intralesional steroids, or weekly application of 10% aqueous silver nitrate, which reduces the granulation tissue, can be used for treatment. This type of tissue can also be removed by electro-drying. Photodynamic therapy has been reported to be a good therapeutic alternative since it has been shown to have the potential to completely resolve lesions or, at least, produce significant and symptomatic improvement, in addition to being very well-tolerated by patients. Occasionally, a partial phenol matrixectomy or treatment dose adjustment should be made if lesions are acutely painful, multiple, or persistent [10,13].

Recently, the use of topical beta-blockers for the treatment of paronychia and/or pyogenic periungual granulomas induced by EGFR inhibitors has been investigated. The results demonstrated that 0.5% timolol gel applied twice a day in occlusion for one month is a promising and safe treatment well tolerated by patients [29,30].

Taxanes

Taxanes—specifically, paclitaxel and docetaxel (Figs. 7a and 7b)—are commonly used in the treatment of breast, lung, and genitourinary cancers. Nail changes caused by these drugs have been reported in 40% to 89% of patients, manifesting themselves most often as onycholysis and discoloration of the nails and less frequently as acute paronychia. Capriotti et al. determined the general incidence of acute paronychia caused by these agents by a review of published clinical trials, and estimated it at 38.9% (1,481 / 3,812) [7,23,31].

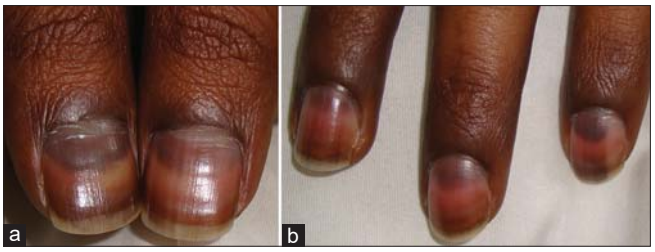

Figure 7: (a-b) Periungual fold dyschromia of the twenty digits accompanied by melanonychia.

It has recently been reported that the use of 2% polyvidone iodine in dimethyl sulfoxide solution applied twice daily for 4 to 8 weeks is an effective topical treatment for paronychia induced by EGFR inhibitors and taxanes [32].

MEK, mitogen-activated ERK (extracellular signal-regulated kinase) activating kinase inhibitors

Periungual lesions have been observed in the use of MEK inhibitors. The frequency and severity of the condition are slightly less than of the lesions caused by EGFR inhibitors. Selumetinib, a member of the second generation of this group of drugs, induces paronychia, which is characterized by a late onset and resolution of lesions until drug discontinuation. According to one study, this adverse event appears in 9% of patients treated with selumetinib [10,23].

mTOR (mammalian Target of rapamycin)

mTOR inhibitors, such as everolimus and temsirolimus, induce periungual lesions in 15% of cases and are similar to EGFR and MEK inhibitors. This suggests that paronychia may be associated with a signaling inhibition of the pathways of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K; phosphoinositide 3-kinase). Additionally, mTOR regulates the cellular signaling pathway of EGF, which could explain the appearance of pyogenic granulomas with this therapy [5,10,33].

Other drugs reported to have the potential to cause paronychia and/or periungual pyogenic granulomas are methotrexate, cyclophosphamide, vincristine, 5-fluorouracil, capecitabine, cephalexin, topical cyclosporine, ibrutinib, mitoxantrone, bevacizumab, rituximab, vemurafenib, and sorafenib (Fig. 8) [1,7,11,21,22,34,35].

General Measures

These injuries can become particularly debilitating, lead to functional impairment, and significantly

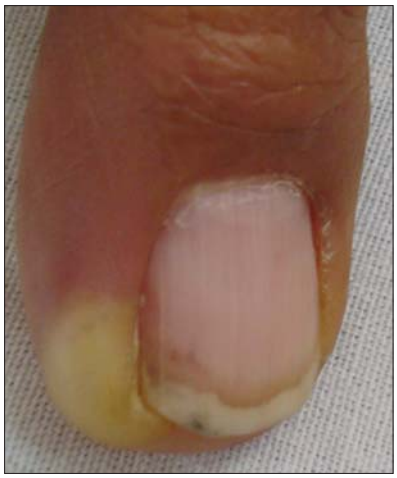

Figure 8: Paronychia from sorafenib in a patient undergoing kidney cancer treatment.

affect the quality of life of patients under such treatment. Patients should be advised to use emollient lotions, wear gloves for housework and cleaning and frozen gloves and socks during the infusion of the drug, avoid impact, friction, and compression to the fingers, cut nails properly, use wide footwear, and take antiseptic baths, which can prevent painful periungual injuries [8,10,11,32,36].

ACKNOWLEDGMENT

We would like to thank Angela Alvarado Chew for translating this document.

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

Clinical Image

Pigmented plaque on the thigh: Atypical location of a basal cell carcinoma

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Basal cell carcinoma (BCC) is the most common type of skin cancer, usually occurring on sun-exposed areas, such as the head and neck [1]. Chronic sun exposure is the cause of most of its cases but it may also develop on unexposed areas. BCC on extrafacial sites accounts for 17% of all basal cell carcinomas [2]. In these cases, dermoscopy can be especially helpful in diagnosis.

A 43-year-old female presented herself with a slowly growing, slightly itchy pigmented lesion on the right thigh persistent for the past two years. A clinical examination revealed a 2-cm well-limited pigmented plaque with excoriations on the periphery (Fig. 1). Dermoscopy showed multiple maple-leaf–like areas, digitiform structures with rosettes (Fig. 2). The lesion was subsequently excised with 6-mm margins. A histopathological report confirmed the diagnosis of superficial basal cell carcinoma with clear margins.

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.

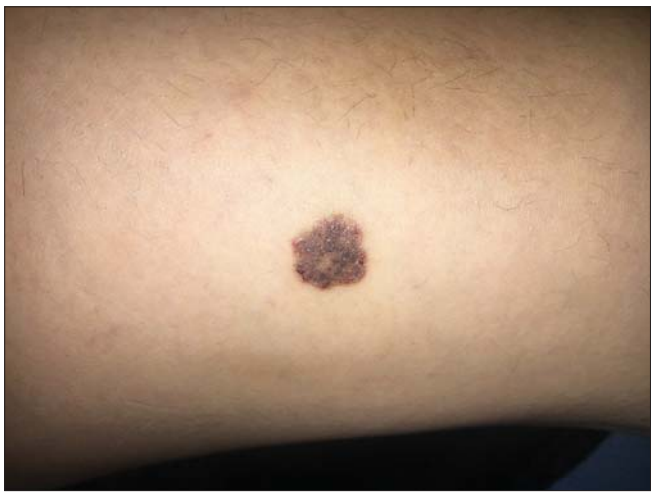

Figure 1: Clinical image showing a 2-cm well-limited pigmented plaque with excoriations on the periphery.

Figure 2: Dermoscopic image showing multiple maple-leaf–like areas, digitiform structures with rosettes.

How to cite this article: Mrabat S, Douhi Z, Elloudi S, Baybay H, Mernissi FZ. Pigmented plaque on the thigh: Atypical location of a basal cell carcinoma. Our Dermatol Online. 2021;12(2):195-196.

Submission: 28.08.2020; **Acceptance:** 31.10.2020

DOI: 10.7241/ourd.20212.24

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

Our Dermatology Online

Clinical Image

Severe acral erythrodysesthesia and docetaxel

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Acral erythrodysesthesia can have a serious impact on the patient's quality of life and on their ability to continue or complete treatment [1].

We report a case of a 42-year-old female followed for breast cancer: cT4d N2 M0; RH + / HER2 3+. She received neoadjuvant chemotherapy based on anthracycline sequentially by docetaxel associated with trastuzumab and pertuzumab in HER2 dual-blocking strategy. The evolution was marked, after the first cycle of docetaxel dual-blocking, by the occurrence of severe skin toxicity in the form of acral erythrodysesthesia in the soles of the feet and causing the patient an inability to walk. (Figs. 1a and 1b). She was immediately referred to a plastic surgery department and was made aware of the physical measures to be observed for good remission of the skin toxicity. The administration of docetaxel treatment was immediately discontinued, after which the patient completed the treatment with paclitaxel.

Preventive measures and early recognition of acral erythrodysesthesia remain the essential strategies to ensure timely treatment and avoidance of dose reductions or treatment discontinuation [2].

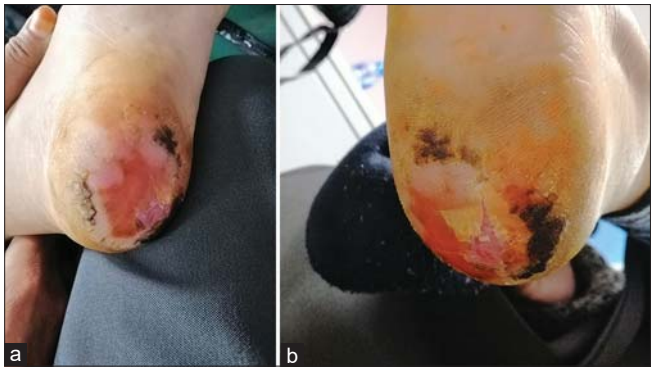

Figure 1: (a-b) Grade III acral erythrodysesthesia in the soles of the feet, one week after the first dose of docetaxel–trastuzumab–pertuzumab chemotherapy.

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.

How to cite this article: Bagorane J, El Fadli M, Negamiyimana G, Kintossou EL, Adjade G, Cisse K, Benhima N, Belbaraka R. Severe acral erythrodysesthesia and docetaxel. Our Dermatol Online. 2021;12(2):197.

Submission: 29.08.2020; **Acceptance:** 31.10.2020

DOI: 10.7241/ourd.20212.25

Clinical Image

Rectangular alopecic patch: A possible suspicion

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A 65-year-old female was referred to the dermatology department because of an alopecic patch located on the frontal-parietal region of the scalp, gradually progressing over the previous month. The patient had undergone fluoroscopically guided endovascular embolization of an anterior communicating artery aneurysm fifteen days before its development. The patient did not have a family or personal history of alopecia. She denied having a history of drug use, suspicious hair care practices, and pruritus or other symptoms.

A physical examination revealed a sharply-delineated, rectangular, alopecic area located on the referred region of the scalp, 14 × 10 cm in size (Fig. 1). The alopecic patch was skin-colored. No erythema, scarring, or scaling was found on clinical and dermoscopy examination. No exclamation mark hairs were evident on dermoscopy and the hair pull test was negative. Thus, the diagnosis of radiation-induced transient alopecia (RITA) was reached.

Hair growth returned six months after the endovascular procedure and no other interventions were necessary (Fig. 2).

RITA is explained by the high sensitivity of anagenic hair follicles to radiation. RITA is becoming more frequent due to the increasing use of endovascular interventional procedures in the last twenty years [1]. It is characterized by a non-scarring geometrical, mostly rectangular, alopecic patch restricted to the area of radiation [2]. RITA is usually asymptomatic and without signs of scalp inflammation [2]. Alopecia usually begins two to five weeks after the endovascular procedure [1].

The diagnosis of RITA is based on a typical clinical presentation and a history of exposure to radiation.

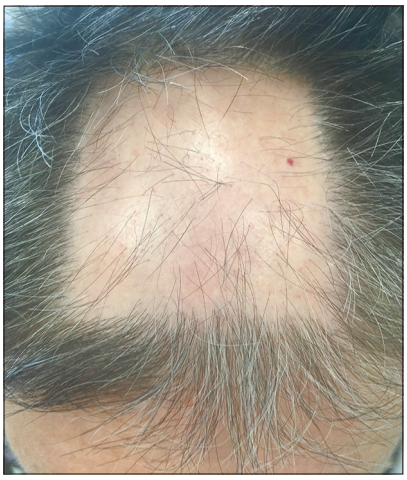

Figure 1: Rectangular, sharply-demarcated, alopecic area located on the central frontoparietal area of the scalp with a tendency toward hair regrowth visible.

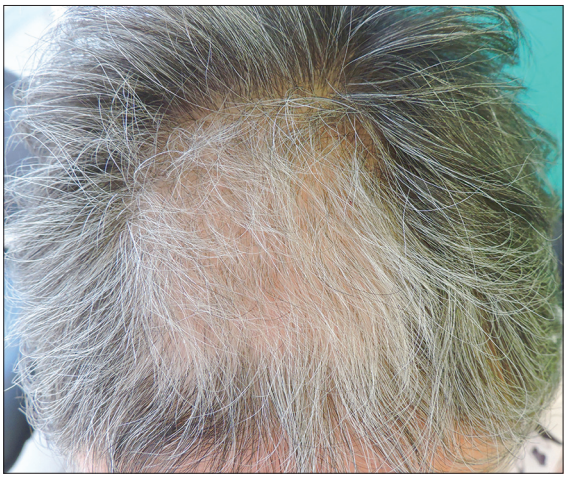

Figure 2: Six months after the endovascular procedure.

