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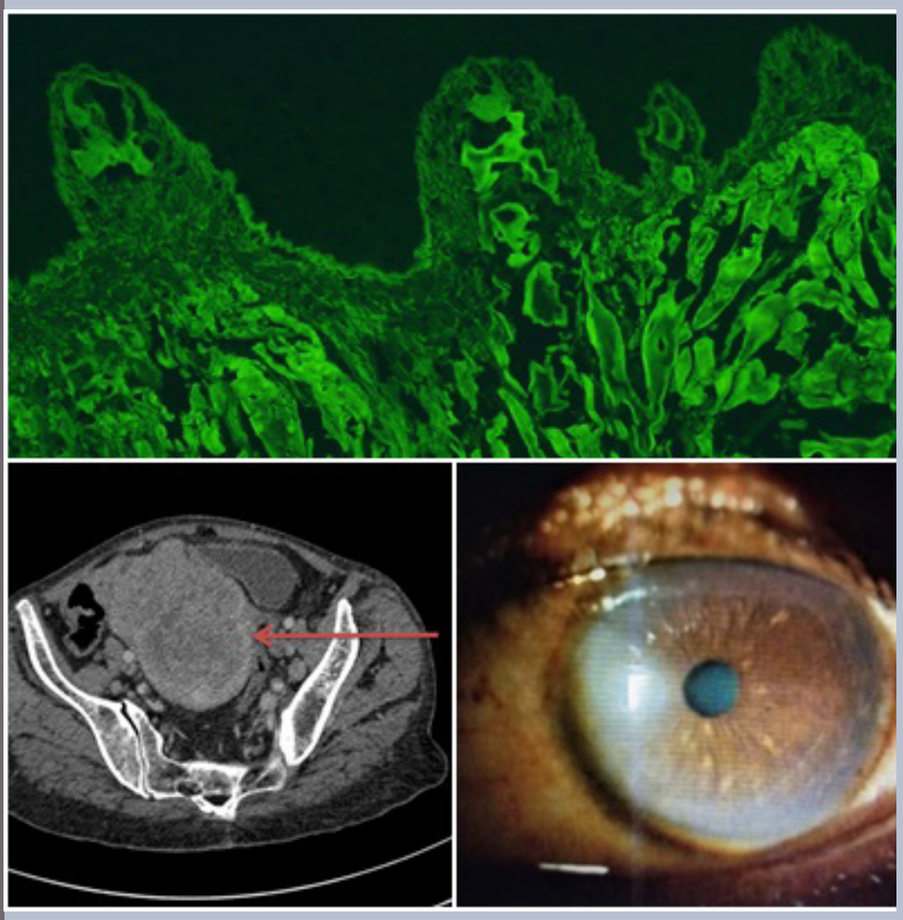

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Our Dermatology Online

Original Article

Pressure ulcers from prone positioning in COVID-19 patients: Developing clinical indicators in evidence-based practice: A retrospective study

Hassiel Aurelio Ramírez-Marín[1], Adrian Soto-Mota[2], Jorge Alanis-Mendizabal[2], Juan Manuel Escobar-Valderrama[2], Judith Guadalupe Domínguez-Cherit[3]

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ABSTRACT

Background: A notable pandemic arisen during the COVID-19 pandemic has developed globally in intensive care units, with patients developing pressure ulcers (PUs) after being ventilated mechanically in the prone position. **Objectives:** The aim was to identify risk factors independently predictive of the development of PUs in adult patient populations treated with prone positioning and to evaluate a possible epidemiological association between the prevalence of PUs and specific clinical characteristics so as to develop clinical indicators for the prevention of PUs. Finally, the aim was to examine our study participants against the incidence of PUs with respect to the length of their stay. **Methods**: This retrospective study enrolled patients hospitalized during the period of May 2020 through January 2021. Data was collected from 299 patients hospitalized and having required prone positioning ventilatory therapy in critical care areas (short-stay units, emergency units, and intensive care units), all of which had developed Pus of at least grade two according to the classification system proposed by the NPUAP/EPUAP. **Results**: Patients who had developed PUs had a longer hospitalization stay overall and were more prone to die during hospitalization. Patients who developed Pus were more frequently males, with higher initial levels of CPK and ferritin. **Conclusions:** The study reveals valuable information on the most important risk factors in the development of PUs due to prone positioning. We have described how the total number of days of hospitalization is significantly related to the development of PUs. Even a PU is not a life-threatening lesion, the implementation of improved positioning protocols may enhance results in critical patient care. We believe that this is a current, globally underestimated problem as the incidence of COVID-19 patients requiring prone positioning—and, therefore, at risk for PUs—is increasing daily.

Key words: SARS-CoV-2; COVID-19; pressure ulcers; prone position; chronic wounds; dressings

INTRODUCTION

The COVID-19 pandemic has dramatically influenced healthcare systems globally, affecting both epidemiology and the organization of patient management [1]. In a number of countries, emergency departments were suddenly put under pressure by an overwhelming number of patients with COVID-19 infection and with acute respiratory insufficiency requiring respiratory therapy in intensive care units (ICUs) [1]. Recent literature has demonstrated a variety of dermatologic manifestations among children and adults with COVID-19 [2]. Skin rashes associated with COVID-19 have primarily presented with erythematous, urticarial, and vesicular (chicken pox-like or varicelliform) manifestations [3,4]. Prolonged prone positioning (PP) is required for some surgical operations and in the management of ARDS [5]. A number of complications

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are known to be associated with these procedures, and researchers have identified pressure ulcers (PUs) as being a serious concern. Thus, implementing evidence-based strategies is essential for the reduction of pressure ulcers in patients treated with PP. PUs are common complications that affect at least 10% of patients in acute care [6]. PUs affect largely intensive-care patients, and their prevalence has been reported to exceed 80% in those in prone positioning [5]. Clinically, a pressure ulcer (PU) is defined by the confined destruction of a skin area and of the underlying tissue due to external pressure, leading to the necrosis of the ischemic area. These ulcers are painful and reduce quality of life significantly. They are expensive to treat, increase the risk of infections. and lead to long hospital stays. The frequent prone positioning as part of COVID-19 treatment creates an additional risk for the development of PUs in unusual topographies. The most important risk factors include immobility and reduced perfusion, which are also characteristics of patients with COVID-19 in critical condition.

As the pandemic began to be established with an increasing number of cases in March 2020, the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" (INCMNSZ) began to treat patients with COVID-19 exclusively. In this unprecedented situation, the department of dermatology noticed an increasing number of PUs as a complication in hospitalized patients. Particularly impressive is the large number of PUs in patients in intensive care units (ICUs) who needed ventilatory therapy in the prone position.

It has been argued consistently that pressure ulcer risk assessment scales need to be developed on the basis of multivariable analysis to identify factors independently associated with PU development [7].

A deepened understanding of the relative contribution that risk factors make to the development of PUs and an improved ability to identify patients at high risk of PUs would enable us to target resources more effectively in practice.

As prone positioning is likely to become frequent in ICUs during the coming months, this article hopes to inform clinicians and nurses of the main risk factors for the development of PUs. The aim of this study was to identify risk factors independently predictive of PUs in adult patient populations treated by PP, to estimate the prevalence of PUs, and evaluate a possible epidemiological association between the prevalence of PUs and specific clinical characteristics so as to develop clinical indicators for the prevention of PUs. Our secondary aim was to examine our study participants against the incidence of PUs with respect to the length of their stay.

MATERIAL AND METHODS

This retrospective study enrolled patients hospitalized during the period of May 2020 to January 2021, Data was collected from 299 patients hospitalized and having required prone positioning ventilatory therapy in critical care areas (short-stay units, emergency units, and intensive care units). The main variables captured included the development of a PU of at least grade two according to the classification system proposed by the NPUAP/EPUAP, the service in which the patient was admitted, the month during which the hospitalization took place, the patient's sex, age, and BMI, a history of smoking, the presence of diabetes mellitus, systemic arterial hypertension, the days of the patient's hospital and CCA stay, and the state of the patient's life. Finally, the aim was to assess the inflammatory state of the patients. Acute phase reactant values at the beginning of hospitalization and the highest value recorded were captured, including PCR, DHL, CPK, ferritin, D-dimer, and fibrinogen.

Statistical Analyses

Descriptive Statistics

Data wrangling and statistical analyses were performed by R, version 4.0.3, with the use of the following packages: *tidyverse*, *readxl*, *performance*, *gtools*, *MASS*, *bootStepAIC*, *lmtest*, and *car*. Descriptive statistics were obtained with *tableone:: CreateContTable* | *CreateCatTable* and quantile values were obtained with *stats:: quantile* for the 5th, 25th, 50th, 75th, and 95th percentiles. Residuals were tested for normality with *stats:: shapiro.test*.

As the first step for identifying which factors are associated with PUs, we grew random classification trees with *rpart:: rpart* with default values for categorical outcomes. Results suggested that the optimal cut-off for hospitalization length was seventeen days. A variable "*long hospitalization=TRUE/FALSE*" if *hospitalization length > 17 days* was created with *dplyr:: mutate*.

Afterward, we ran multivariable linear models with *stats:: glm*. Subsequently, we evaluated the relevance of potential predictors by analyzing their contribution

to the explanatory capacity of the model (AIC), the consistency of their coefficient signs, and the consistency of their statistical relevance. This was done via a bootstrap AIC consistency diagnosis, in which a hundred independent samples were drawn at random from the dataset with *bootStepAIC:: boot.stepAIC*. Model assumptions were evaluated with *performance:: check_model*. Statistical plots were built with *ggstatsplot:: ggbetweenstats*, and APA standard statistical reports were employed with their default parameters.

Due to the descriptive nature of our study, no outcome-based sample size was considered. In a *post hoc* calculation, we had power to detect f2 differences as small as 0.05, with an alpha of 0.05, and a statistical power of 0.8 in linear multiple regressions with as a many as three predictors; and to detect R2 as low as 0.1 with ORs above 2.0, assuming the same statistical error parameters. Nonetheless, interaction terms were avoided and no more than three predictors were evaluated in each linear model. Statistical power and sample size assessments were performed with G*Power, version 3.1.9.4.

Raw Data and Analysis Code Availability

Anonymized raw data from the web survey and the step-by-step, commented code used for wrangling and analysis are publicly available at https://github.com/AdrianSotoM/PU.

Ethics Statement

The realization of this study was approved by the ethics committee of the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán." All photographs of the patients with severe cutaneous affection during their stay in the ICU were published with their approval or one of its proxies. The patients in this manuscript gave written informed consent to the publication of their case details.

RESULTS

Figs. 1 and 2 summarize data analysis.

Factors Associated with the Development of PUs

We found a significant association between hospital stay lengths above seventeen days and the development of PUs. Other characteristics that showed a correlation with PU development were a critical care area stay longer than eleven days, basal ferritin > 597 μg/L, and basal C-reactive protein > 19 mg/L.