Because of its benign and transient nature, RITA requires no particular treatment. Complete hair regrowth generally occurs within two to six months after irradiation [1]. Due to its self-limiting nature, the main therapeutic goal is to recognize this entity in

How to cite this article: De la Torre Gomar FJ, Gimeno Castillo J, Saenz Aguirre A. Rectangular alopecic patch: A possible suspicion. Our Dermatol Online. 2021;12(2):198-199.

Submission: 02.12.2020; **Acceptance:** 14.02.2021

DOI: 10.7241/ourd.20212.26

order to avoid unnecessary interventions as well as to reassure the patient,

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

A febrile exanthem revealing COVID-19

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Sir,

We report the case of a 74-year-old male with no previous medical history admitted to the emergency department for an acute itchy febrile generalized rash present for the last three days. The patient reported no recent history of drug ingestion. A clinical examination revealed a generalized maculopapular exanthem (Figs. 1 and 2) and a fever of 39°C. There was no hypotension or respiratory symptoms. RT-PCR for SARS-CoV-2 was positive and serology revealed positive IgM and negative IgG. Normal paraclinical examinations and a thoracic CT scan revealed that 10% of the lesions were CO-RADS 6.

Since the beginning of the pandemic, numerous have authors described skin manifestations associated with COVID-19, including morbilliform and roseoliform exanthems [1], maculopapular rashes on the face, generalized hives [2,3], and rashes such as chickenpox [4-5], but erythema multiforme and purpuric rashes [6] have also been reported in the scientific literature [7] and in medical social networks [8]. These eruptions are, indeed, known to be associated with viral infections and are commonly referred to as viral rashes or paraviruses. However, they are not specific to SARS-CoV-2 and may also lie in other causes, especially in drugs. Patients affected by COVID-19 are, indeed, likely to develop unwanted responses to drugs administered for infections (including carrying drugs and anti-infectives) causing secondary skin reactions at any time during the evolution of the disease.

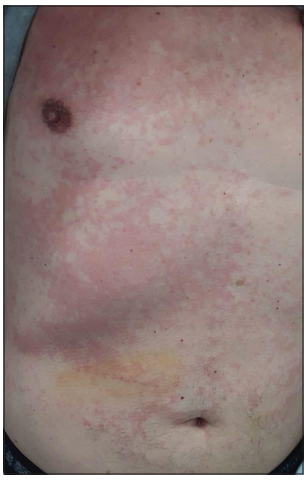

Figure 1: An exanthem on the right lateral aspect of the thorax and abdomen.

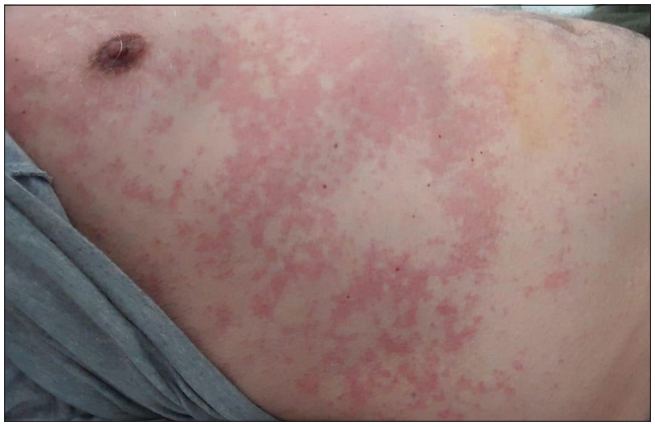

Figure 2: An exanthem on the anterior aspect of the thorax.

Consent

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How to cite this article: Oujidi Y, Housni B. A febrile exanthem revealing COVID-19. Our Dermatol Online. 2021;12(2):200-201.
Submission: 08.09.2020; **Acceptance:** 10.01.2021
DOI: 10.7241/ourd.20212.27

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

Letter to the Editor

Erythema multiforme-like lesion: A COVID-19 manifestation?

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Sir,

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported as pneumonia in December 2019 in Wuhan, China. Since then, it has been spreading rapidly and WHO has declared it a pandemic on March 11, 2020 [1]. As of October, COVID-19 had affected about 8,029,217 cases worldwide and 111,802 cases in Nepal alone. Cutaneous manifestations have been reported in 20% of COVID-19 patients [2]. We report a case of erythema multiforme-like lesions in a young patient who was likely a case of a COVID-19 infection.

A 32-year-old male presented himself to our OPD with the chief complaints of fever and erythematous palpable rashes over the bilateral feet, legs, and hands persistent for one week. The mucous membranes were spared. The patient also complained of pain over the bilateral knee joint and fatigue. The patient gave no history of diarrhea, dyspnea, anosmia, or dysgeusia and no history of drug intake prior to the onset of lesions. A physical examination revealed an erythematous targetoid lesion distributed over the dorsum of the bilateral feet (Fig. 1) and the distal half of the bilateral legs and several lesions scattered over the dorsum of the bilateral hand and over the abdomen and back. A systemic examination was normal. The patient was clinically diagnosed with erythema multiforme minor.

On laboratory investigation, ESR was 40, CRP was positive (+++), and ANA was 1:100. Other laboratory investigations, such as complete blood count, a renal function test, a liver function test, RA factor, and a urine routine examination, were normal. A chest X-ray revealed prominent bilateral pulmonary vessels and an otherwise normal chest.

As erythema multiforme is one of the cutaneous manifestations of COVID-19 and positive CRP is an important laboratory marker, the patient was advised RT-PCR, but denied it. Yet, the patient was counseled regarding the cutaneous manifestations and was advised home isolation.

New reports of COVID-19-related cutaneous manifestations are emerging rapidly. According to a study conducted by Daneshgaran et al., erythema multiforme-like eruptions account for 3.7% of the total cutaneous manifestations of COVID-19 [3]. Several case reports of erythema multiforme-like lesions in COVID-19 patients were published in the literature by Demirbas et al. [1], Garguilo et al. [4], Recalcati et al. [5], Torrelo et al. [6], and Janah et al. [7].

Most people are well aware about the fever and pulmonary manifestations of COVID-19 but the fact that COVID-19 can present other manifestations is still poorly recognized. Because of this, there may be skepticism around accepting a present COVID-19 infection that manifests itself in other ways and so there may be hesitance against taking confirmatory tests. We experienced the same situation with our patient, who had little knowledge regarding the cutaneous manifestations of COVID-19 and was hesitant to take a confirmatory test despite constant counseling.

Numerous positive cases remain undiagnosed due to the lack of awareness about the various manifestations

How to cite this article: Mainali P, Thapa DP. Erythema multiforme like lesion: A COVID-19 manifestation? 2021;12(2):202-203.

Submission: 15.10.2020; **Acceptance:** 12.12.2020

DOI: 10.7241/ourd.20212.28

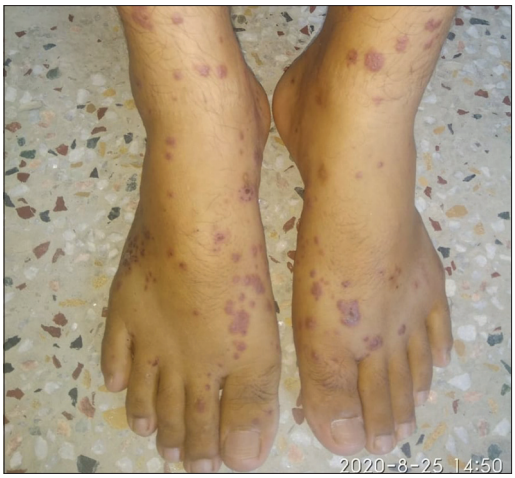

Figure 1: Multiple erythema multiforme-like lesions over the dorsum of the bilateral feet, ankles and, distal legs.

of the disease. Additionally, there appears a greater risk of spreading the disease in a community and, thus, a greater risk of an increased disease burden.

Proper knowledge about atypical cutaneous manifestations may help to increase surveillance and decrease the transmission of COVID-19 as a high index of suspicion is the major factor that brings a patient to the hospital for screening.

Consent

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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

The experience of mobile teledermatology during the COVID-19 pandemic in Nepal: A feasible alternative even in the developing world

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Sir,

Because of the COVID-19 pandemic, our lives have become devastated and affected like never before. It has truly challenged the entire medical world. We, healthcare providers, are looking for the best ways of providing patient care in our respective fields. Although the first COVID-19 case in Nepal was confirmed on January 23, cases have been rising rapidly for the last two months, once national lockdown ended on July 21. To date (i.e., October 6, 2020), there have been 89,263 confirmed cases and 554 deaths [1]. Although the lockdown has been eased in a phase-wise way, public mobility is still restricted only to urgent cases to combat the infection. At the same time, some people might be making unnecessary health visits due to the lack of a proper referral and triage system in our country. Likewise, a specialist visit is especially difficult because of the varying geographical landscape and centralization of the healthcare system [2]. For this reason, teledermatology might be a promising platform for triaging dermatology patients at a distance without face-to-face consultations. The skin being a visible organ, we have the potential to diagnose many cases with a medical history and a detailed visual inspection of lesions. Hence, by the use of teledermatology, we can easily segregate our patients with minimum patient mobilization using the store-and-forward technique, even in a resource-poor setup. Dermatology being a visual discipline, we are very much privileged to practice teledermatology.

Mobile teledermatology—the use of smartphone teleconsultation applications—is another rapidly growing field [3]. As smartphones are becoming cheaper, more user-friendly, and more easily available, it might be a good alternative for teleconsultation even in underdeveloped nations. There have been specific guidelines for using mobile devices in dermatology practice as well [4].

Targeting this pandemic, I have been practicing free mobile teleconsultation since May 17, 2020, different social media. A total of 411 patients have contacted me for skin problems through the following social platforms: Facebook (386; 93.91%) [5], WhatsApp (22; 5.35%), and Viber (3; 0.74%). However, the required details could be gathered from only 350 patients. The mean age was 35.05 ± 16.0 years, through with a minimum of 6 months and a maximum of 88 years). Females (51.1%) predominated males. Almost half (47.4%) were from semiurban areas, followed by 23.1% from rural areas. Some people (10.3%) even contacted from abroad. Dermatitis and eczema were the most common (22.6%) issues (Table 1). Several people (5.14%) also contacted for genital issues without hesitating to share clinical photographs. The majority of people (78.6%) contacted for their own issues, whereas several health workers (3.1%) contacted for secondary teleconsultation for their patients. Establishing and maintaining a dialog with mobile teledermatology was particularly easy both for the patient and the dermatologist (Fig. 1). From the shared photographs and information, diagnosis and advice were possible in 90.9% of cases, thus obviating

How to cite this article: Marahatta S. The experience of mobile teledermatology during COVID-19 pandemic in Nepal: A feasible alternative even in the developing world. Our Dermatol Online. 2021;12(2):204-205.

Submission: 07.10.2020; **Acceptance:** 10.12.2020

DOI: 10.7241/ourd.20212.29

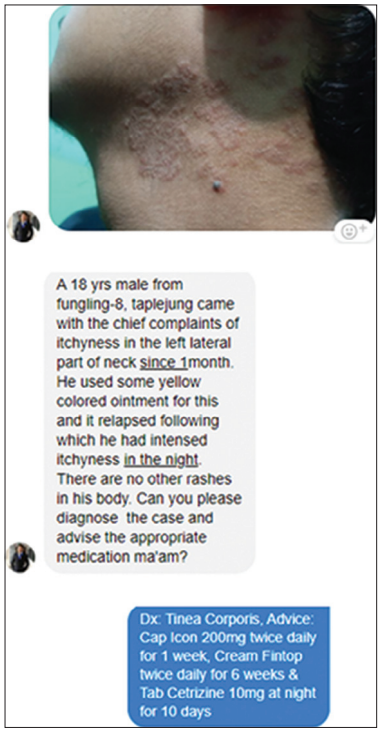

Figure 1: A dialogue during a mobile teledermatology consultation.

immediate specialist visits. For the rest (9.1%), however, a diagnosis could not be established on such a platform.

From this small experience, we see huge possibilities of mobile teledermatology, even in developing countries, as it may significantly reduce the need for unnecessary hospital visits and mobilization of many dermatology patients during the pandemic, even in the future. Hence, we strongly agree with some proposed models of teledermatology [6]. An expert committee can prepare a common sustainable protocol of utilizing teledermatology to its fullest throughout the world during this crisis as well as in the days to come.

Table 1: The clinicodemographic profiles of the patients

Characteristic	Category	Number	Percentage
Gender	Male	171	48.9
	Female	179	51.1
Residence	Urban	67	19.1
	Semiurban	166	47.4
	Rural	81	23.1
	Abroad	36	10.3
Contacted by	Self	275	78.6
	Family member or friend	64	18.3
	Health worker	11	3.1
Diagnosis	Fungal infection	48	13.7
	Bacterial infection	11	3.1
	Viral infection	14	4.0
	Dermatitis and eczema	79	22.6
	Acne and acne scars	60	17.1
	Pigmentary problems	65	18.6
	Nevus, cyst, growth	16	4.6
	Urticaria	18	5.1
	Alopecia	9	2.6
	Others	9	2.6
	Diagnosis impossible	32	9.1

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

Letter to the Editor

A case of a long-neglected basal cell carcinoma on the scalp

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Sir,

A 73-year-old Japanese male first noticed a bean-sized lump on the scalp twenty years ago, which gradually became larger and more friable. The patient concealed the mass with a hat and pursued no medical consultation before visiting us. As for the past medical history, the patient underwent cholecystectomy ten years ago and distal antrectomy for an antral gastric cancer seven years ago. He also had diabetes, hypertension, hyperlipidemia, renal dysfunction, and bilateral knee osteoarthritis.

On physical examination, the well-developed and well-nourished patient showed a rounded, flat, friable, and malodorous tumor mass 10 × 15 cm in size spreading from the right frontal scalp to the upper right eyelid (Fig. 1a). There was no palpable cervical or preauricular lymphadenopathy. Dermoscopy revealed ulceration, large blue-gray ovoid nests, and an arborizing vessel [1], suspicious of basal cell carcinoma (Fig. 1b). Laboratory investigation revealed normocytic anemia, decreased renal function, and elevated levels of serum amylase and LDH. CT of the head revealed invasion of the tumor into the subcutaneous fat tissue but not into the bone. There was no metastasis.

Under the diagnosis of basal cell carcinoma, the tumor mass was excised to the level below the galeal aponeurosis with a 1 cm margin. The wound was temporally closed by synthetic dermis (Teldermis®, Olympus Terumo Biomaterial Co., Ltd., Tokyo, Japan).

Histopathology of a specimen from the surgically excised tumor revealed a pedunculated exophytic tumor and invasion up to the subcutaneous tissue (Fig. 1c). The surgical margins were free of tumor. The subepidermal tumor mass showed a palisading arrangement and proliferation of the surrounding connective tissue with a cleft formation between them (Fig. 1d). Furthermore, the tumor tissue had continuity with the epidermis (Fig. 1d). Basaloid tumor cells showed a high nucleocytoplasmic ratio, large elliptical nuclei, and low atypism (Fig. 1e).

After a histopathological evaluation of the excised tumor, second surgery with a skin graft from the abdomen was performed with a good result.

Management for patients with long-neglected externally visible masses is challenging [2]. Such patients tend to carry negative traits, such as depression, on the Minnesota Multiphasic Personality Inventory (MMPI-2) [3]. A French study of patients with head and neck cancers revealed that patients at a later stage of the disease tended to be more isolated, less involved with their spouses, and less anxious [4].

Our patient was socially vulnerable and did not receive enough public assistance. Fortunately, although scalp basal cell carcinomas are generally aggressive [5], and although the tumor in our patient was very large, it was not markedly invasive. However, our patient first refused the treatment of the mass. This was speculated to reflect the resignation from the treatment due to insufficient financial support and a sense of imminent death due to the severe disease. This case highlights

How to cite this article: Furukawa H, Sowa-Osako J, Ozawa T, Hashimoto T, Tsuruta D. A case of a long-neglected basal cell carcinoma on the scalp. Our Dermatol Online. 2021;12(2):206-207.

Submission: 15.10.2020; **Acceptance:** 06.01.2021

DOI: 10.7241/ourd.20212.30

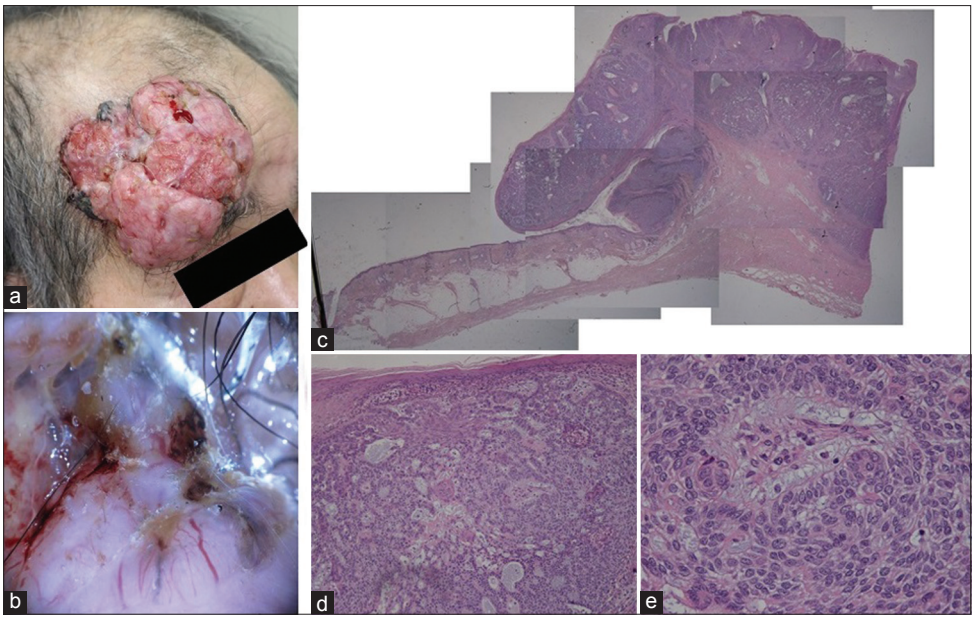

Figure 1: Clinical, dermoscopic, and histopathological features of this case. (a) A large tumor on the forehead. (b) Dermoscopic images. (c-e) Histopathological findings in a skin biopsy under magnification: (c) 20×, (d) 100×, and (e) 400× (H&E).

the need for psychosocial care for patients with long-neglected externally visible masses of skin tumors.

The patient provided written informed consent for publication.

This study was approved by the Ethical Committee of Osaka City University Graduate School of Medicine.

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

A case of prostate cancer revealed by erythroderma

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Sir,

Paraneoplastic cutaneous disorders (PCDs) are skin conditions associated with internal malignancies but that are not malignant themselves [1]. There are numerous skin diseases categorized as PCDs, such as dermatomyositis, bullous dermatosis, erythroderma, prurigo, lichen planus, and porokeratosis. Most importantly, there are no malignant cells infiltrating into the skin lesions of PCDs [2].

A 79-year-old man presented to our dermatology department with a generalized rash persistent for the last two months and importantly associated with itching. The patient had no history of drug allergy or a past dermatological condition. A clinical examination showed a generalized erythematous rash with scaling (Fig. 1). A skin biopsy revealed acanthosis and parakeratosis, but found no cause for the rash. The patient was treated with potent topical steroids and antihistamines but with no relief. Given the patient's complaint of dysuria and frequent urination, we measured the level of prostate-specific antigen (PSA) to find it abnormally high, at 45. A CT scan revealed iliac lymph node metastases. Prostate MRI revealed a suspicious lesion in the central area, corresponding to prostate cancer (Fig. 2). A prostate biopsy confirmed the diagnosis of adenocarcinoma classified as Gleason 8 (4 + 4). The patient was put under hormone therapy and radiation therapy. Two months after beginning the treatment, the patient achieved remission of the rash, but the itching remained unaffected.

Erythroderma is a complex multifactorial dermatosis, whose prognosis depends on the causative agent. Despite the fact that it rarely appears as a paraneoplastic syndrome, a clinical finding of a rapidly extending erythema along with various degrees of scaling, especially in a patient without previous dermatological disorders, should prompt further investigation for underlying malignancies, as in this extremely rare case of erythroderma associated with prostate cancer.

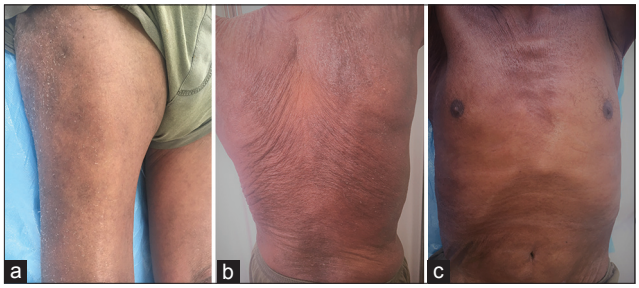

Figure 1: (a-c) Generalized erythematous rash of the trunk and extremities.

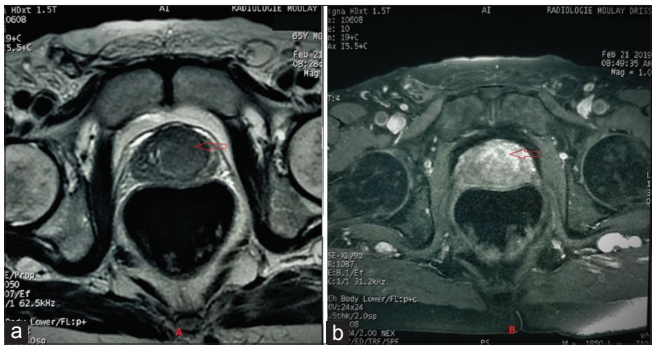

Figure 2: Cross sections of prostate MRI; a T2 sequence (a) and a dynamic injected sequence (b) showing a suspicious lesion in the central area, corresponding to prostate cancer.

Consent

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

How to cite this article: Mrabat S, Elloudi S, Baybay H, Douhi Z, Mernissi FZ, Ennaciri S, Chama O, Ahsaini M, Mellas S, El Ammari J, Tazi MF, El Fassi MJ, Farih MH. A case of prostate cancer revealed by erythroderma. Our Dermatol Online. 2021;12(2):208-209.

Submission: 12.05.2020; **Acceptance:** 03.08.2020

DOI: 10.7241/ourd.20212.31

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

Letter to the Editor

Cutaneous metastases of prostatic carcinoma: A new case report

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Sir,

Infiltration of the skin by a nonmelanocytic tumor is rare, with its incidence varying from 0.6% to 10% of cases. SM is associated with less than 10% of deep cancers [1,2]. It is usually mammary and pulmonary carcinomas that produce SM [3]. In the genitourinary tract, prostatic cancer occupies the third place in cancers metastasizing to the skin [2]. Usually, patients present themselves with multiple eruptive bluish nodules [1,2,4,5], and may undergo surgical excision, chemotherapy, or radiation therapy [5].

A 74-year-old male operated for prostatic carcinoma persistent for one year presented himself with purplish nodules on the left groin. A microscopic examination of biopsy specimens revealed the occupation of the dermis by a malignant proliferation. The tumor cells were arranged in clusters (Fig. 1). Nuclei were pleomorphic with prominent nucleoli (Fig. 2). Immunohistochemical staining revealed positivity for PSA antibodies (Fig. 3). The diagnosis of cutaneous metastasis from a prostatic carcinoma was maintained.

Prostatic cancer is the most frequent non-cutaneous cancer in males [3-5]. Studies published in the literature have shown that SM occurs in elderly patients aged above 60 years, as in our case [1]. SM from prostatic cancer accounts for nearly 0.36% of cases, and has lately been increasing in frequency [3]. Cases of prostatic cancer revealed by SM have been reported in the literature, yet these are rare [1]. The diagnosis of SM from prostatic cancer may be reached by fine needle aspiration or from biopsy specimens, although some authors believe that a histological examination is needless if the patient already suffers from an advanced stage of the disease [5]. On gross examination, SM from prostatic cancer manifests itself as pinkish and fleshy nodules [2]. The pathologic features of SM from prostatic cancer are the same as those described for primary tumors [1,3,4]. In the case of a poorly differentiated or undifferentiated carcinoma, the diagnosis may be difficult, and SM from prostatic cancer is hard to differentiate from primary skin tumors in such cases [2]. PSA is highly specific of prostatic carcinoma but negative staining does not exclude the diagnosis of prostatic carcinoma, especially in the case of the undifferentiated forms. PSA may be expressed in undifferentiated neuroendocrine carcinomas and small cell carcinomas of the lungs [5]. Other immunohistochemical markers, such as NKX3.1, have been tested. The last showed positivity of tumor cells in

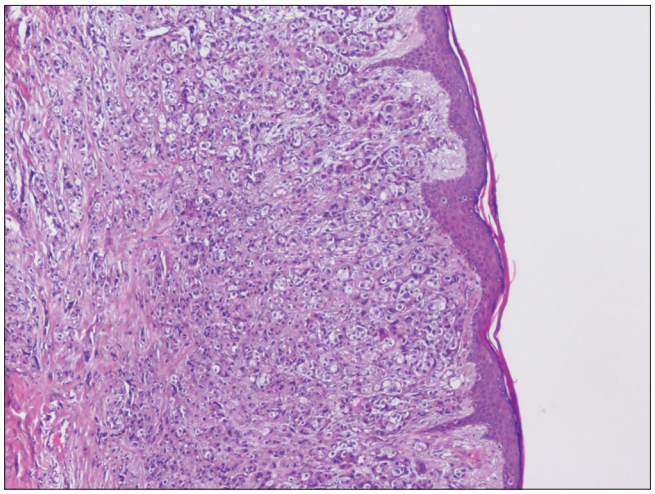

Figure 1: A malignant proliferation invading the dermis, with the tumor cells arranged in narrow cords and clusters (H&E, 40×).