Patients who developed PUs at the end of their stay in a CCA were compared with patients who did not develop PUs during their stay in a CCA. Patients from the former group were mostly males; also, they presented with higher initial levels of CPK and ferritin on their laboratory studies. A significant relationship between the development of PUs and the length of the stay in a CCA was found; additionally, patients who had developed PUs had a longer hospitalization stay overall and were more prone to die. The behavior of acute phase reactants during follow-up showed the highest level recorded during their hospital stay of CPK, ferritin, and fibrinogen among patients who had developed a PU when compared to those who had not. All patients required sedatives and anesthetics, including fentanyl, midazolam, propofol, ketamine, dexmedetomidine, vecuronium, and cisatracurium. All patients required norepinephrine with a maximum dose of 0.99 μg/kg/min, with a median of 0.19 μg/kg/min.

DISCUSSION

PUs in the context of prone positioning ventilatory therapy have become a major problem in intensive care units worldwide. They may be of a huge extent and depth and compromise the health and recovery of the patient (Fig. 3). We are still in the middle of the pandemic and it does not seem to be ending any time soon [8]. We assessed the prevalence of PUs and explored their association with specific clinical characteristics among patients. Our data analysis revealed that prolonged hospitalization is, by far, the most important risk factor associated with developing PUs. Importantly, pressure ulcers could be explained by the length of hospital stay alone, as other previously reported risk factors such as diabetes and a high BMI lost significance after adjusting for hospitalization length.

In agreement with our finding, a study conducted in Greece [6] also found that the length of stay was the most significant predictor of developing PUs, similarly to a study in Saudi Arabia [9] showing that the length of stay and advanced age were the most significant predictors for PUs. Among the limitations of this study is the fact that the overall incidence of PUs (84.2%) is

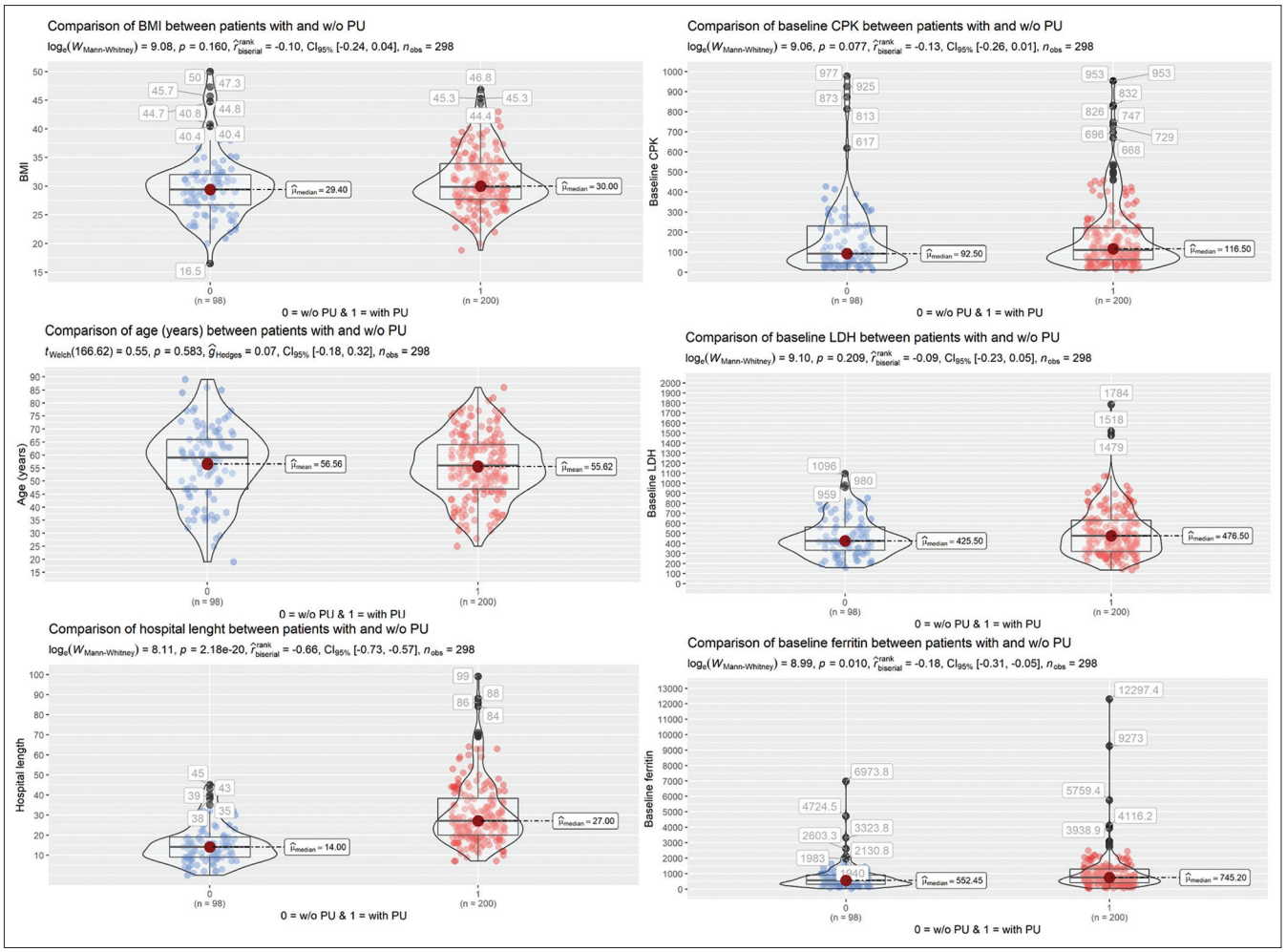

Figure 1: Diagrams comparing the distribution of patients when put against different risk factors related to the development of PUs. Note the significant association between hospital lengths above seventeen days and the development of PUs.

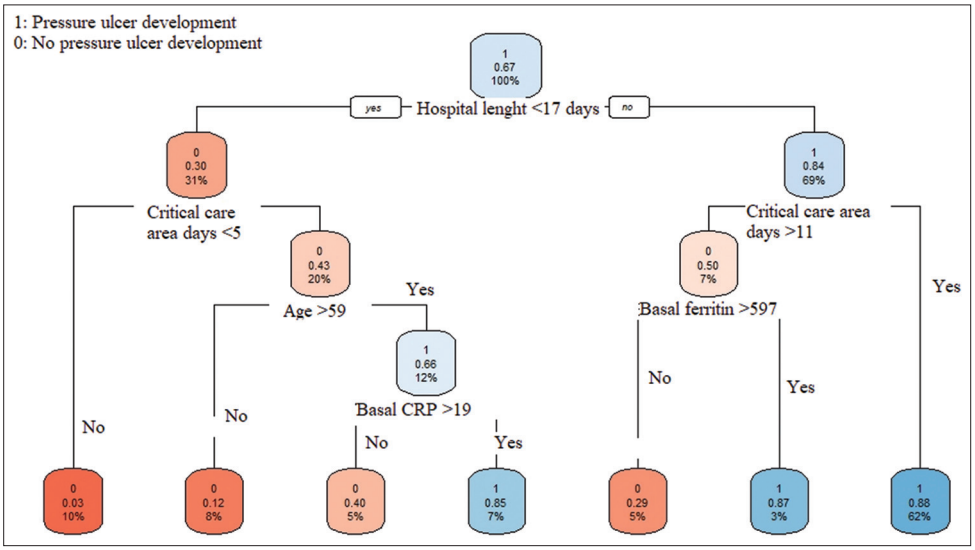

Figure 2: Diagram illustrating the patients' characteristics showing a greater correlation with PUs development, such as the total hospital stay longer than seventeen days, the critical care area stay longer than eleven days, basal ferritin > 597 µg/L, and basal C-reactive protein > 19 mg/L.

extremely high, which leaves a small group without the outcome as to observe differences; also, determinations were made in a single facility, which could have limited the external validity of the study.

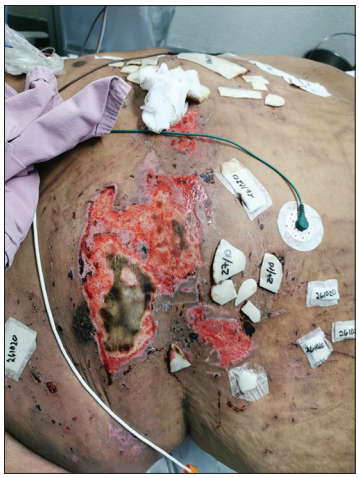

Figure 3: Pressure ulcer related to prone positioning in a COVID-19 patient.

Even if hospitalization length is a well-known risk factor for PUs, these results yield insight into anticipating these complications and are unique for prone-positioned patients. Keeping in mind that prone positioning has proven beneficial even for non-intubated COVID-19 patients [10], it is reasonable to expect an increase in the incidence of these complications.

PUs have proven to be inconstantly associated with a myriad of risk factors. While some studies [11] have put forward prediction tools for identifying risk factors such as age, sex, BMI, and comorbidities such as diabetes [12] or obesity, others have not found good predictors for these complications [7]. Anticipating this, we evaluated both adjusted and unadjusted models with AIC directed bootstrap and corroborated the inconsistency of these factors with the exception of hospital length.

As hospital length is a well-discussed risk factor and probably the only one well established for the development of PUs, it is important to highlight that hospital length is, in many cases, a non-modifiable factor and an unknowable factor. The interactions and point of care taken to the patient receive the most attention regarding PU development. The Braden scale evaluates the possibility of developing PUs, being accurate in 50% [13]. The real factors intervening are the individualized decisions taken by the multidisciplinary team (nurses, physicians, primary caregivers, etc.) to establish prevention strategies, which, when applied, may become the most important modifiable factors in the development of PUs [14,15].

On the other hand, and as our data correlates, using acute phase reactants as predictors factors or docking them into a prediction tool does not show an adequate predicting value [11]. Possibly because of the intrinsic nature of PUs, ideally, these should not happen. Therefore, it was difficult to establish a linear relation regarding attempts to employ inflammation markers [16] to estimate the potential for PU development.

Notoriously, the widely used Braden scale for assessing the risk of developing PUs does not consider hospital length and has shown to be more predictive after 72 hours [17]. While this discrepancy could be explained by a different clinical context in our study (involving only COVID-19 patients), our results highlight the importance of identifying context-specific predictors or refining their definition cut-offs for anticipating these complications and, potentially, avoiding them.

The design and data of our study are not enough to develop prediction tools, yet highlight the need for considering other overlooked factors, such as hospitalization length, and for identifying context-specific risk factors[18].