How to cite this article: Laabidi B, Khemir A, Gargouri F, Mansouri N, Msakni I. Cutaneous metastases of prostatic carcinoma: A new case report. Our Dermatol Online. 2021;12(2):210-211.

Submission: 10.10.2020; **Acceptance:** 10.12.2020

DOI: 10.7241/ourd.20212.32

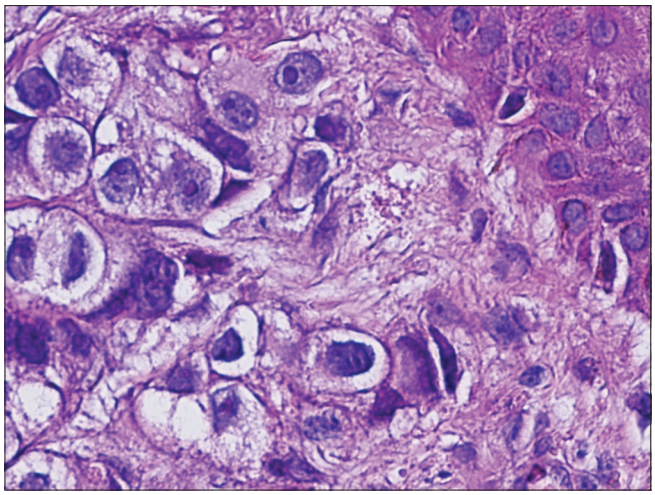

Figure 2: Malignant cells with hyperchromatic irregular nuclei and prominent nucleoli (H&E, 400×).

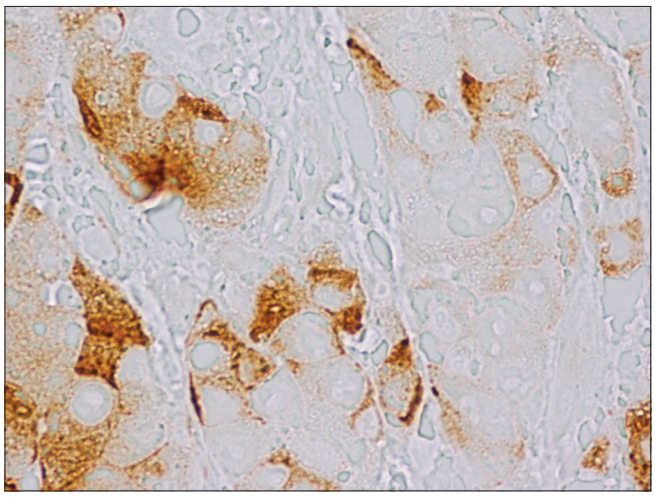

Figure 3: PSA antibody staining showing strong and diffuse cytoplasmic positivity of the tumor cells (400×).

SM from prostatic cancer and, therefore, may be helpful in the diagnosis [1,4]. Primary adnexal carcinoma is the main differential diagnosis. Lymphovascular invasion is in favor of cutaneous metastases [1,3,4]. Ivan et al., in their study, have shown that p63 antibodies may help in distinguishing primary adnexal carcinoma from SM. p63 was positive in all adnexal carcinomas and negative in metastases. The same results were found with D2-40 antibodies [1]. Therapeutics are limited to palliative options. Patients may undergo surgical excision, chemotherapy, or radiation therapy. SM from prostatic cancer is a rare phenomenon. Survival rates in patients with SM do not, on the average, exceed seven months [5]. Since SM presents itself at an advanced stage of the disease, it is usually associated with poor prognoses. Almost 95% of the patients die within a year of being diagnosed with SM [1].

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.

Letter to the Editor

Cutaneous lymphangioma circumscriptum after mastectomy for breast cancer

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Sir,

Lymphangioma circumscriptum (LC) is a superficial cutaneous cystic malformation secondary to abnormalities of lymphatic development [1]. LC is a rare benign tumor, and so are cutaneous lymphangiomas, accounting for 4% of all vascular tumors [1]. LC is usually congenital but may appear later. Acquired LC is reported to occur from trauma, as from surgery, radiotherapy, or the combination thereof [2]. Herein, we report a case of cutaneous lymphangioma complicating the radiosurgical treatment of breast cancer. A 42-year-old female, with a history of vitiligo persistent for ten years prior, was diagnosed with carcinoma of the left breast in 2017. She underwent a mastectomy of the left breast with axillary lymph node clearance followed by chemotherapy and radiotherapy. The patient presented herself to our department of dermatology with multiple vesicles on the left axillary fold evolving for the last two months. A dermatological examination revealed multiple small skin-colored vesicles on the left axillary fold (Fig. 1a), which were neither itchy nor painful. A dermoscopic examination revealed lacunas of brown-orange discoloration associated with fine linear vessels (Fig. 1b). A biopsy revealed lymphatic ducts with thin walls in the papillary dermis and with erythrocytes in the lumens of lymphatic vessels (Fig. 2). Based upon all clinical, dermoscopic, and histological findings, a diagnosis of lymphangioma circumscriptum was given. The patient was treated with surgical excision with excellent results. There was no recurrence within a one-year follow-up period.

Cutaneous lymphangioma circumscriptum (CL), also known as a superficial lymphatic malformation, is a rare benign tumor and the most common kind of lymphangioma [1]. CL may compromise any cutaneous or mucosal surface, but mainly the neck, axilla, breast, chest, buttocks, thighs, and oral mucosa [2]. CLC is frequently observed in females and is clinically characterized by the presence of multiple translucent small vesicles, either isolated or confluent. Dermoscopy is useful for diagnosis of CL, showing multicolored—white, yellow, brown, orange—lacunae in addition to vascular structures [3]. Histology confirms the diagnosis suspected clinically and dermoscopically, showing lymphatic ducts in the papillary dermis with thin walls and sometimes with erythrocytes in the lumens of lymphatic vessels [4]. Although dermoscopy is a tool for the rapid diagnosis of CLC, histology remains the gold standard for the definitive [5]. The differential diagnosis of CL may include herpes zoster, hemangiomas, angiokeratomas, viral warts, molluscum contagiosum, and epidermal nevi [1,2]. Surgical excision, as performed in our patient, is the preferred approach producing low rates of recurrence [1,4]. Other treatment options may include cryosurgery, electrodessication, ablative CO2 laser therapy, and radiotherapy. Because a recurrence may develop after treatment, close follow-ups are recommended. Lymphangiomas may be localized or generalized, and may be congenital or acquired, as in our case [1].

In fact, the CLC in our patient appeared after radiotherapy for breast cancer. Radiotherapy can lead to tissue complications. Lesions caused by radiotherapy occur mainly at the junction of the reticular dermis and adipose tissue, resulting in fibrosis, lymphatic obstruction, increased local pressure, and, consequently, lymphatic fluid accumulation. Clinically,

How to cite this article: Zaouak A, Koubaa W, Hammami H, Fenniche S. Cutaneous lymphangioma circumscriptum after mastectomy for breast cancer. Our Dermatol Online. 2021;12(2):212-213.

Submission:16.04.2020; **Acceptance:** 10.08.2020

DOI:10.7241/ourd.20212.33

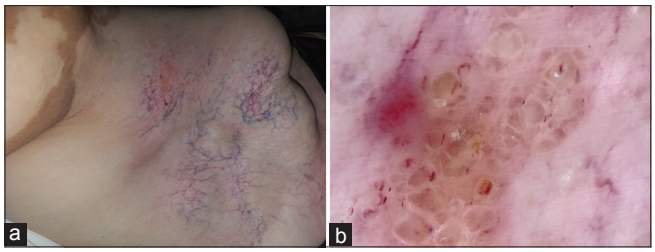

Figure 1: (a) Multiple translucent small vesicles on the left axillary fold. (b) Dermoscopy showing lacunas of brown-orange discoloration with fine linear vessels.

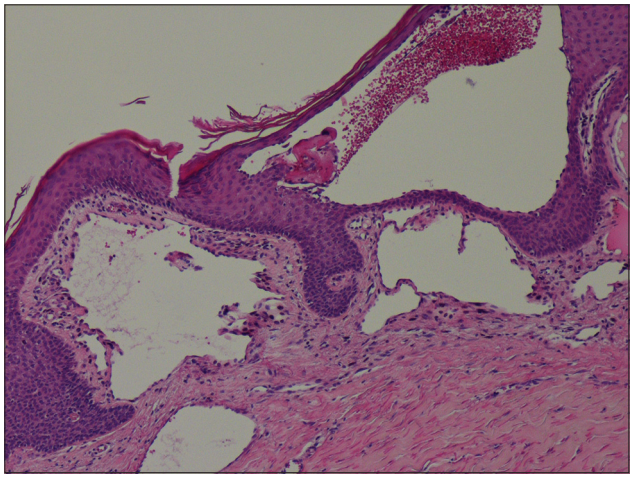

Figure 2: Lymphatic ducts with thin walls in the papillary dermis and with erythrocytes in the lumens of lymphatic vessels (H&E, 100×).

due to saccular dilatation of the superficial lymphatic channels, lesions may vary from vesicles to reddish nodules [2].

In summary, CLC is a rare benign cutaneous neoplasm, and clinicians should be aware of the probability of its appearance after radiotherapy for breast cancer.

ACKNOWLEDGEMENTS

We would like to thank the patient.

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

Letter to the Editor

An itchy genital eruption

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Sir,

A 26-year-old male without a significant medical history was referred to our dermatology department for evaluation of an itchy eruption on the pubic area persistent for ten days prior. A skin examination revealed multiple brownish macules 1–2 mm in size in the hair of the thighs and genitalia and overlying particles attached near the base of the pubic hairs (Fig. 1). Dermoscopy showed moving pubic lice (Fig. 2) and nits firmly attached to the pubic hair. There was no inguinal lymphadenopathy. Hence, the diagnosis of pediculosis pubis was confirmed. The patient was treated with a 25% benzyl benzoate lotion one week apart and advised to shave the pubic hairs. After a week of treatment, there was a resolution of the genital pruritus and no lice were seen on a follow-up. A screening for sexually transmitted disease was performed and was negative.

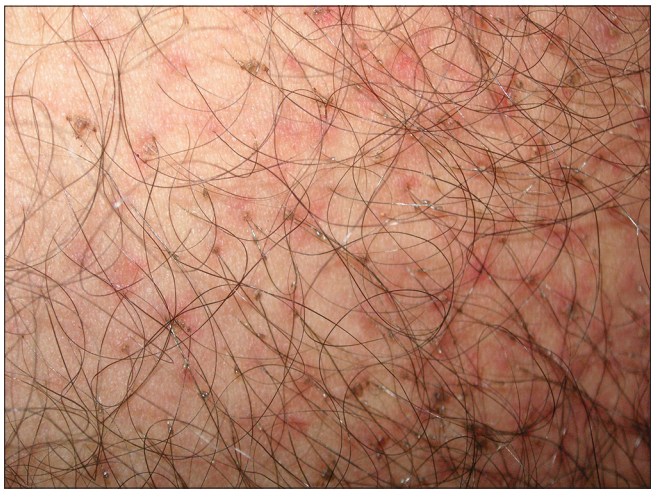

Figure 1: Multiple pigmented macules and overlying particles attached near the base of the pubic hairs.

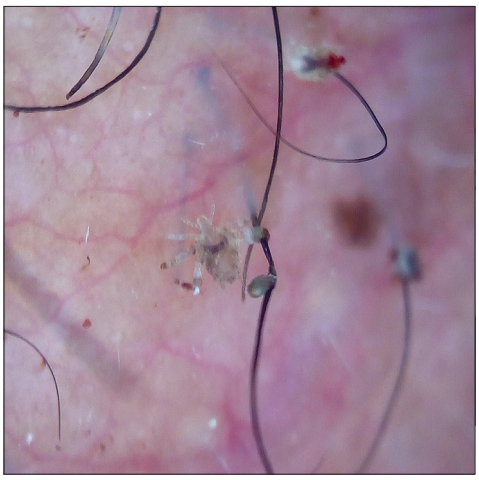

Figure 2: A clear visualization of pediculus pubis near the base of the pubic hairs by dermoscopy (DermLite DL4, 10×).

Pediculosis pubis is an infectious disease caused by the louse *Pthirus pubis*. Its diagnosis is based mainly on clinical findings, and its main clinical diagnostic feature is severe itching in the pubic area [1,2]. Infested patients may also develop asymptomatic bluish-gray macules (*maculae ceruleae*) secondary to hemosiderin deposition from louse bites [3].

Dermoscopy allows for the visualization of nits and moving lice on the pubic hairs, yielding definitive evidence of active infestation [2].

Dermoscopy appears to be a quick, accurate, reliable, and adjuvant tool in confirming the diagnosis by exposing lice with crab-like claws and body shapes firmly attached to the pubic hairs [4]. Apart from the pubic area, other body areas may be involved, such as the scalp, eyelashes, eyebrows, chest, axillary regions, thighs, and buttocks [1]. Pediculosis pubis is considered a sexually transmitted infection transmitted by direct contact [1,2,5]. Hence, screening such patients for other sexually transmitted infections is strongly recommended [1,5]. Genital pruritus accompanying pediculosis pubis may be complicated by bacterial

How to cite this article: Zaouak A, Magdoud O, Hammami H, Fenniche S. An itchy genital eruption. Our Dermatol Online. 2021;12(2):214-215.
Submission: 16.04.2020; **Acceptance:** 24.08.2020
DOI: 10.7241/ourd.20212.34

superinfection of excoriations [5]. Patients should be re-examined after one week especially if the symptoms persist and retreated if lice are discovered [1]. Sexual partners should be treated to prevent repeat transmission [6].

In summary, we strongly recommend dermoscopy as an accurate and rapid diagnostic tool for the diagnosis of pediculosis pubis.

ACKNOWLEDGMENTS

We would like to thank the patient.

Consent

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

Letter to the Editor

Subacute cutaneous lupus erythematosus induced by antituberculous drugs

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Sir,

Drug-induced lupus erythematosus is an autoimmune disorder usually appearing as a result of chronic exposure to certain drugs (from months to years) and resolving after their cessation. It was first described by Hoffman in 1945, when he reported lupus-like symptoms following sulfadiazine treatment [1]. In 1985, hydrochlorothiazide was reported to induce subacute cutaneous lupus erythematosus (SCLE), thus introducing the concept of drug-induced subacute cutaneous lupus erythematosus [2]. To date, over a hundred drugs from more than ten categories have been implicated in DILE [3]. As with idiopathic lupus, DILE is classified into three forms: systemic DILE, drug-induced subacute cutaneous lupus erythematosus (DISCLE), and chronic cutaneous DILE [4].

A 37-year-old female patient was treated with antituberculosis drugs for the previous four months for tuberculous pleurisy. She noticed asymptomatic erythematous lesions on the face two months after starting the treatment. She had also been complaining of an acute hair loss, arthralgia, and dry-eye and dry-mouth syndrome. A clinical examination found annular erythematous squamous plaques with clear borders and telangiectatic surfaces sitting at the level of the cheeks and the nose with respect to the nasolabial folds (Fig. 1). Dermoscopy revealed erythema, linear vessels, and keratin plugs (Fig. 2). A skin biopsy confirmed the diagnosis of SCLE by showing vacuolar degeneration of the basal membrane, apoptotic keratinocytes, edema, and a lymphocytic infiltrate in the upper dermis (Fig. 3). Immunological tests were positive for anti-nuclear antibodies, anti-native DNA antibodies, and anti-SSA/anti-SSB antibodies. Blood work found anemia, lymphopenia, and consumption of complement C3 with no renal failure or proteinuria. The diagnosis of isoniazid-induced lupus was reached, indicating its discontinuation and replacement by a combination of ethambutol and pyrazinamide in addition to rifampicin.

The patient was then treated with hydroxychloroquine and systemic steroids for one year due to the persistence of the arthralgia. However, the rash resolved completely three months after beginning treatment.

Drug-induced SCLE is the most common form of DILE, accounting for 20% of all SCLE cases [5]. Most patients affected by drug-induced SCLE are female (72%), with a mean age of 58 years [4]. SCLE may present weeks to years after the initiation of medication [6]. The lesions begin as erythematous papules/plaques, which progress to

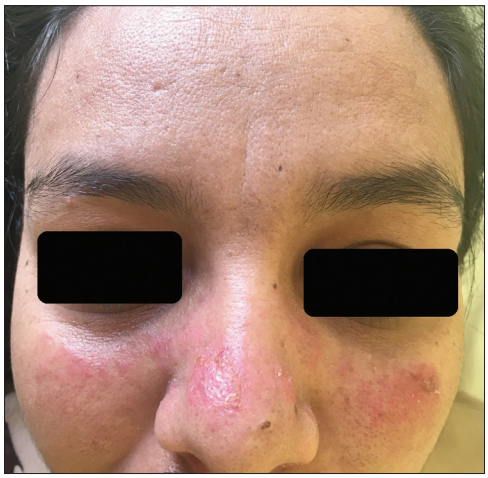

Figure 1: A clinical image showing annular erythematous and squamous plaques with clear borders on the cheeks and the nose with respect to the nasolabial folds.

How to cite this article: Mrabat S, Eloudi S, Douhi Z, Baybay H, Mernissi FZ. Subacute cutaneous lupus erythematosus induced by antituberculous drugs. Our Dermatol Online. 2021;12(2):216-217.

Submission: 26.09.2020; **Acceptance:** 03.12.2020

DOI: 10.7241/ourd.20212.35

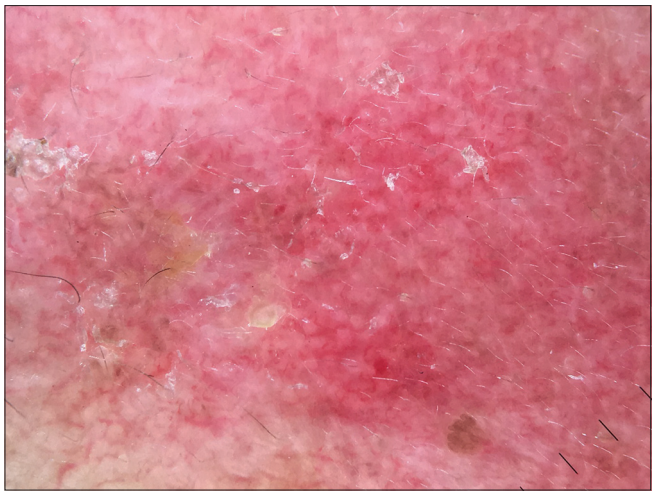

Figure 2: A dermoscopic image revealing the presence of erythema, linear vessels, and keratin plugs.

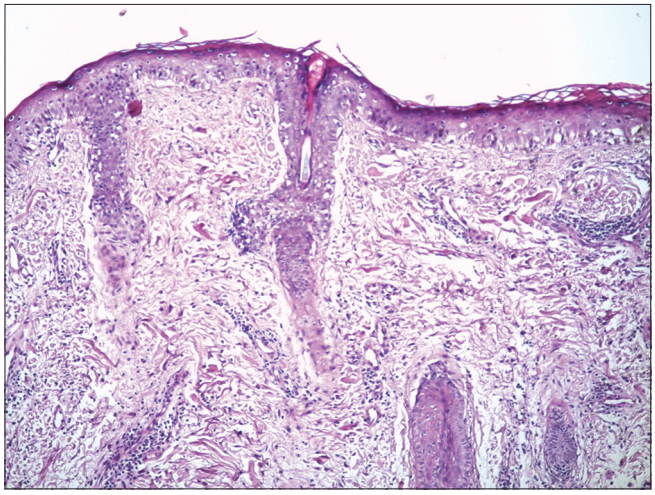

Figure 3: A skin biopsy showing vacuolar degeneration of the basal membrane, apoptotic keratinocytes, and a lymphocytic infiltrate in the upper dermis.

widespread annular, polycyclic lesions with central clearing or papulosquamous lesions. SCLE is strongly associated with the anti-Ro/SSA antibodies (70% of cases). 60% to 80% of cases present positive ANA and 30% to 50% present anti-La/SSB antibodies, which was the case in our patient. The patient may also exhibit features of Sjögren syndrome: in our case, the patient complained of dry-eye and dry-mouth syndrome. The criteria for the diagnosis of drug-induced lupus have not been determined. The diagnosis of drug-induced SCLE may be suspected upon characteristic clinical features combined with a relevant drug history supported by positive histopathology and anti-Ro/SSA antibodies [7]. Regression of the lesions after stopping treatment also allows making the diagnosis of drug-induced lupus.

Spontaneous resolution of DI-SCLE commonly occurs within six to twelve weeks of drug withdrawal. Administration of topical corticosteroids may accelerate the healing process [5]. In our case, isoniazid was interrupted once the diagnosis of DI-SCLE was reached, and the patient was put under topical corticosteroids in addition to hydroxychloroquine and oral steroids for a period of one year. Within three months, the rash resolved completely.

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.

Letter to the Editor

Discoid lupus erythematosus with genital manifestations

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Sir,

A 56-year-old male with a long history of cutaneous lupus erythematosus affecting the ear and elbow had abandoned treatment for the last five years and presented with new lesions. A clinical examination revealed typical lesions of lupus discoid in the ear and right elbow (Fig. 1), as well as a well-demarcated, atrophic, erythematous, keratotic plaque with scales, 6 × 8 cm in size, affecting the scrotum (Fig. 2). Dermoscopy revealed follicular keratotic plugs, white scales, and structureless whitish areas (Fig. 3).

In all types of lupus erythematosus, skin lesions appear typically in sun-exposed areas [1], but rarely on the genitalia, with a few cases reported in the literature.

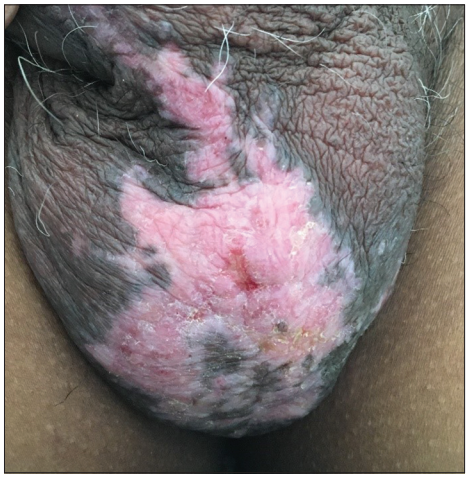

Figure 2: A well-demarcated, atrophic, erythematous, keratotic plaque with scales on the scrotal skin.

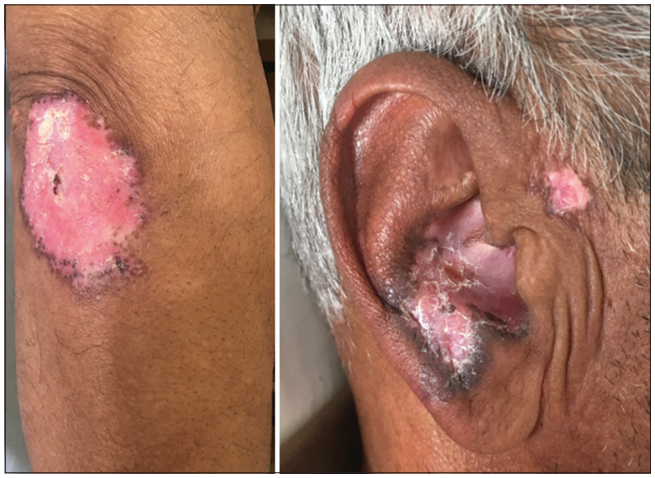

Figure 1: Erythematous plaques on the ear and elbow.

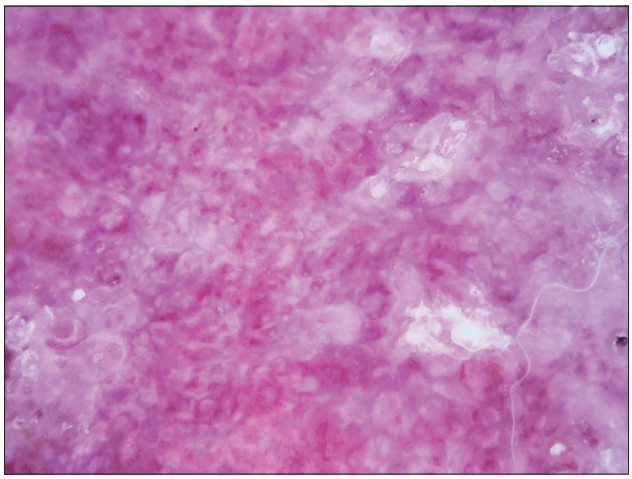

Figure 3: Follicular keratotic plugs, white scales, and structureless whitish areas.

How to cite this article: Mrabat S, Elloudi S, Kassel J, Douhi Z, Baybay H, Mernissi FZ, Ennaciri S, Hassan Farih M. Discoid lupus erythematosus with genital manifestations. Our Dermatol Online. 2021;12(2):218-219.