CONCLUSION

This study has shared valuable information on the most important risk factors in the development of PUs due to prone positioning. We have described how the total number of days of hospitalization are significantly related to the development of PUs. Although PUs are not life-threatening lesions, the implementation of improved positioning protocols may enhance results in critical patient care. We believe that this is a current, globally underestimated problem as the incidence of COVID-19 patients requiring prone positioning—and, therefore, at risk for PUs—is increasing daily. We also emphasize the establishment of individualized prevention strategies in the context of a multidisciplinary team. We hope that the results of our effort are able to heighten the awareness about and improve the prevention of PUs due to PP, so that patients who survive COVID-19 may live without these preventable sequelae.

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involved in the assessment and record-keeping of the patients with pressure ulcers hospitalized in critical care areas. All authors revised the manuscript and provided critical feedback. All authors approved the final version of the manuscript for submission.

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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Our Dermatology Online

Original Article

Frequency of skin infections and tumors among patients with psoriasis

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ABSTRACT

Background: Autoimmune diseases are a vast array of organ-specific and systemic diseases whose pathogenesis results from the activation of B and T lymphocytes reacting against the body's own tissues. Psoriasis is a common, chronic, inflammatory, autoimmune, and proliferative condition of the skin with genetic, immunological, and environmental influences. The objective of the study was to find the frequency of skin infections and tumors in patients with psoriasis with and without immunosuppression in comparison with healthy controls. **Patients and Methods:** An observational, analytic, cross-sectional, controlled study in which a hundred psoriasis patients without treatment and a hundred psoriasis patients on systemic immunosuppression for at least six months were included and compared with two hundred healthy individuals in terms of infections and tumors in the Center of Dermatology in Baghdad, Iraq, from March 1, 2019, through November 1, 2020. **Results:** Psoriasis patients without therapy (group A) and those on systemic therapy (group B) had statistically significant less infection rates than the control group, as 23% of group A and 21% of group B had no infections, while only 6% of controls had no infections (P = 0.0001 for both groups), whereas individuals who were free of tumors both benign or malignant were significantly more numerous in group A (63%) and group B (62%) than in the control group (40.5%) (P = 0.0002 and P = 0.0008, respectively). **Conclusion:** Patients with psoriasis are less susceptible to infections and tumors than the general population. However, psoriasis is less protective than other autoimmune diseases such as pemphigus vulgaris, lupus erythematosus, and vitiligo.

Key words: autoimmune diseases; psoriasis; infections; tumors

INTRODUCTION

Autoimmune diseases are a group of organ-specific as well as systemic diseases whose pathogenesis results from the activation of B and T lymphocytes reacting against antigens of the body's own tissues [1,2].

Psoriasis is a common, chronic, disfiguring, inflammatory, autoimmune, and proliferative condition of the skin in which multiple etiological factors are involved, such as genetic, immunological, and environmental influences [3,4].

ASSOCIATION BETWEEN AUTOIMMUNE DISEASES AND SKIN INFECTION AND TUMORS

Sharquie et al. have conducted and published a number of studies that found that autoimmune diseases such as pemphigus, systemic lupus erythematosus, and vitiligo had protection against skin tumors and infections, although these diseases were treated by immunosuppressive drugs for a long period of time [5].

Vitiligo demonstrates a protective effect against the development of skin tumors and photosensitivity, and the

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absence of melanin in the epidermis is not a significant risk factor for the development of skin tumors [6]. In addition, vitiligo has been causally associated with a reduced risk of several cancers, suggesting that vitiligo as an autoimmune disease may play a role in the suppression of cancer, and these findings are well correlated with the presence of p53 [7,8].

Psoriatic plaques are rarely complicated by recurrent infections with bacterial, viral, and fungal pathogens, as only 7% of patients with psoriasis have bacterial or viral skin infections, as compared with 30% of patients with atopic dermatitis [7].

Psoriasis lesions are seldomly impetiginized. This resistance to secondary bacterial infection may be explained by the increased production of skin-derived antimicrobial peptides, for instance, defensins [8].

PSORIASIS AND VITILIGO AS CLOSE RELATIVES

Both vitiligo and psoriasis are inflammatory autoimmune diseases in which T_h1 helper cells play a role in their pathogeneses and have genetic elements [3,9].

A study from China found that rs9468925 in HLA-C/HLA-B is associated with both psoriasis and vitiligo, providing the first important evidence that two major skin diseases share a common genetic locus in the MHC and a basis for elucidating the molecular mechanism of skin disorders [10]. Additionally, a meta-analysis revealed that psoriasis and vitiligo are associated with each other [11].

Furthermore, in 2017, Sharquie et al. conducted the first clinical study, which showed that vitiligo and psoriasis are closely linked diseases, as both commonly occur in the same patients and their families. Patients may show psoriasis first, then progress into vitiligo, or the same patch may contain lesions of both psoriasis and vitiligo [3].

In addition, psoriasis has been associated with autoimmune diseases other than vitiligo [12].

Therefore, the objective of this work was to evaluate the frequency of infections and tumors among patients with psoriasis and healthy controls and to be compared with other studies that included the frequency of these infections and tumors among other autoimmune diseases such as pemphigus and vitiligo.

PATIENTS AND METHOD

An observational, analytic, cross-sectional, controlled study was conducted during a period of twenty months, starting on March 1, 2019, and ending on November 1, 2020. Formal consent was taken from each patient after fully explaining the goals and nature of our study. In addition, ethical approval was taken from the Scientific Council of Dermatology and Venereology/Arab Board of Health Specializations. Two hundred patients with psoriasis—110 females (55%) and 90 males (45%)—were evaluated. The patients were seen in the Center of Dermatology, Baghdad Teaching Hospital, Medical City, Baghdad, Iraq.

The patients were divided into two groups. Group A included 100 patients with psoriasis—53 females (53%) and 47 males (47%)—with their ages ranging from 5 to 66 years; these patients had taken no medications for their psoriasis. Group B included 100 patients with psoriasis—57 females (57%) and 43 males (43%)—with their ages ranging from 7 years to 64 years; these patients were on continuous systemic therapy for at least the last six months, excluding patients on systemic retinoids or apremilast.

INCLUSION CRITERIA FOR GROUP A

Patients with a diagnosis of psoriasis for at least six months, not on any form of therapy for their psoriasis currently or in the past.

EXCLUSION CRITERIA FOR GROUP A

1. Patients taking any oral or parenteral immunosup pressants for psoriasis or other diseases during their lifetime or topical therapies.
2. Pregnant females.
3. Associated diabetes mellitus.
4. Any other associated immunosuppressive condition.
5. Patients on or previously exposed to phototherapy.

INCLUSION CRITERIA FOR GROUP B

Patients with a diagnosis of psoriasis on continuous systemic immunosuppressive therapy for at least the last six months.

EXCLUSION CRITERIA FOR GROUP B

1. Patients with any interruption of systemic therapy in the last six months.

2. Patients on a systemic retinoid or apremilast.
3. Pregnant females.
4. Any associated immunosuppressive diseases.
5. Patients with diabetes mellitus.
6. Patients on or previously exposed to phototherapy.

In addition, two hundred apparently normal individuals—93 males (46.5%) and 107 females (53.5%)—were included as controls, with their ages ranging from 4 to 67 years; these were non-diabetic and had no history of taking any immunosuppressing drugs during their lifetime.

A full history was taken from each patient and control, including age, sex, duration of disease, and a detailed history of treatment protocols. A physical examination was performed, including a complete skin examination for both the covered and exposed skin for dermatological tumors, infections, and other skin lesions, as well as an examination of the nails, hair, and mucous membranes. The affected body surface area was assessed and the calculation of the PASI score for the patients with psoriasis with an Android application (Psoriasis Calc) was performed.

Calculations were performed with Microsoft Excel 2013. Categorical variables were expressed as frequencies and percentages, and continuous variables as means and standard deviations. The chi-square test was used to assess the significance of the relationship between two categorical variables, while ANOVA was used to evaluate the differences among three groups and P values, with values ≤ 0.05 considered statistically significant. The results are demonstrated in tables and/or graphs.

RESULTS

This study was conducted to demonstrate the frequency of skin infections and tumors in psoriatic patients without therapy (group A) and those on systemic therapy (group B) in comparison with healthy controls.

Demographic Data

Group A included 100 psoriasis patients without treatment—47 (47%) males and 53 (53%) females—with their age ranging from 5 to 66 years; they had had psoriasis for a mean of 64.61 months (SD = 75.046; ranging from 6 to 360 months), their mean psoriasis area and severity index (PASI score) was 7.9595 (SD = 7; range: 1–33), their mean body surface area was 12.44% (SD = 17; range = 1–90%), and their mean age was 36.9 years (SD = 14.8).

Group B included 100 psoriasis patients—43 (43%) males and 57 (57%) females—with their age ranging from 7 to 64 years; the mean duration of their psoriasis was 81.72 months (SD = 70.30; range = 12–360 months), their mean PASI score was 8.59 (SD = 10.58; range = 1–70); their mean body surface area was 10.3% (SD = 14; range: 1–90%), and their mean age was 40.63 years (SD = 11.87). They had been on systemic therapy for at least six months (73 patients were on etanercept, 24 were on methotrexate, two were on a combination of methotrexate and etanercept, and one was on a combination of methotrexate and cyclosporine).

The control group included 200 apparently healthy individuals—93 (46.5%) males and 107 (53.5%) females—with their age ranging from 4 to 67 years; their mean age was 38.96 years (SD = 12.9).

FREQUENCY OF INFECTIONS

Psoriatic patients without therapy and those on systemic therapy, in general, showed a smaller statistically significant infection rate than the control group, as 23% of psoriatic patients without therapy (group A) and 21% of psoriatic patients on systemic therapy (group B) had no infections, while only 6% of the controls had no infections. Table 1 presents details on the different infections. However, as per the analysis of variance (ANOVA) comparing mild, moderate, and severe psoriasis within each group, there was no statistically significant correlation between the severity of psoriasis and the frequency of infection across both groups (P = 0.49 for group A; P = 0.34 for group B).

FREQUENCY OF TUMORS

Individuals free of tumors (benign or malignant) were significantly more numerous in groups A and B than in the control group (63% of group A were free of tumors, 61% of group B were free of tumors, 40.5% of the controls were free of tumors; P = 0.0002 for group A, P = 0.0008 for group B). Table 2 presents details on the different infections.

However, as per ANOVA comparing mild, moderate, and severe psoriasis within each group, there was no statistically significant correlation between the severity

Table 1: The distribution of skin infections in psoriatic patients without treatment (group A) and on systemic drugs (group B) in comparison with controls.

Skin infection	Psoriatic patients without treatment n (%)	P	Psoriasis patients on systemic drugs	P	Controls n (%)
No infections	23 (23%)	0.0001*	21 (21%)	0.0001*	12 (6%)
Individuals with infections	77 (77%)	0.0001*	79 (79%)	0.0001*	188 (94%)
Chicken pox	46 (46%)	0.2	44 (44%)	0.4	78 (39%)
Folliculitis	26 (26%)	0.01*	27 (27%)	0.02*	118 (59%)
Wart	3 (3%)	0.003*	4 (4%)	0.008*	28 (14%)
Herpes simplex	21 (21%)	0.01*	23 (23%)	0.03*	70 (35%)
Herpes zoster	1 (1%)	0.004*	3 (3%)	0.03*	20 (10%)
Candida	3 (3%)	0.03*	3 (3%)	0.03*	20 (10%)
Tinea	1 (1%)	0.01*	2 (2%)	0.04*	16 (8%)
Molluscum contagiosum	4 (4%)	0.02*	4 (4%)	0.02*	24 (12%)
Cutaneous leishmaniasis	0	0.2	0	0.2	3 (1.5%)
Skin infection	**Psoriasis patients without treatment n (%)**	**P**	**Psoriasis patients on systemic drugs n (%)**	**P**	**Controls n (%)**
Carbuncle	0	0.04*	0	0.04*	8 (4%)
Foruncle	3 (3%)	0.03*	3 (3%)	0.03*	20 (10%)
Hand, foot, and mouth disease	0	0.04*	0	0.04*	8 (4%)
Impetigo	1 (1%)	0.04*	0	0.01*	12 (6%)
Cellulitis	0	0.02*	0	0.02*	10 (5%)
Pityriasis versicolor	1 (1%)	0.01*	2 (2%)	0.03*	16 (8%)
Echthyma	0	0.01*	1 (1%)	0.04*	12 (6%)
Erythrasma	0	0.01*	1 (1%)	0.01*	12 (6%)
Total bacterial infections	30 (30%)	0.0001*	32 (32%)	0.0001*	192 (96%)
Total infections	110		117		487

* Significant difference when P was equal or below 0.05

Table 2: The distribution of benign and malignant skin tumors in psoriatic patients (without therapy and with systemic therapy) and controls.

Skin tumors (benign and malignant)	Psoriatic patients without treatment n (%)	P	Psoriatic patients on systemic drugs n (%)	P	Controls n (%)
No tumors	63 (63%)	0.0002*	61 (61%)	0.0008*	81 (40.5%)
Tumors	37 (37%)	0.0001*	39 (39%)	0.0001*	119 (59.5%)
Skin tag	10 (10%)	1	8 (8%)	0.5	20 (10%)
Epidermoid cyst	3 (3%)	0.4	1 (1%)	0.08	10 (5%)
Melanocytic nevi	23 (23%)	0.01*	25 (25%)	0.03*	74 (37%)
Seborrhiec keratosis	4 (4%)	0.008*	5 (5%)	0.01*	28 (14%)
Actinic keratosis	2 (2%)	0.02*	2 (2%)	0.02*	18 (9%)
Cherry angioma	2 (2%)	1	2 (2%)	1	4 (2%)
Basal cell carcinoma	0	0.3	0	0.3	2 (1%)
Squamous cell carcinoma	0	0.3	0	0.1	2 (1%)
Keratoacanthoma	0	0.4	0	0.4	1 (0.5%)
Kaposi sarcoma	0	-	0	-	0
Melanoma	0	-	0	-	0

* Significant difference when P was equal or below 0.05.

of psoriasis and the frequency of tumors across both groups (P = 0.08 for both groups).

DISCUSSION

There are clinical studies supporting the theory stating that autoimmune diseases present less frequent infections and tumors in comparison with healthy controls. In 2014, Sharquie et al. were the first to document that patients with pemphigus vulgaris are less susceptible to infections and tumors compared with patients with renal transplants and healthy controls [5].

Moreover, Sharquie et al., by subsequent studies, also showed that patients with lupus erythematosus and with alopecia areata are less susceptible to infections and tumors compared with renal transplant patients and healthy individuals [1].

Similarly, Sharquie et al. revealed that the severity of vitiligo is closely correlated with the frequency of viral warts and tumors, as patients with mild vitiligo had more frequent warts and tumors than patients with severe vitiligo [6]. They noticed that patients with localized vitiligo had 44.5% of warts and tumors, in contrast to patients with generalized vitiligo, who had 10% of warts and tumors. On the other hand, patients with universal vitiligo had only 2%. Control individuals had 66.2% of warts and tumors [6].

Further studies demonstrated that vitiligo and psoriasis are closely linked diseases [3,13]. These interesting findings had encouraged us to conduct the present work. The results of this study confirmed that 78% of psoriatic patients have a history of infections, as compared with 94% of controls with a history of infections, and this is a statistically significant finding (P = 0.0001).

In addition, patients with psoriasis had statistically significantly fewer tumors collectively (38%) when compared with controls (59.5%) (P = 0.0001).

In comparison with vitiligo patients in Sharquie's study [1], psoriatic patients showed a higher frequency of infections (78% in psoriatic patients vs. 10% in vitiligo patients; P = 0.0001) and a higher frequency of tumors (38% in psoriatic patients vs. 9% in vitiligo patients; P = 0.0001). Accordingly, vitiligo patients are more immune to infections and tumors than patients with psoriasis.

In comparison with pemphigus vulgaris in the previous study [1], psoriasis also appears to be less protective against infections (the infection rate was 78% in psoriatic patients vs. 18% in patients with pemphigus vulgaris; P = 0.0087) and less protective against tumors (the tumor rate was 38% in psoriatic patients vs. 20% in patients with pemphigus vulgaris; P = 0.0001). Accordingly, patients with pemphigus vulgaris are more immune to infections and tumors than patients with psoriasis.

Moreover, in comparison with patients with lupus erythematosus in the previous study [1], psoriasis appears to be less protective against infections (the infection rate was 78% in psoriatic patients vs. 56% in patients with lupus erythematosus; P = 0.0002) and less protective against tumors (the tumor rate was 38% in psoriatic patients vs. 16% in patients with lupus erythematosus; P = 0.0014). Accordingly, patients with lupus erythematosus are more immune to infections and tumors than patients with psoriasis.

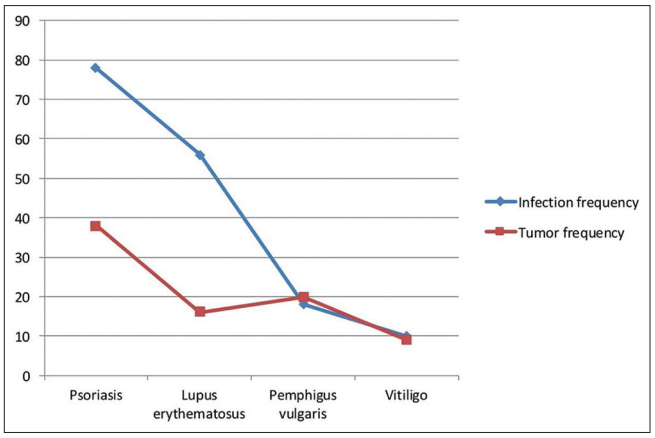

Figure 1: Comparison of the frequencies of infections and tumors among different autoimmune skin diseases.

Hence, when these autoimmune diseases are compared with one another, the findings appear to be that vitiligo, pemphigus vulgaris, and lupus erythematosus are more protective than psoriasis against infections and tumors (Fig. 1).

The question to be raised is why these autoimmune diseases are protective against infections and tumors. This cannot be easily explained and documented. We may, however, put forth some ideas based on the results of the previous studies. For instance, the overexpression of the p53 gene in vitiliginous areas confers protection in cases of vitiligo [14].

With regard to psoriasis, these findings may also be applied, as it is considered an autoimmune disease. In addition, a recent study conducted in Berlin by Kerstin et al. found that psoriatic patients are immune to viral infections due to the presence of antiviral peptides, and the level of these antiviral peptides correlates directly with the level of interleukin-29 produced by Th17 cells [15].

CONCLUSION

Patients with psoriasis, as an autoimmune disease, are less susceptible to infections and tumors than the general population. However, other autoimmune diseases such as pemphigus vulgaris, lupus erythematosus, and vitiligo are more protective than psoriasis. A further study assessing the frequency of the p53 marker in the skin of patients with psoriasis is highly recommended.

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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Our Dermatology Online

Original Article

The role of patch and photopatch tests in facial melanoses: A cross-sectional, observational study

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ABSTRACT

Background: Facial pigmentation includes various entities such as melasma, lichen planus pigmentosus (LPP), and pigmented contact dermatitis. The pathogenesis may involve certain allergens, which may be responsible for causing a disturbance in the dermoepidermal junction. The elimination of such inciting allergens may aid in the successful treatment of these patients. **Objective:** The aim was to detect contact allergens with patch and photopatch testing in facial pigmentary disorders. **Methods:** Fifty patients with facial pigmentary disorders were enrolled. After taking a demographic profile and detailed clinical history and performing an examination, patch and photopatch testing was done using a common suspected allergen series. **Results:** Out of the fifty patients tested, 28 (56%) showed a positive patch test, while 2 (4%) showed a positive photopatch test. The most common allergen found was a fragrance mix in 17 (34%) patients, followed by paraphenylenediamine (PPD) in 11 (22%). Other allergens showing positivity were nickel sulfate, benzocaine, parthenium, benzophenone-3, octyl methoxycinnamate, etc. **Conclusion:** Patients with facial pigmentation may have an underlying component of contact dermatitis, which may be a causative or aggravating factor. The avoidance of these allergens may help in increasing the efficacy of treatment in these patients.

Keywords: Patch testing; Photopatch testing; Melasma; Lichen planus pigmentosus; Pigmented contact dermatitis

INTRODUCTION

Facial hyperpigmentation has always been a significant therapeutic challenge. Melasma is the most common cause, others being ashy dermatosis, Riehl's melanosis, lichen planus pigmentosus, drug-induced, post-inflammatory hyperpigmentation, etc. Most of these conditions are inflammatory, causing a disturbance in the dermoepidermal junction, leading to the deposition of melanin in the dermis. This points toward the role of some allergens in the pathogenesis. Ultraviolet light in sunrays may interact with certain chemicals such as sunscreens and cosmetics to form allergens and provoke a delayed type of hypersensitivity. All these mechanisms may lead to clinically visible hyperpigmentation. Patch testing and photopatch testing form the cornerstone of the diagnosis of contact and photocontact allergies. In this study, we utilized both of these techniques and attempted to find the common allergens that may have a causative or aggravating influence on facial pigmentation.