Submission: 21.10.2020; **Acceptance:** 26.12.2020

DOI: 10.7241/ourd.20212.36

The lesions that have been described are usually erosions or ulcers and erosive plaques on the mucous membranes and may be confused with other diseases [2]. A physician's increased awareness of this unusual manifestation of discoid cutaneous lupus is important. Untreated patients may be prone especially to scarring and disfigurement, and such sequelae are preventable by early diagnosis and treatment [3].

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

Multiple vegetative lesions revealing superficial granulomatous pyoderma

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Sir,

First described by Wilson-Jones and Winkelmann in 1988 [1], superficial granulomatous pyoderma (SGP) is a rare disease that is considered a variant of pyoderma gangrenosum. SGP differs from the classic form by its indolent clinical course, a lack of an associated and underlying disease, the presence of a granulomatous infiltrate on histology, and a better prognosis with less aggressive therapies [2].

A sixty-year-old male with no known past medical history presented himself with multiple verrucous skin lesions. These started eight months earlier as nodules and rapidly progressed into vegetating purplish erythematous plaques gradually increasing in size, localized on the abdomen, pubic area, and buttocks. A clinical examination revealed crusty and purplish verrucous plaques on the abdomen (Fig. 1), vegetative nodular lesions in the pubic area (Fig. 2), and an ulcerative painful lesion on the buttocks (Fig. 3). There was also a cribriform scar on the left shoulder. Besides, the patient had no systemic symptoms and otherwise felt well. The first biopsy revealed a neutrophilic infiltrate suggestive of an infectious origin. The patient was treated with antibiotics for fifteen days without an improvement. A second biopsy was performed, along with histological, bacteriological, mycological, and parasitological studies. Histology revealed pseudoepitheliomatous hyperplasia, a polynuclear neutrophilic infiltrate with eosinophils, and focal vasculitic lesions (Fig. 4). Mycological, bacteriological, and parasitological examinations were unremarkable. In light of this, the main differential diagnoses were excluded: vegetative tuberculosis, verrucous leishmaniasis, and deep mycosis. Syphilitic serology was unremarkable. Eventually, the diagnosis of superficial granulomatous pyoderma was made. Complete blood count, serum protein electrophoresis, and paraneoplastic workup were normal. Colonoscopy was performed, ruling out Crohn's disease. Systemic corticosteroid therapy was initiated at a dose of 1 mg/kg/day, but, in the absence of improvement after one month, dapsone was introduced at a dose of 150 mg/day with favorable progress and good tolerance.

Superficial granulomatous pyoderma (SPG) is a rare variant of granulomatous pyoderma, differing from its classic form by its painless nature, its clinical and histological appearance, and, most often, the absence of an associated pathology [3]. SGP appears as a superficial ulceration with a clean base and vegetative edges, most often single, painless, and localized at the level of the trunk or the limbs. Histology reveals a granuloma with three zones: an innermost zone of necrotic debris and neutrophils, surrounded by histiocytes and giant cells, and, lastly, encircled by plasma cells and eosinophils [2]. Other histological features include pseudo-carcinomatous hyperplasia, focal hemorrhages, vasculitic lesions, and a neutrophil infiltrate [4]. The main differential diagnoses are infectious bacterial, mycobacterial, and parasitic etiologies. The evolution of SGP is slower than the classic form and not especially aggressive and, most often, responds to simpler treatments, such as local corticosteroid therapy [4].

Our observation presents some peculiarities. The topography and the multiplicity of the lesions are

How to cite this article: El Gaitibi FA, Sialiti S, Khalaayoune M, Znati K, Meziane M, Ismaili N, Benzekri L, Senouci K. Multiple vegetative lesions revealing superficial granulomatous pyoderma. Our Dermatol Online. 2021;12(2):220-221.

Submission: 02.11.2020; **Acceptance:** 11.01.2021

DOI: 10.7241/ourd.20212.37

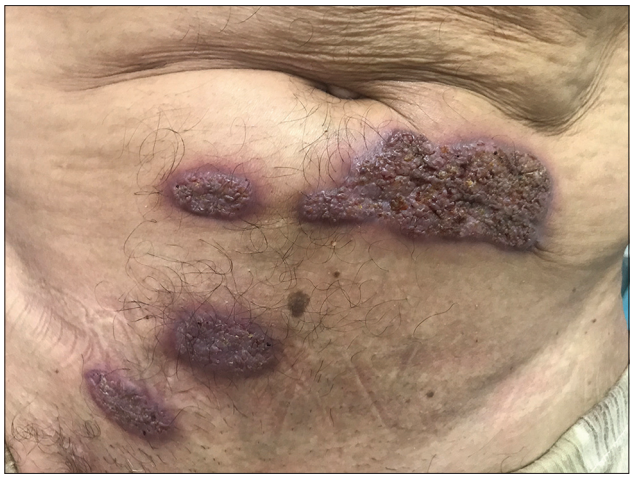

Figure 1: Crusty and purplish verrucous plaques on the abdomen.

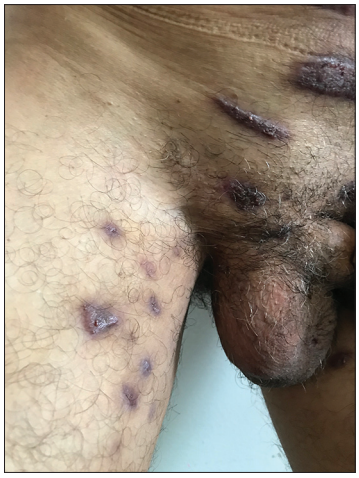

Figure 2: Multiple ulcerated nodules and plaques of the pubis and the right inguinal fold.

rarely reported in the literature [5]. In addition, the absence of a histological granuloma commonly found in SGP makes the diagnosis more difficult. The clinical and histological heterogeneity of this entity is the challenging factor faced by clinicians. SGP remains a diagnosis of exclusion based on the appearance of any vegetative lesion, evolves slowly even in the absence of a granuloma, and is composed of three histological zones.

Consent

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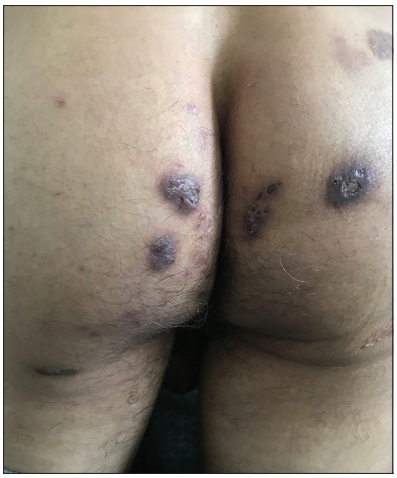

Figure 3: Multiple ulcerated purplish nodules with vegetative edges located on the buttocks.

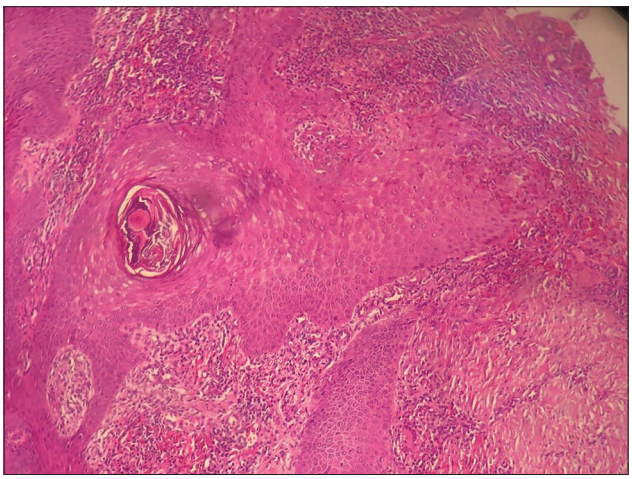

Figure 4: Histologic image showing a polynuclear neutrophilic infiltrate and focal vasculitic lesions (H&E; 20×).

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

Letter to the Editor

Lipedema with genital lymphatic vesicles

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Sir,

Lipedema (or the "pole leg" disease) is a rare and painful disorder of the adipose tissue. It mainly affects females and is generally misdiagnosed as lymphedema or obesity. It may progress to involve the venous system (venolipedema) or the lymphatic system (lympholipedema), adding to the difficulty in its diagnosis. Herein, we report a case of lipedema with genital lymphatic vesicles.

A 56-year-old female presented herself with a symmetrical increase in the volume of both lower limbs persistent since a young age, painful and with repetitive bruising. The patient reported the same condition in her 45-year-old sister. A clinical examination revealed a bilateral and symmetrical enlargement of the legs without the involvement of the feet, with a sharp demarcation between normal and anormal tissue at the ankle. The skin was firm in consistency, irregular, painful on pressure, and of a normal color. Stemmer's sign was absent (Fig. 1). A genital examination revealed papillomatous formations, which failed to whiten after the application of acetic acid and which corresponded to lymphatic vesicles and not to condylomas (Fig. 2). The patient was advised to lose weight, engage in regular physical activity with lymphatic drainage sessions, and wear compression stockings. Moreover, the lymphatic vesicles were not touched because of the risk of lymphorrhea.

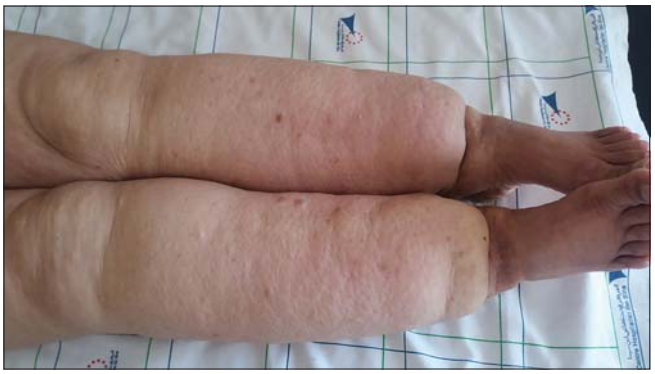

Figure 1: The "pole leg" presentation without the involvement of the feet.

Figure 2: The lymphatic vesicles at the genital level that did not bleach after the application of acetic acid.

Lipedema is considered to be a rare disorder of the adipose tissue. Its etiology is unknown and its pathophysiology is not clearly elucidated [1]. Lipedema exhibits sex-linked, X-linked, dominant or autosomal dominant inheritance [2]. The diagnosis of lipedema is quite frequently missed because of the clinician's usual unfamiliarity with this condition, because of the overdiagnosis of lymphedema, and because of its occasional misdiagnosis as obesity [3,4]. Lymphedema is commonly asymmetric, without associated pain or bruising. Lipedema is bilaterally symmetrically distributed and is associated with pain, edema, and easy bruising. It commonly affects females after puberty but also during pregnancy and after menopause [2,5]. The disease progresses in three stages and the typical presentation is that of a female with bilateral "stovepipe" enlargement of the legs and without the involvement of the feet, with a sharp demarcation between normal and abnormal tissue at the ankle, referred to as the "cuff"

How to cite this article: Abdelmouttalib A, Khallayoune M, Ismaili N, Senouci K. Lipedema with genital lymphatic vesicles. Our Dermatol Online. 2021;12(2):222-223.

Submission: 06.12.2020; **Acceptance:** 21.02.2021
DOI: 10.7241/ourd.20212.38

sign. Lipedema is, however, a chronic progressive disease and advanced cases may deteriorate to involve either the lymphatic system (lympholipedema) or the venous system (venolipedema), or both, which adds to the confusion in the diagnosis. The diagnosis of lipedema is clinical and it is essential to recognize this unique entity in order to establish proper treatment [1]. Treatment involves maintaining a healthy weight, engaging in physical activity, wearing class 2 venous compression stockings, and, possibly, undergoing liposuction for esthetical reasons.

Lipedema is a pathological entity that poses a diagnostic problem, especially being misdiagnosed as lymphedema and, sometimes, obesity. Characteristics observed during the interrogation and clinical examination allow the diagnosis to be reached even if an association with the abnormalities of lymphatic drainage appears in some advanced cases, as in ours.

Consent

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

Our Dermatology Online

Historical Article

Anthology of dermatopathological signs

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ABSTRACT

Dermatopathology is the keystone of dermatology that demands a thorough knowledge and a trained eye to accurately interpret the various microscopic changes and histopathological patterns. Therein, important diagnostics lie in guiding practicing dermatologists as well as postgraduate dermatology residents. This article makes assiduous effort to compile the important signs described by dermatopathology.

Key words: Sign; Mycosis fungoides; Eyeliner; Cookie cutter; Marquee

INTRODUCTION

Dermatopathology is the core subspecialty of dermatology, which has evolved intensively throughout the years. Numerous patterns and changes involve different layers of the skin, whose observation requires careful collection of biopsy samples, proper staining, and meticulous examination. There are many characteristic marks and signs reported by dermatopathology, which, if identified correctly, can be of remarkable importance for timely and precise diagnosis. Because no compilation of dermatopathological signs is to be found in databases such as PubMed, PubMed Central, SCOPUS, MEDLINE, EMBASE, and Web of Science, the following is an alphabetically-arranged compilation of the important signs described by dermatopathology.