MATERIALS AND METHODS

For the present study, fifty cases of facial hyperpigmentation presenting to the outpatient department of a tertiary-care hospital were enrolled. The study period was over two years. The diagnosis was based on the clinical appearance of lesions and was provisional. Malar, centrofacial, or mandibular pigmentation (brown or gray) was diagnosed as melasma. The involvement of the forehead and the preauricular and neck areas with brown or dark brown pigmentation with a history suggestive of some allergen exposure on or near the face was classified as pigmented contact dermatitis. The involvement of the

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face, neck, and extrafacial sites such as the arms and back with grayish to violaceous hues of pigmentation were diagnosed as lichen planus pigmentosus. A history suggestive of an inflammatory event preceding the onset of pigmentation was diagnosed as post-inflammatory pigmentation. Patient selection was non-consecutive and was performed according to the following criteria. Patients with facial pigmentation and an age above eighteen years were included. Pregnant or breastfeeding females and patients with extensive eczema on the back, on oral steroids (> 15–20 mg daily) or immunosuppressive drugs in the month preceding the test, with a history of topical steroid application on the back in the eight days prior to the test, or with a history of other photosensitive conditions such as systemic lupus erythematosus or systemic conditions with abnormal skin hyperpigmentation such as thyroid disease and Addison's disease were excluded from the study. Antihistamines, if any, were withdrawn at least seven days before testing. After taking pre-informed written consent, demographic details, a clinical history, details of the application of any cosmetic product (such as oils) over the face and scalp, and a history of drug intake were recorded.

Patch and Photopatch Testing

A total of nineteen allergens were tested (Table 1). Twelve of these were obtained from the Indian Standard Battery and Cosmetic and Fragrance Series approved by the Contact and Occupational Dermatoses Forum of India (CODFI). The rest of the allergens, that is, sunscreens and drug-related allergens, were prepared in the pharmacology laboratory of the institute from raw material obtained from HiMedia Laboratories, Mumbai. Readymade aluminum patch test chambers were employed to load the allergens. Allergens were applied in duplicate sets to the mid-upper back avoiding the paravertebral groove. After keeping them in position for 48 hours, the chambers were removed. Subsequently, one site was covered with a light-impermeable occlusive dressing while the other was irradiated with a broad-spectrum UVA source at a dose of 5 J/cm^2). The grading of the results was conducted twice, before irradiation and 48 hours after irradiation, using the International Contact Dermatitis Research Group (ICDRG) scoring system. The relevance was recorded using the COADEX system (current, old or past, actively sensitized, do not know, and exposed or cross-reaction).

The interpretation of photopatch testing was performed according to standard photopatch criteria. That is, if only the irradiated side showed a positive reaction, it was labeled as a photoallergic reaction. If both sides showed a positive reaction, with the irradiated side showing a greater than 1+ positivity, it was termed contact dermatitis with photoaggravation. If both sides showed an equal reaction after irradiation, a contact allergy was the result.

Statistical evaluation was done with the chi-squared test.

Ethics Statement

The present study was conducted after taking approval from the Institutional Ethics Committee. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

RESULTS

Demographic and Clinical Profile

Out of the fifty patients, 41 (82%) were females and 9 (18%) were males. The age of the patients ranged from 21 to 53 years, with a mean age of 38 years. Out of the fifty patients, the most were housewives, that is, 26 (52%), 7 (14%) were teachers, and 3 (6%) were nurses. The rest were various skilled workers. Out of 36 married females, 13 (36%) gave a positive history of facial pigmentation during the previous pregnancy. The duration of facial pigmentation varied from less than six months to more than ten years. A history of

Table I: List of allergens and their concentration

Serial number	Allergen	Concentration (vehicle-Petrolatum)
1.	Balsam of Peru	10%
2.	Nickel Sulphate	5%
3.	Epoxy Resins	1%
4.	Paraben mix	9%
5.	Paraphenylene diamine	1%
6.	Parthenium	15%
7.	Benzocaine	5%
8.	Fragrance mix	8%
9.	Cetyl alcohol	5%
10.	2-Hydroxy-4-Methoxy Benzophenone (Benzophenone-3)	2%
11.	Musk mix	5%
12.	Chlorhexidine Digluxonate	0.5%
13.	Benzophenone-4	2%
14.	Para amino benzoic acid	10%
15.	Diclofenac sodium	5%
16.	Ibuprofen	5%
17.	Ofloxacin	1%
18.	Octylmethoxy cinnamate	7.5%
19.	White Petrolatum	100%

drug intake was present in 22 (44%) patients, with the most taking various analgesics, including non-steroidal anti-inflammatory drugs (NSAIDS). Seasonal variation was present in 38%, with 13 patients (26%) giving a history of summer aggravation. 72% (36) of the patients gave a history of cosmetic use. A history of mustard oil application was present in 25 (50%), amla oil in 21 (42%), hair dye in 28(56%), henna application to the scalp in 21 (42%), perfume application in 15 (30%), and an allergy to artificial jewelry in 10 (20%). A majority of the patients belonged to Fitzpatrick skin type IV (70%), followed by type III (30%). Regarding the color of pigmentation, 30 (60%) patients had dark brown pigmentation, followed by 12 with light brown (24%) as well as 4 with bluish and 4 with mixed pigmentation (8%). Among the clinical patterns, a centrofacial pattern was the leading in 22 (44%) patients, followed by a malar pattern in 9 (18%). Other sites of pigmentation were various periorbital, temple, mandibular, forehead, perioral, preauricular, and nasal patterns in the rest 38% of the patients. Extrafacial pigmentation was present in 10 (20%) patients, that is, V of the neck, nape of the neck, back, arms, and forearms.

Clinical Diagnosis

Melasma was the most common clinical diagnosis in 33 (66%) patients, followed by pigmented contact dermatitis in 10 (20%), lichen planus pigmentosus in 6 (12%), and post-inflammatory pigmentation in 1 (2%).

Patch and Photopatch Test Results

Out of the fifty patients, 28 (56%) showed a positive patch test. A total of 45 patch tests were positive. One was doubtful. The most common allergen showing patch test positivity was the fragrance mix in 17 patients (34%), followed by paraphenylenediamine (PPD) in 11 (22%). Fig. 1 shows the results of the patch test. Out of the 28 patients showing patch test positivity, 17 patients showed positivity to only one allergen, 6 patients showed positivity to two allergens, and 5 patients showed positivity to three or more allergens. Table 2 shows positive patch tests amongst contactants vs non-contactants and the statistical analysis of the same. The comparison of a positive patch test with a positive history of contact with the allergen was found to be statistically significant in most of the allergens, except octyl methoxycinnamate. The relevance was old (O) in 8, exposed (E) in 31, and difficult to assess (D) in 6.

Two patients (4%) showed photopatch positivity to a total of five antigens: epoxy resin, benzophenone-3, a musk mix, chlorhexidine, and benzophenone-4 (Fig. 2). One patient showed photoaggravation to a fragrance mix with the degree of sensitivity increasing from + to ++ after photo exposure. The relevance was difficult to assess in all.

Provisional Diagnosis vs. Positive Patch Tests

Fig. 3 shows a comparison between provisional diagnosis based on clinical examination and actual cases with positive patch tests.

DISCUSSION

Cosmetic dermatitis is on the rise nowadays and has various presentations, with facial pigmentation being one. Patch testing is an important tool for the diagnosis of underlying allergens causing dermatitis. The role of

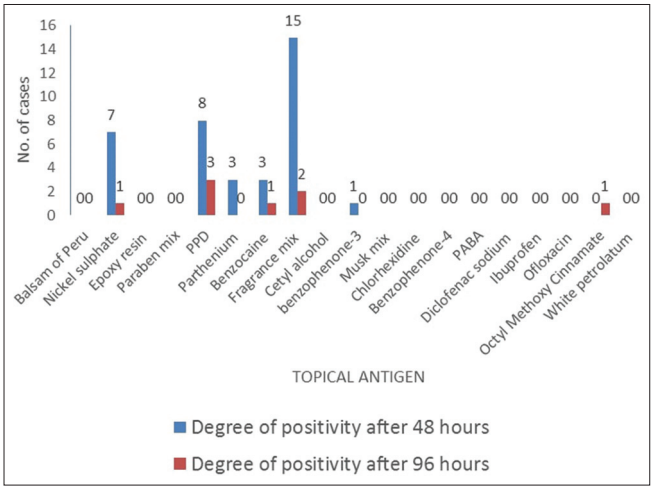

Figure 1: Results of patch testing, with the fragrance mix being the leading allergen, followed by PPD and nickel sulfate.

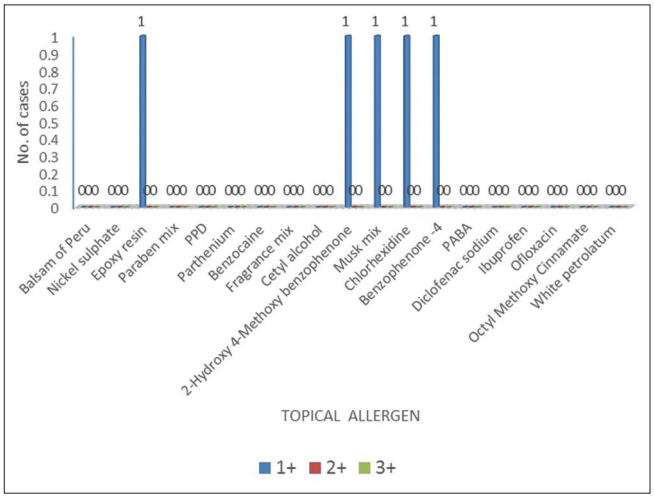

Figure 2: Results of photopatch testing with each photopatch test positive to epoxy resin, 2-hydroxy 4-methoxy benzophenone-4.

Table 2: Positive patch tests vs. number of contactants and non-contactants, and statistical analysis of the same (p > 0.05: non-significant, p < 0.05: significant, p < 0.001: highly significant [S: significant, NS: non-significant])

Allergen	Contactants			Non-contactants			*p* value	Statistical Significance
	Total Cases	+ve cases		Total cases	+ve cases			
		No.	%		No.	%		
Nickel	10	7	70.00	40	1	2.50	X^2:27.1; p = 0.001	S
PPD	28	10	35.71	22	1	4.55	X^2:6.97; p = 0.008	S
Parthenium	10	2	20.00	40	1	2.50	X^2:4.34; p = 0.037	S
Benzocaine	2	2	100.00	48	2	4.17	X^2:24.0; p = 0.001	S
Fragrance	41	17	41.46	9	0	0.00	X^2:5.65; p = 0.001	S
Octyl methoxy cinnamate	22	1	4.55	28	0	0.00	X^2:1.30; p = 0.254	NS
2-hydroxy-4-methoxybenzophenone	0	0	-	50	1	2.00	-	-

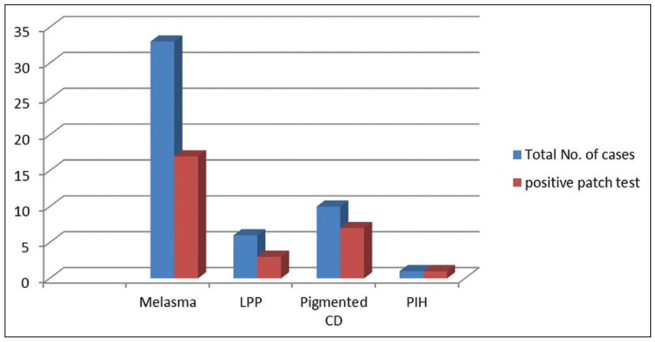

Figure 3: Graph showing the comparison of clinical diagnosis vs. positive patch tests in our cases.

sun exposure is crucial as a causative and aggravating factor, since some allergens become activated only by exposure to sunlight. The combined role of sunlight and allergens may be detected with photopatch testing. The standard patch test series as well as a cosmetic series are able to detect more than 80% of the allergens responsible for dermatoses [1]. The age of the patients in the present study ranged from 21 to 53 years. This is comparable to studies by Bhattarai et al. [2]. Our study showed a female preponderance (82%). This is comparable to studies by Bhattarai et al., Krupa Shankar et al., and Goh et al., who showed a female preponderance ranging from 67.9% to 80.13% [2-4]. This may be explained by the more cosmetic and aesthetic concerns in females. Housewives were the leading group in our study (52%). This was in accordance with a study by Sardesai et al. conducted in 2013, in which 62% of melasma patients were housewives [5]. Although sun exposure was not a significant factor among housewives, exposure to chronic infrared radiation while working in front of a gas stove could have been an aggravating factor. Thirty-six percent of married females gave a history of facial pigmentation during pregnancy. This could be attributed to the role of hormonal factors, especially in melasma. These findings are close to results in studies by Sanchez et al. and Tamega et al., who reported the incidence of melasma in previous pregnancies in 30–32% of subjects [5,6].