1. Bare underbelly sign: In mycosis fungoides (MF), superficial perivascular lymphocytic infiltrates are concentrated more on the epidermal side of the superficial vascular plexus and the postcapillary venules than on the dermal side (Fig. 1). This sign appears inconsistently, but indicates lymphocytic epidermotropism, a major pathogenic process in mycosis fungoides [1].
2. Brass knuckles sign: Histopathologic examination of lobomycosis shows chains of thickly walled, yeast-like cells referred to as the brass knuckles sign [2].
3. Checkerboard sign: Histopathology of pityriasis rubra pilaris (PRP) shows alternations of orthokeratosis and parakeratosis in a vertical and horizontal direction resembling the checkerboard and, therefrom, referred to as the checkerboard sign [3].
4. Cookie-cutter sign: Magnified scans of punch biopsy specimens of the fully developed lesions of morphea show distinct straight lateral edges called cookie-cutter signs or squared-biopsy signs (Fig. 2) [1].
5. Cornflake sign: A ruptured epidermoid cyst that reacts as a foreign body with neutrophils, macrophages, and multinucleated giant cells, sometimes with the inclusion of scales, is known as the cornflake sign (Fig. 3) [4].
6. Eyeliner sign: Bowen's disease, also referred to as an in situ squamous cell carcinoma, is characterized by full-thickness epidermal atypia and complete loss of polarity in keratinocytes. This, coupled with the fact that the basement membrane remains intact and basal keratinocytes are spared, produces a windblown appearance known as the eyeliner sign (Fig. 4) [4].
7. Flag sign (also known as the pink-and-blue sign): This type of sign appears in actinic keratosis as alternating orthokeratosis above the spared ostia of acrosyringia and acrotrichia and parakeratosis above the interadnexal epidermis [5].
8. Floating sign: Histiocytes wrapping the collagen bundles of the middle and deep layers of the dermis, observed in morphea and interstitial granulomatous

How to cite this article: Tiwary AK. Anthology of dermatopathological signs. Our Dermatol Online. 2021;12(2):224-229.
Submission: 25.04.2020; **Acceptance:** 02.09.2020
DOI: 10.7241/ourd.20212.39

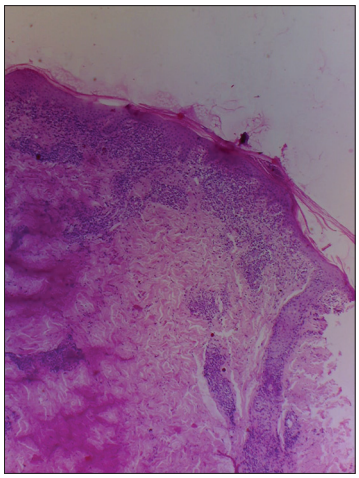

Figure 1: Localization of lymphocytes above the superficial vascular plexus (bare underbelly sign) (H&E, ×100).

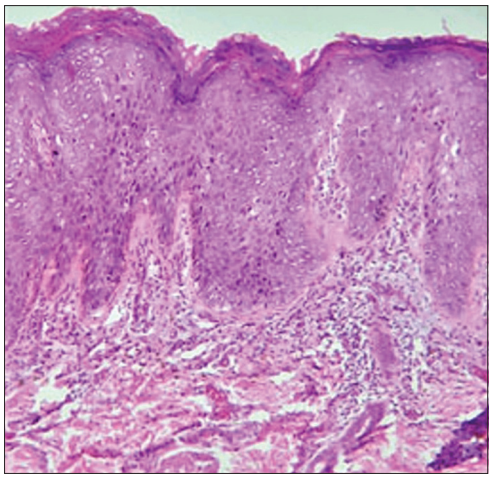

Figure 4: An intact basal layer and keratinocytes in Bowen's disease (H&E, ×200).

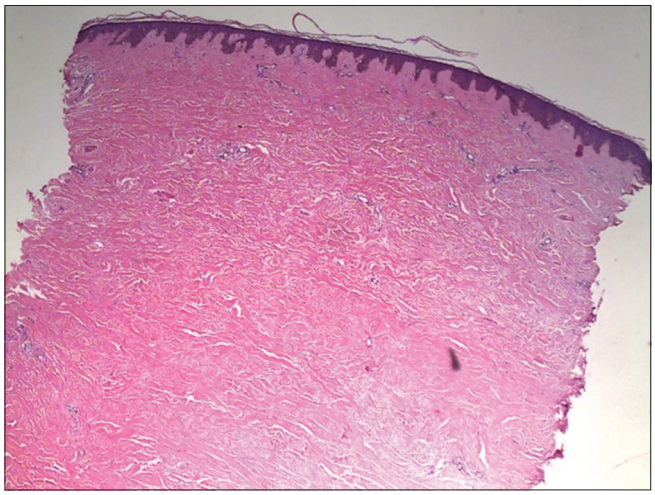

Figure 2: The cookie-cutter sign with sharp and straight edges (H&E, ×100).

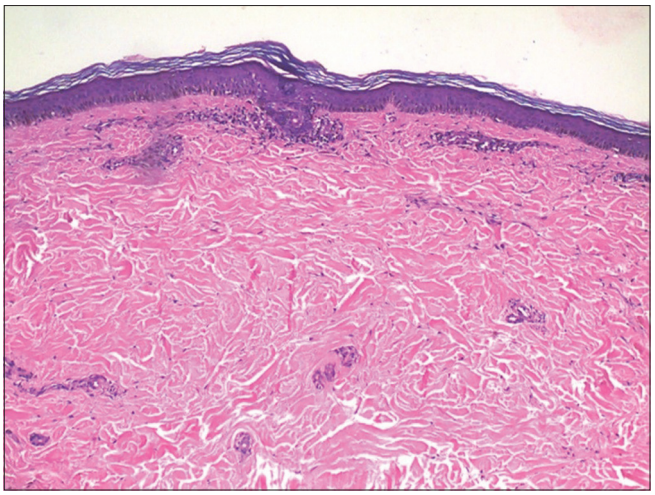

Figure 5: Histiocytes around collagen fibers in morphea (floating sign) (H&E, ×200).

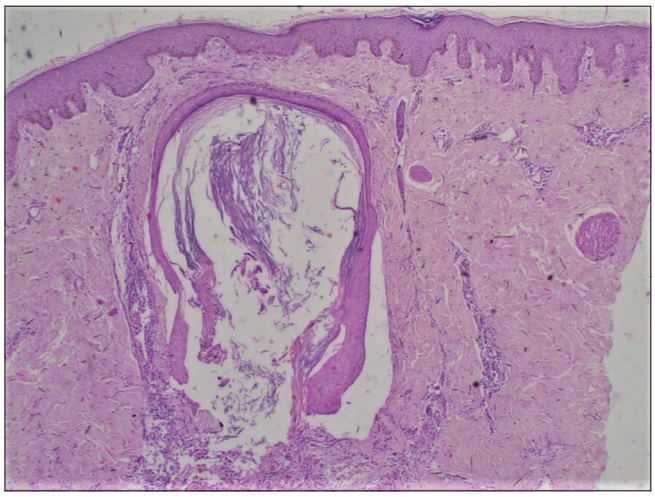

Figure 3: An epidermoid cyst (H&E, ×200).

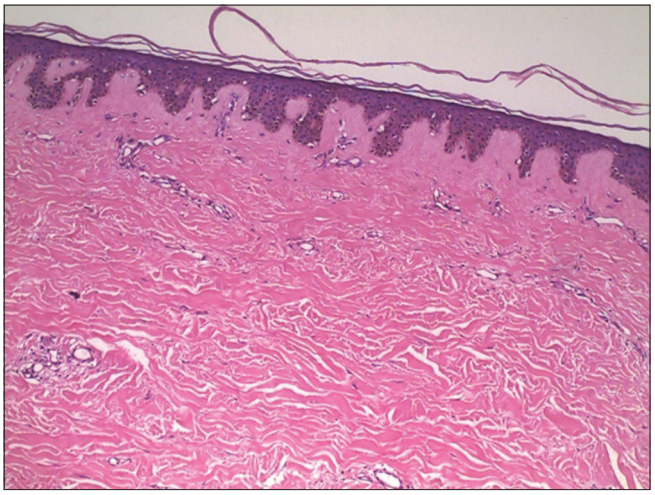

Figure 6: Another case of morphea with the floating sign (H&E, ×200).

dermatitis, are known as the floating sign (Figs. 5 and 6) [6].

9. Goggle sign: Central centrifugal cicatricial alopecia (CCCA), an example of lymphocytic

scarring alopecia, involves perifollicular fibrosis of compound follicles, resembling the frame of a pair of glasses, and fused outer root sheaths, resembling the lenses. Other histological findings are follicular miniaturization, eccentric thinning of the follicular epithelium, premature desquamation of inner root sheaths, and loss of sebaceous glands [7].

10. Hairy palm sign: Histopathology of prurigo nodularis (PN) demonstrates thick compact orthohyperkeratosis, mimicking palmar skin histology (Fig. 7). The presence of folliculosebaceous units in prurigo nodularis reassures the diagnosis [8].
11. Hand-holding sign: A thickened interdigitating epidermis from the slightly tangentially cut biopsy sections of psoriasis forms the hand-holding sign (Fig. 8) [9].
12. Line sign: In morphea, the demarcation between the dermis and the subcutaneous layer becomes sharp and straight due to the loss of the rounded contour of subcutaneous fat lobules at the dermal interface and very dense collagen fibers [10].
13. Lowenbach's sign: The absence or attenuation of the granular cell layer in pityriasis rosea, first reported by Lowenbach, is known as Lowenbach's sign [11].
14. Marquee sign: In acute cutaneous leishmaniasis, amastigote leishmania can easily be seen at the periphery of macrophagic cytoplasm (Fig. 9). The marquee sign was named for its resemblance to the light bulbs arranged around a dressing room mirror [12].
15. Mesa sign: Papillomatous tips in epidermal nevi are flat-topped unlike in other papillomatous skin diseases with pointed or rounded tips, such as verruca vulgaris and seborrheic keratosis (Fig. 10) [1].
16. Murky sign: Merkel cell carcinoma is a deeply basophilic, highly cellular skin tumor with neuroendocrine differentiation. Histopathology reveals small- to medium-sized tumor cells with sparse cytoplasm and blurred cellular outlines, which is referred to as the murky sign [4].
17. Pizza sign: A trichoblastoma consists of two zones and types of neoplastic epithelial cells: the peripheral zone with dark palisading basophilic basaloid cells and the central zone with pale eosinophilic squamoid cells, a configuration known as the pizza sign [13].
18. Promontory sign: The patch and plaque stage of Kaposi's sarcoma (KS) has characteristic histopathological findings consisting of a dermal proliferation of irregular, jagged, thin-walled, dilated vessels lined with thin endothelial cells that surround preexisting small vascular channels and spindle cells. The protrusion of the preexisting vessels into

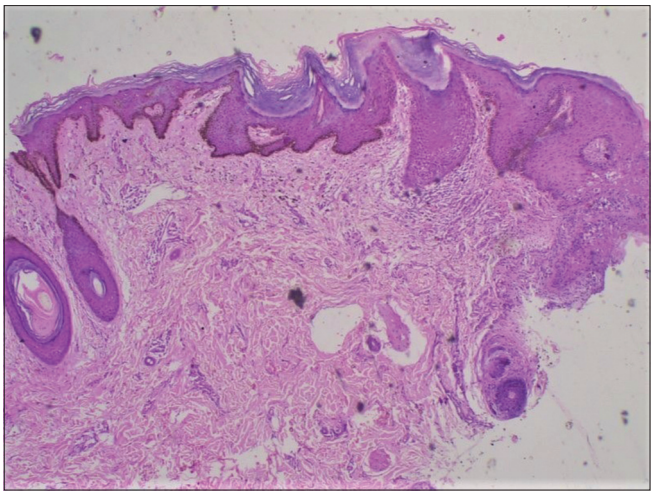

Figure 7: The hairy palm sign in thick compact orthohyperkeratosis (H&E, ×200).