Seventy-two percent of patients gave a history of the use of one cosmetic or another in the form, for instance, of over-the-counter fairness creams. The exact composition of these cosmetics was unavailable, which was a hindrance to the specific testing of their ingredients. Prabha et al. determined cosmetic contact dermatitis to be an important causative factor in melasma [7].

A history of amla oil and mustard oil application was present in 42% and 50% of the patients, respectively. Mustard oil contains allyl isothiocyanate and other photosensitizing substances, which further aggravate the hyperpigmentation on the face [8,9].

Fragrances were the leading allergen in our study in 17 (34%) patients (Fig. 4) and were proven to be a cause of cosmetic dermatitis in 30–40% of the cases in previous studies [10,11]. All these patients gave a history of the application of perfumes or OTC cosmetics with fragrances as ingredients. An important fact is that, although some cosmetics are labeled as fragrance-free, they contain some added covert fragrances to mask their original odor. Since these fragrances are also present in household products such as room fresheners, soaps, toothpaste, and haircare products, the wide use of these products in everyday chores makes tracing the source difficult.

Twenty-eight cases gave a history of the application of hair dyes, yet only ten showed positivity to PPD (Fig. 5). One patient in our study applied only henna to the scalp, yet showed positivity to PPD. Past reports of contact sensitivity to henna tattoos have shown that PPD is added to enhance the final color [12-14]. This could be the reason why a patch test to PPD was positive in the patient who had never applied synthetic dyes yet had used henna. Nickel alloy is present in artificial jewelry, which is widely popular among females in our country. It is also present in cosmetics, utensils, metallic objects, coins, foods, dental crowns, etc.

Tienthavorn et al. found nickel to be the most common allergen in a study on patients with LPP, pigmented CD, and erythema dyschromicum perstans [10]. In our study, eight patients showed a positive patch test to nickel sulfate (Fig. 6), among which seven had a history of allergy to artificial jewelry.

The occupation of the patient was significant as four patients showed patch test positivity to benzocaine, among which two were nurses by profession working in an operation theater, and possible exposure in the workplace may be an explanation for prior sensitization. Both patients showed positivity to PPD as well. Thus, cross-reactivity between the two may be another explanation for positivity in these patients [15].

Musk ambrette is a fragrance fixative employed both by the food and cosmetic industries. In past, it was found to be the leading allergen in photopatch studies, now replaced by sunscreen agents. Benzophenone-3 was found to be the leading allergen in photopatch testing carried out in Thailand and Bagota [16,17]. UV filters such as benzophenone-4, benzophenone-3, and cinnamates have largely replaced PABA (para-aminobenzoic acid) in sunscreens. These have also replaced musk ambrette in being the leading photoallergens in Western studies [18].

Photopatch tests were positive in two (4%) of the fifty patients in our study. One showed photopatch positivity to three allergens—a musk mix, chlorhexidine, and benzophenone-4 (Fig. 7)—while the other showed positivity to epoxy resin and benzophenone-3.

The lower incidence of photopatch positivity to these in our study may be attributed to the less frequent routine use of sunscreen by people in India as well as to the low availability of photopatch allergen series. No definite correlation between a history of exposure and patch test results was found. Polysensitivity may be because of cross-reactivity, simultaneous exposure to multiple allergens in predisposed individuals, or non-specific hyperreactivity.

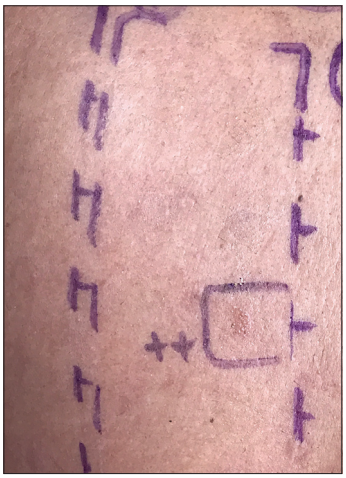

Figure 4: Positive patch test ('++') to the fragrance mix.

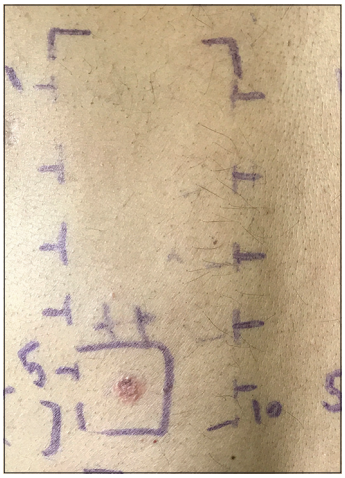

Figure 5: Positive patch test ('++') to paraphenylenediamine.

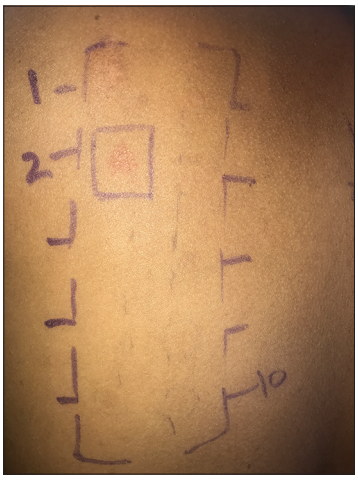

Figure 6: Positive patch test ('++') to nickel sulfate.

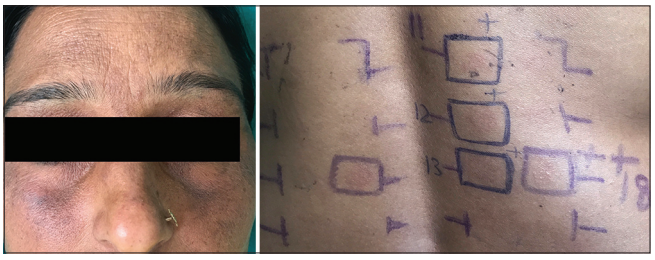

Figure 7: Centrofacial pigmentation in a patient with a patch test '+' positive to octyl methoxycinnamate and a photopatch test positive '+' each to the musk mix, chlorhexidine, and benzophenone-4.

It is of concern that 51.5% of cases clinically diagnosed as melasma showed positive patch tests to various allergens. Similarly, 50% of the patients clinically diagnosed with LPP showed positive patch tests (Fig. 3). This suggests that underlying dermatitis is an important factor and may not manifest with classical symptoms and signs since the amount of allergen to which a person is exposed is very low. It causes a disturbance in the dermoepidermal junction (DEJ), which is sufficient to cause basal membrane damage and pigment incontinence, clinically visible as hyperpigmentation.

The limitations of the present study were that we did not correlate histopathology with clinical features, since the patients were reluctant to facial biopsy. The number of allergens tested was small due to the low availability of photopatch series in India, thus a wider series should have been included.

CONCLUSION

In patients with facial pigmentation, clinical diagnosis alone is insufficient, and further histopathology and patch testing are needed to exclude pigmented CD. The elimination of these allergens aids in the better management of these patients.

The authors certify that written consent was taken regarding the publication of images of lesions for research purposes without disclosing the identity of the patients. The patients understood 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.

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.

ABBREVIATIONS

LPP (lichen planus pigmentosus), CD (contact dermatitis).

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Our Dermatology Online

Original Article

Quality of life of psoriatic patients in Ouagadougou, Burkina Faso

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ABSTRACT

Background: Psoriasis is a chronic, displaying inflammatory dermatosis. The evaluation of the psychosocial impact of chronic dermatoses on the quality of life of patients may help to orientate the objectives of management in order to improve their daily life, hence the interest of our study with the objective to evaluate the impact of psoriasis on the quality of life of patients followed in the dermatology, venereology, and rheumatology departments of the city of Ouagadougou, Burkina Faso. **Patients and Method:** This was a descriptive, cross-sectional study that took place from March 1 to June 28, 2019, in six public hospitals in the city of Ouagadougou. The Dermatology Life Quality Index (DLQI) and Psoriasis Disability Index (PDI) were the quality of life tools employed for this study. **Results:** Forty-eight (48) patients with psoriasis met the inclusion criteria. The mean age of the patients was 46.20 years, ranging from 22 to 79 years. There were 18 females and 30 males, with a sex ratio of 1.6. The measurement of the patients' QoL by the DLQI reported a mean score of 9.14 out of 30. There was a low impact of the disease on the QoL for seventeen patients. The evaluation of the QOL with the PDI noted an alteration of daily activities (3.95/15) and alteration of the patients' psychosocial relationships (2.66/18). The analysis of the QoL according to sociodemographic and clinical variables noted an alteration significantly related to age, level of education, and severity of the disease. An alteration in professional relationships was significant in female patients. An alteration in the different dimensions of the QoL was more significant in patients with a low level of education. The duration of the disease seemed to have no impact on the patients' quality of life. Daily activities were significantly altered for patients with a PASI between 7 and 10. The DLQI did not correlate with disease severity (PASI) ($r = 0.228$; $p = 0.120$), unlike the PDI ($r = 0.371$; $p = 0.009$). **Conclusion:** The QoL of psoriatic patients in Ouagadougou seemed to be slightly altered. This alteration was more significant for females. Professional relationships were altered for young subjects while daily activities were altered for those older.