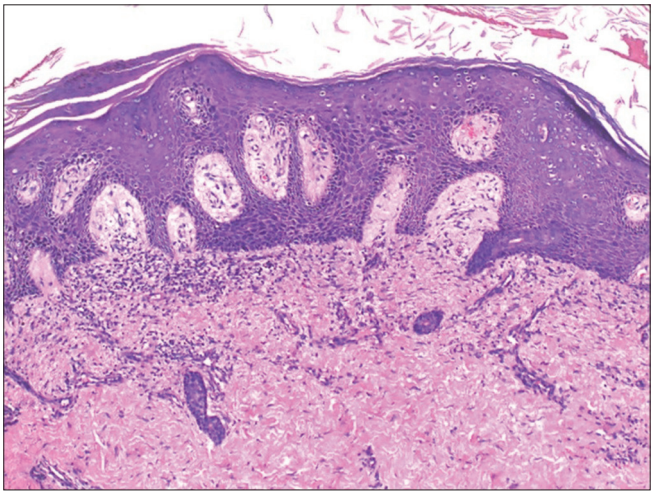

Figure 8: Histopathology of psoriasis showing an interdigitating acanthotic epidermis (H&E, ×200).

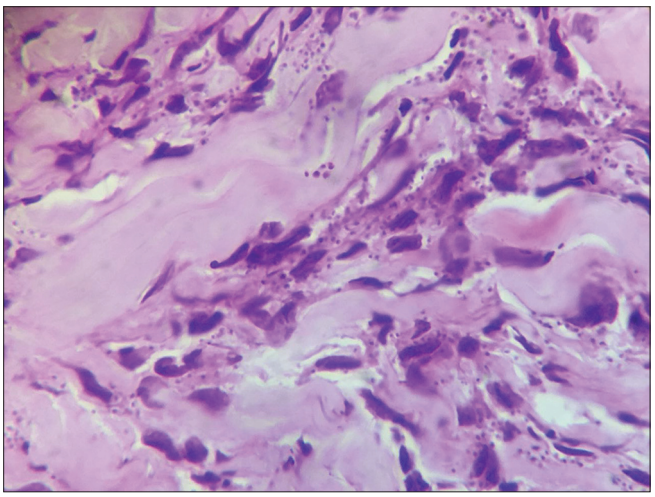

Figure 9: The marquee sign in cutaneous leishmaniasis (H&E, ×400).

the surrounding dilated vascular space is referred to as the promontory sign, noted also in other vascular neoplasms, such as lymphangioendothelioma, retiform hemangioendothelioma, angiosarcoma, and spindle cell hemangioma [14].

19. Purple fiber sign: Elastotic fibers, which are usually admixed with the dermal component of melanocytes in acquired melanocytic nevi, often have a purple tincture. Absent in melanoma, this observation may help in differentiating benign and malignant melanocytic proliferations [15].
20. Recovery sign (also known as the last week's sign): In cured or treated cases of scabies, a normal lamellar stratum corneum with a basketweave pattern is seen underlying parakeratosis or orthokeratosis with mild dermal inflammation indicating prior inflammation [16].
21. Sabouraud's sign: This sign is an extravasation of erythrocytes in pityriasis rosea primarily into the papillary dermis and partly into the epidermis [11].
22. Salute sign (also known as the teapot spout sign or the teapot lid sign or the teapot sign): Pityriasis rosea involves an angulated parakeratosis attached at one end and free on the other, which very much resembles a salute, a sign that can also be seen in psoriasis, subacute eczema, and pityriasis lichenoides chronica (PLC) (Fig. 11) [11].
23. Sampaio sign: This sign is a manifestation of Pseudopelade of Brocq as a gelatinous mass observed close to the bulbar portion created by the removal of an atrophic plaque [17].
24. Sandwich sign: In dermatophytosis, fungi are seen in the stratum corneum, sandwiched between the upper zone of the normal basketweave layer and the lower zone of parakeratosis and orthokeratosis, sharing features of psoriasis such as psoriasiform epidermal hyperplasia and neutrophilic collections (Fig. 12) [14].
25. Screeching halt sign: Incompletely removed acquired melanocytic nevi (pseudomelanoma) reveals a melanocytic proliferation over the scarring. Interestingly, melanocytic nests do not spread beyond either end of the scarring, a pattern known as the screeching halt sign, also called the vertical line sign because both melanocytes and the scarring meet in the same place [14].
26. Signet-ring sign: Signet-ring cell carcinoma (SRCC) is an uncommon histological subtype of malignancy of the stomach, intestines, breasts, prostate, etc. Rarely, SRCC may metastasize to the skin and appear as nodules, giving a poor prognosis and being difficult to diagnose. Histopathology of nodular lesions shows that signet-ring cells appear because of the peripheral location of the nucleus from the accumulation of cytoplasmic mucins. This observation is referred to as the signet-ring sign, also

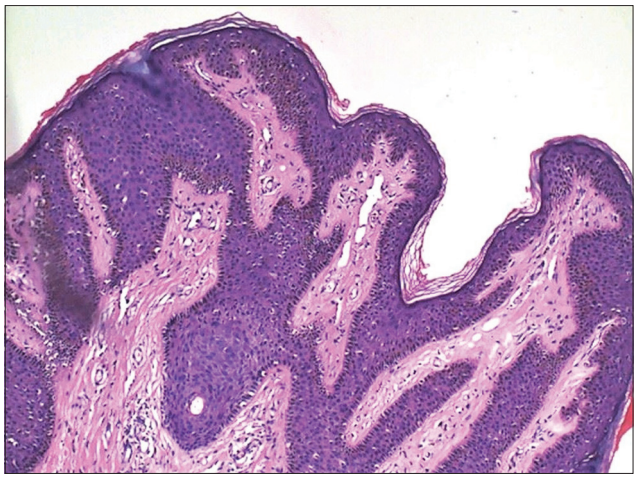

Figure 10: The flat-topped tips of the papillomatous epidermis of an epidermal nevus showing the mesa sign (H&E, ×200).

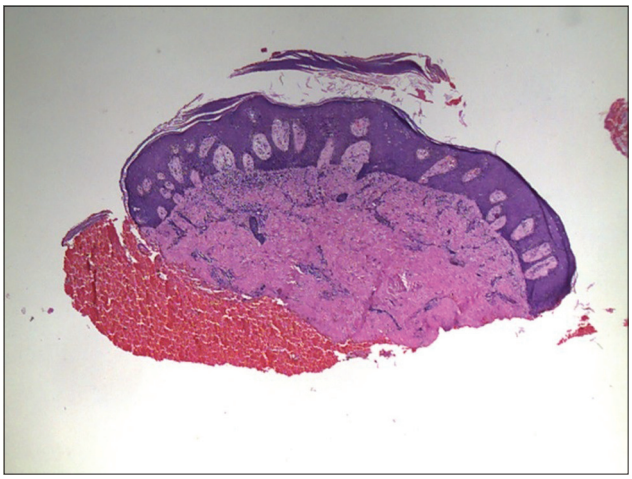

Figure 11: The salute sign in psoriasis (H&E, ×100).

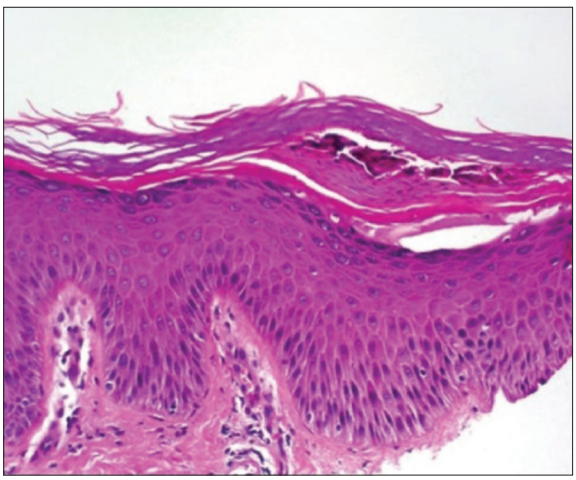

Figure 12: Fungal hyphae sandwiched between the upper normal and lower parakeratotic layers in dermatophytosis (H&E, ×200).

observed in other conditions, such as erysipelas and contact dermatitis, and after formalin fixation as a cytoplasmic shrinkage artifact [18].

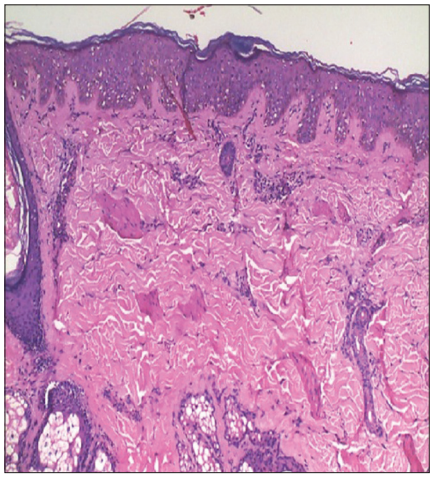

Figure 13: The swarm-of-bees sign (peribulbar lymphocytic infiltrates) in alopecia areata (H&E, ×200).

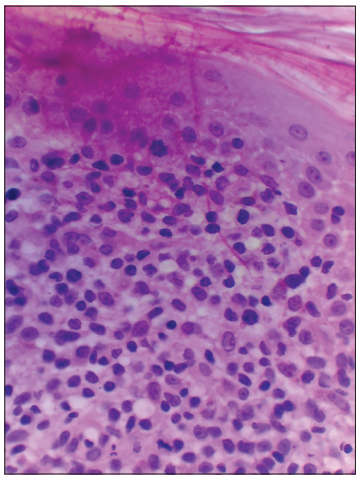

Figure 14: The toy soldier sign in neoplastic lymphocytes lined up along the DEJ in MF (H&E, ×400).

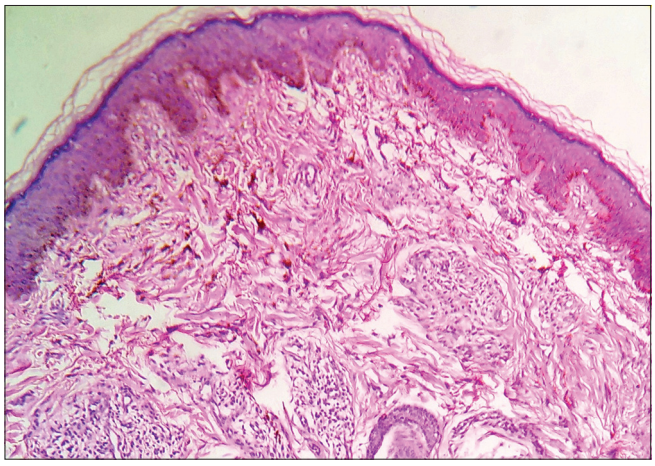

Figure 15: The umbrella sign in elastotic fibers below nevomelanocytes (H&E, ×200).

27. Swarm-of-bees sign: Histopathologic examination of an active and expanding edge of a patch of alopecia areata shows follicles mostly in the late catagen or telogen phase, few in the anagen phase, situated in the subcutis or the middle layer of the dermis. The bulbs of these anagen follicles are surrounded by lymphocytic infiltrates and macrophages creating a pattern known as the swarm-of-bees sign (Fig. 13). The swarm-of-bees sign is usually observed in acute/active inflammation in the anagen phase [17].
28. Toy soldier sign: Malignant T lymphocytes in mycosis fungoides (MF) line up along the dermal–epidermal junction (DEJ) to produce a pattern known as the toy soldier sign (Fig. 14). These atypical, irregular lymphocytes may also invade the epidermis [19].
29. Tram track sign: In nephrogenic fibrosing dermopathy (NFD), also known as nephrogenic systemic fibrosis (NSF), plump CD34+ spindle or epithelioid cells with dendrites orient themselves parallel to elastic fibers and collagen bundles to produce a pattern known as the tram track sign [1].
30. Tricolor sign: This sign occurs in orf and Milker's nodules and owes its name to the three components in its structure: the red cornified layer, the white necrotic epidermis, and the blue basophilic dermal infiltrate.
31. Umbrella sign: Solar elastosis and melanocytic proliferations are common histological features of benign acquired melanocytic nevi and melanoma. The pattern of solar elastosis carries some diagnostic importance. In melanocytic nevi, elastic fibers are present in between melanocytes to receive protection from solar damage and are, for this reason, referred to as the umbrella sign (Fig. 15). This pattern is absent in melanoma, wherein elastotic fibers are pushed downward in the dermis by the expansion of malignant melanocytes [15].
32. Unna's sign: The eczematoid pattern in pityriasis rosea was first described by Unna in 1894 and is eponymously known as Unna's sign [11].

Consent

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

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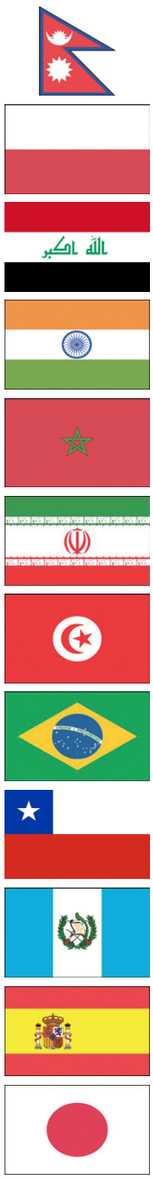
Source of Support: Nil, **Conflict of Interest:** None declared.



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