Key words: PASI; DLQI; psychosocial impact; quality of life

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INTRODUCTION

Psoriasis is a chronic inflammatory dermatosis characterized by erythematous, squamous lesions related to hyperproliferation of keratinocytes with accelerated epidermal turnover and aberrant differentiation [1]. The pathogenesis of psoriasis is complex and may be attributed to factors such as genetics, immunology, and environmental triggers. The importance of inflammasomes as part of innate immunity in the pathogenesis of psoriasis is also discussed in the literature [2]. It is a display dermatosis that may have an impact on the patient's quality of life [3-5].

Health-related quality of life may be defined as the set of health-related conditions that diminish well-being and performance and interfere with social roles and/or alter the subject's psychological functioning [4].

Assessing the psychosocial impact of chronic dermatoses on the patient's quality of life may help to guide management goals to improve their daily experience [5,6]. Numerous studies on the quality of life of patients with psoriasis have been conducted worldwide, particularly in Latin America, Europa, and Asia [1,3-5,7]. They reported a significant impairment in the quality of life of psoriatic patients, with a high prevalence of depressive symptoms. In West Africa, there are few studies on the quality of life of psoriatic patients [5], hence the interest of our study, with the objective to evaluate the impact of the disease on the quality of life of psoriatic patients followed in the dermatology, venereology, and rheumatology departments of the city of Ouagadougou, Burkina Faso.

PATIENTS AND METHODS

This was a descriptive, cross-sectional study that took place from March 1 to June 28, 2019, in six public hospitals in the city of Ouagadougou: Yalgado Ouedraogo University Hospital (YOUH), Tingandogo University Hospital (TUH), Bogodogo University Hospital (BOH), Saint Camille Hospital of Ouagadougou (SCHO), Raoul Follereau center (RFC), and Medical Center of Camp Sangoulé Lamizana (MCSL). The patients included in the study were those followed in the dermatology and rheumatology departments of these hospitals for psoriasis, aged at least eighteen years, and consenting.

A questionnaire was used to collect sociodemographic and clinical data. The Wallace rule of nines was employed to calculate the body surface area (BSA). The Psoriasis Area and Severity Index (PASI) was employed to assess disease severity. The Psoriasis Disability Index (PDI) and the Dermatology Life Quality Index (DLQI) were employed to assess quality of life [8-10].

The data collected was analyzed by Epi Info, version 7.2.2.6, and SPSS Statistics, version 20. For the comparison of variables, the Kruskal–Wallis chi-squared test was employed. The ANOVA test allowed the comparison of more than two variables. The p probability was significant at $p < 0.05$. The Pearson correlation coefficient was employed to investigate the relationship between the different tools, with a significant probability for $p < 0.01$.

The study respected the rules of ethics and deontology in the conduct and analysis of the data.

RESULTS

Forty-eight (48) patients with psoriasis met the inclusion criteria for the study. The two oldest dermatology facilities, YOUH and Raoul Follereau Center, accounted for half of the patients (24/48).

Sociodemographic Characteristics

The average age of the patients was 46.20 years, ranging from 22 to 79 years. There were eighteen females and thirty males, with a sex ratio of 1.6. Thirty-three patients were married, fifteen were single, four were divorced or widowed. In terms of educational level, 27 patients had at least secondary education. As for place of residence, 36/48 lived in urban areas. With regard to occupation, eleven patients worked in the informal sector in precarious and irregular jobs. The average monthly income was €173, ranging from €38 to €1525 (Table 1).

Table 1: Sociodemographic characteristics of the patients

Category	Value
Mean age	46.20 yrs. (22–79 yrs.)
No. of females	18/48
No. of males	30/48
Sex ratio	1.6
Marital status	married (33/48), single (11), divorced (2), widowed (2)
Educational level	secondary (14/48), university (13), primary (11), not in school (10)
Residence	urban (36/48), rural (7), undeveloped area (5)
Profession	unformal (15/48), civil servant (4), student (4), liberal activity (3), unemployed (8), farmer (3), retired (9)
Monthly income	€173 (€38–€1525)

Clinical and Therapeutic Characteristics

The average duration of the disease was 7.91 years, ranging from six months to forty years. All patients reported pruritus, ten reported asthenia, and five reported insomnia. The disease was in remission for 31 patients. The number of relapses varied from one to five per year.

The triggers for psoriatic flareups were stress, seasonal variation, and emotional shock in twenty, eight, and six patients, respectively. The lesions were erythematous and squamous. The average body surface area affected was 17.89%, ranging from 1% to 90%. Thimble-like nail involvement was visible in four patients.

Thirty-four patients were on topical treatment (dermocorticoid + keratolytic), ten were on methotrexate, and eleven had no treatment.

The mean severity score (PASI) was 6.26 out of 72, corresponding to mild psoriasis, ranging from 0.1 to 39.9. Psoriasis was mild (PASI < 7) in 33 patients, moderate (7 ≤ PASI ≥ 10) in six, and severe (PASI > 10) in nine.

Quality of Life (QoL)

The measurement of the patients' QoL by the Dermatology Life Quality Index (DLQI) yielded a mean score of 9.14 out of 30. Seventeen patients reported a low impact of the disease on QoL. Fourteen patients reported a significant impact and eight reported an extremely significant impact. For six patients, the disease had no impact on QoL (Table 2).

The Psoriasis Disability Index (PDI) assessment of QoL revealed an alteration in daily activities of 3.95/15 and in the psychosocial relationship between the patient and their environment at 2.66/18 (Table 3).

The analysis of QoL according to sociodemographic and clinical variables revealed an alteration significantly related to age, level of education, and severity of the disease. Thus, QoL was altered for older patients and this alteration concerned all dimensions: daily activities, professional relationships, psychosocial relationships, and the type of treatment used (P = 0.00) (Table 4). The alteration in work relationships was significant for female patients. The alteration of the QoL was more significant for patients with a low level of education. The duration of the disease seemed to have no impact on the patients' QoL. Activities of daily living were significantly altered for patients with a PASI between 7 and 10.

The correlation between the two QoL assessment tools (DLQI and PDI) was significant ($r = 0.822$; $p = 0.000$) (Table 5). The psoriasis-specific tool (PDI) was significantly correlated with disease severity (PASI) ($r = 0.371$; $p = 0.009$). No significant correlation was found between the DLQI and the PASI ($r = 0.228$; $p = 0.120$). There was a weak positive correlation between the treatment and the alteration in QoL, as measured by the PDI scale ($r = 0.289$; $p = 0.046$). The treatment, therefore, had a weak impact on the patients' QoL.

DISCUSSION

The majority of the group studied had an average level of education, working in the informal sector with precarious jobs, with an average monthly income of €173, higher than the country's guaranteed minimum wage of €149. It was mainly males, consisting of young adults with an average age of 46 years. These characteristics were similar to studies done by Karelson in Estonia in 2013, Garcia-Sanchez in Mexico in 2017, Nuynt in Malaysia in 2015, Maoua in Tunisia, and Gruchala in Poland [11-14]. Karelson noted a lower mean age (38.30 years), while Garcia-Sanchez reported older patients (51.22 years). Nuynt reported 188/223 patients with at least a secondary school level. Garcia- Sanchez reported 17/72 patients with at least secondary education [12]. Maoua, in their work on QoL and work activity on 58 patients, reported that 62% had a primary, lower level of education [13].

The average PASI in our study was low (6.26). Other authors made the same observation, notably Bronckers

Table 2: Quality of Life assessment by the DLQI

DLQI	Effect on QoL	No. of Patients
0–1	No effect	6
2–5	Weak effect	17
6–10	Moderate effect	3
11–20	Significant effect	14
21–30	Strong effect	8

Table 3: Quality of Life assessment by the PDI

Altered Dimension of the PDI	No. of Patients	Mean	SD
Daily activities	40	3.95/15	3.92
Work activities	16	1.20/9	2.36
Psychosocial relationships	27	2.66/18	3.34
Treatment	9	0.33/3	0.75
Total PDI	48	8.16/45	8.03

Table 4: The relationship between QoL and sociodemographic and clinical characteristics

QoL Dimensions / Associated factors	Mean Score of Daily Activities	*p* Value	Mean Score of Professional Activities	*p* Value	Mean Score of Psychosocial Relationships	*p* Value	Mean Score of Treatment	*p* Value
Age range (yrs.)								
18–29	2.00	0.00	1.55	0.00	1.55	0.00	0.22	0.00
30–44	2.16		1.08		1.25		0.33	
45–59	4.75		1.31		2.37		0.18	
60–74	6.10		1.00		2.90		0.60	
75–86	9.00		0.00		0.00		1.00	
Gender								
male	3.33	0.21	0.73	0.05	1.93	0.68	0.40	0.66
female	5.00		2.00		2.11		0.22	
Educational level								
not in school	4.00	0.00	2.33	0.00	2.77	0.00	0.11	0.00
primary	4.81		1.18		2.36		0.27	
secondary	4.78		1.07		2.35		0.71	
university	2.00		0.69		0.92		0.15	
Duration of the disease (yrs.)								
≤ 1	2.54	0.15	1.36	0.97	2.72	0.37	0.09	0.37
2–5	3.23		1.29		1.11		0.23	
6–10	6.25		0.87		2.50		0.62	
≥ 10	4.75		1.16		2.25		0.50	
Severity of the disease (PASI)								
< 7	3.06	0.05	1.06	0.79	1.93	0.97	0.48	0.35
7–10	6.16		1.33		2.16		0.83	
> 10	5.77		1.66		2.11		0.22	

The relationship was significant for $P < 0.05$

Table 5: The correlation between the DLQI, PDI, and PASI

		PASI	PDI	DLQI
PASI	Pearson correlation	1	0.371	0.228
	p (bilateral)	-	0.009	0.120
PDI	Pearson correlation	0.371	1	0.822
	p (bilateral)	0.009	-	0.000
DLQI	Pearson correlation	0.228	0.822	1
	p (bilateral)	0.120	0.000	-

p significant if $P<0.01$

in the Netherlands in 2018 with a cohort of 75 patients, Nyunt in Malaysia with 223 patients, and Maoua in Tunisia with 58 cases [10,13,15].

The DLQI was reported to be low (9.14/30) for the majority of the patients. Our result was comparable to that by Amine in Morocco in 2017 with a mean DLQI of 8 [16].

Sof in Oujda, Morocco, also reported a low DLQI (10.20) for all dermatology patients in the hospital in general [7]. However, patients suffering from severe psoriasis had a high DLQI (16.6) [7,17-19]. This was the case of Jung in South Korea in 2018, who found a mean DLQI of 12.4 [20]. Maoua in Tunisia in 2015 noted a mean DLQI score of 16.1 [13].

The DLQI was not correlated with the PASI ($r = 0.228$; $p = 0.120$), unlike the psoriasis-specific tool PDI ($r = 0.371$; $p = 0.009$). Maoua found a significant correlation between the DLQI and the PASI ($r = 0.38$; $p = 0.003$) [13]. Moradi in Iran in 2015 also found that low DLQI scores were associated with high PASI scores ($r = 0.58$; $p < 0.05$) [19]. This discordance between the DLQI and PASI suggests that the assessment of QoL for psoriasis should necessarily include psychological and social dimensions.

The assessment of QoL by the PDI showed that the patients' daily activities were altered more significantly, followed by psychosocial relationships and work activities.

The alteration in QoL was greater in females ($p = 0.04$). We explain this by the fact that females tend to be more concerned about their appearance. This result is comparable to that reached by Garcia-Sanchez in Mexico in 2017, who found that QoL was more affected in females (58.2%) [12].

There was an association between the alteration in daily and occupational activities and the patient's age ($p = 0.00$). Patients with an age of 15–29 years were the most professionally affected. This could be explained by the fact that this tends to be the time of the most intensive job searching and showing overt psoriasis lesions may interfere or hinder in receiving a job [21].

A lower level of education disturbed the QoL to a greater extent (p = 0.00). Indeed, a higher level of education would allow a better understanding and acceptance of the disease. Maoua in Tunisia came to the same conclusion. In fact, for 62% of the patients with a primary level of education, the alteration in QoL was more significant (avg. DLQI = 16.1) [13]. However, Nyunt in Malaysia in 2015 found no association between education and the alteration in QoL [10].

Drug treatment should improve lesions and, therefore, the QoL of the patient [17,22-24]. In our study, treatment had a weak impact on the patient's QoL. In addition to drug treatments, psychotherapeutic management is beneficial for patients with psoriasis, with a positive impact on QoL [21]. The patients in our study did not systematically receive psychotherapy.

Our study found a strong correlation between the two measures of QoL, the DLQI and the PDI (r = 0.822; p = 000) and the PASI.

CONCLUSION

In our study, the QoL of psoriatic patients in hospital at Ouagadougou, seemed to be slightly altered, with this alteration being more significant for females. Professional relationships were disturbed for young subjects, while daily activities were disturbed for those older. Psychotherapy may be combined with patient management to help improve the patient's QoL.

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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Our Dermatology Online

Original Article

A study on the association between thyroid dysfunction and various dermatoses in northeastern India

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ABSTRACT

Background: Thyroid abnormalities are a well-documented endocrine association seen in numerous dermatological conditions. However, there are few Indian studies analyzing the thyroid status in various dermatoses. **Materials and Methods:** This cross-sectional, observational study was conducted on 805 willing patients with various dermatoses, irrespective of the disease classification. Serum samples were taken and assayed for triiodothyronine (T_3), thyroxine (T_4), and thyroid-stimulating hormone (TSH). **Results:** Out of the 805 patients, 14.2% (n = 115) had abnormal thyroid function. Hypothyroidism accounted for 86.1% (n = 99) and hyperthyroidism for 13.9% (n = 16). Among the 99 hypothyroid patients, 23.2% (n = 23) had overt hypothyroidism while 76.8% (n = 76) had subclinical hypothyroidism. Vitiligo accounted for 36.1% (n = 291) of the patients, among which 12.3% (n = 36) had thyroid dysfunction involving six hypothyroid and three hyperthyroid cases. Out of 58 cases of melasma, 15 (25.8%) had abnormal thyroid function. Among the twenty patients with lichen planus pigmentosus, five had abnormal thyroid levels. **Conclusion:** This study demonstrates a strong association of thyroid disorders in certain conditions, such as vitiligo, alopecia areata, diffuse hair loss, dry skin, chronic urticaria, and melasma. Thus, the inclusion of thyroid function tests in routine investigations of these conditions would be helpful.

Key words: hypothyroidism; hyperthyroidism; dermatoses; vitiligo; melasma; lichen planus pigmentosus

INTRODUCTION

Endocrine disorders are associated with various skin manifestations, specific or non-specific. Identifying the underlying endocrinopathy allows for early diagnosis and appropriate treatment of the patient rather than symptomatic treatment. Thyroid disorders are important endocrine diseases having cutaneous manifestations, as the skin and its appendages are target organs of thyroid hormones [1]. Although most of these cutaneous changes are non-specific, a proper clinical evaluation with a laboratory confirmation may aid in the diagnosis in the early stage [2]. The most frequent thyroid dysfunction in India is hypothyroidism [3]. Some studies have been done in India assessing thyroid function in certain dermatologic conditions, such as vitiligo, melasma, and polymorphic light eruptions, yet studies on a wider range of dermatologic diseases are missing [4-6]. Therefore, the present study was conducted to assess the association of thyroid dysfunction with various dermatoses in northeastern India.

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MATERIALS AND METHODS

A cross-sectional study was conducted on 805 patients presenting with dermatoses, irrespective of the disease classification, to the dermatology OPD of a tertiary center in northeastern India for a period of three years (April 2013 to May 2016). Pregnant females, individuals with known endocrine dysfunction, and those who refused to consent were excluded. Detailed clinical history taking and a physical examination were performed. Serum samples were collected and assayed for serum triiodothyronine (T_3), thyroxine (T_4), and thyroid-stimulating hormone (TSH). Thyroid hormones were assayed by the VIDAS automated quantitative test with an enzyme-linked fluorescent assay. The reference ranges for serum T_3, T_4, and TSH were 0.9–2.5 nmol/L, 60–120 nmol/L, and 0.3–5 IU/mL, respectively. The diagnosis of hypothyroidism was established when thyroid function exhibited raised TSH levels with or without low T_3 and T_4 levels. Subclinical hypothyroidism is defined by normal serum T_3 and T_4 levels but TSH > 5 IU/mL and TSH < 15 IU/mL. Hyperthyroidism was diagnosed if serum T_3 and T_4 were raised and TSH was low. Subclinical hyperthyroidism was diagnosed if the TSH level was undetectable and with serum T_3 and T_4 in the upper limit of the reference range. Ethical clearance was obtained from the institute ethical committee. Data was tabulated and analyzed with SPSS, version 21.

RESULTS

Among 805 patients with various skin disorders, 199 were males (24.7 %) and 606 were females (75.3%). The youngest patient was four months old and the oldest was 84 years old. Most were in the age group 11–20 years (Fig. 1). Abnormal thyroid function was observed in 14.2% (n = 115) of the patients (Fig. 2). Hypothyroidism accounted for 86.1% (n = 99) and hyperthyroidism for 13.9% (n = 16) of the cases (Fig. 2). Vitiligo accounted for 36.1% (n = 291) of the cases, among which 12.3% (n = 36) had thyroid dysfunction involving nine overt thyroid dysfunction cases (six hypothyroid and three hyperthyroid cases). Among 58 cases of melasma, 15 had abnormal thyroid function. Among 20 patients suffering from lichen planus pigmentosus (LPP), five patients had abnormal thyroid levels. Among hair disorders, alopecia areata (AA) and diffuse hair loss had nine and seven abnormal thyroid values, respectively. Among 114 cases of urticaria, 9 (7.9%) had thyroid dysfunction. Table 1 shows various other cutaneous

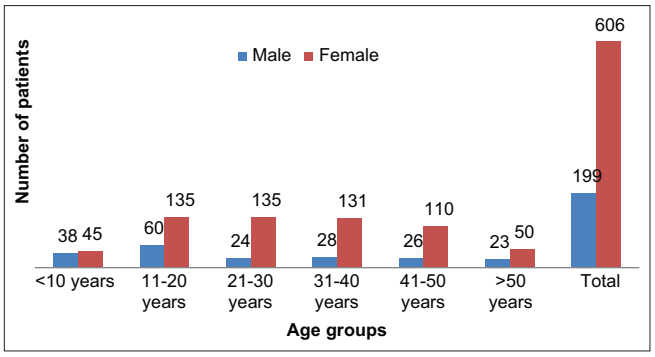
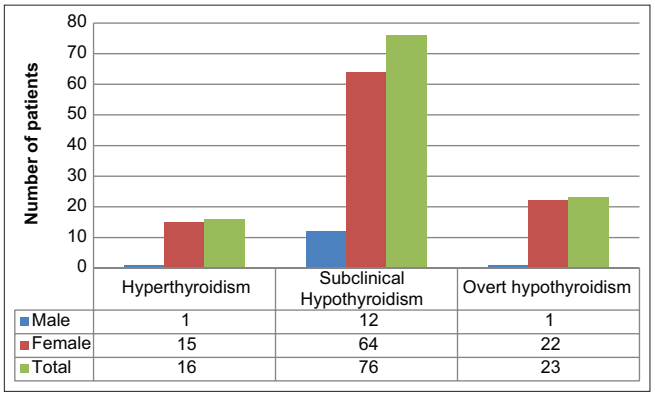


Figure 1: Age and gender distribution.



	Hyperthyroidism	Subclinical Hypothyroidism	Overt hypothyroidism
Male	1	12	1
Female	15	64	22
Total	16	76	23

Figure 2: Distribution of thyroid disorders.

disorders with their respective thyroid levels. Among 99 hypothyroid patients, 23.2% (n = 23) had overt hypothyroidism, whereas 76.8% (n = 76) revealed subclinical hypothyroidism (Fig. 2). Table 2 lists the dermatoses associated with overt hypothyroidism or hyperthyroidism.

DISCUSSION

The present study documented thyroid dysfunction in 12.3% of vitiligo patients. A similar association (12%) was noted by another study from northern India [7]. However, a recent Indian study has shown a higher proportion (28%) of thyroid dysfunction and higher antithyroid antibodies when compared to controls [8]. In concordance with the findings from different parts of India, this study also reveals a high prevalence of thyroid dysfunction with predominant hypothyroidism among vitiligo patients.

A high incidence of thyroid dysfunction among melasma patients was reported by various studies earlier. An earlier study revealed that the frequency of thyroid disorders was higher in melisma patients than in controls [9]. In another study, 26.2% of melasma patients had hypothyroidism [10]. In the present study,

Table 1: Thyroid status in various dermatoses

Dermatosis	Hypothyroid			Hyperthyroid			Normal			Total Tested		
	M	F	T	M	F	T	M	F	T	M	F	T
Connective tissue disorders												
DLE*	0	1	1	0	0	0	0	3	3	0	4	4
Systemic sclerosis	0	2	2	0	0	0	0	3	3	0	5	5
Hair disorders												
Alopecia areata	1	7	8	0	1	1	24	27	51	25	35	60
Diffuse hair loss	0	6	6	0	1	1	2	22	24	2	29	31
Canities	0	0	0	0	0	0	1	2	3	1	2	3
Infections												
Erythrasma	0	0	0	0	0	0	0	1	1	0	1	1
Herpes labialis	0	0	0	0	0	0	0	1	1	0	1	1
Tinea	0	0	0	0	0	0	1	1	2	1	1	2
Papulosquamous disorders												
Eczema	0	10	10	0	1	1	10	90	100	10	101	111
Lichen planus	0	1	1	0	0	0	0	3	3	0	4	4
LSC†	0	0	0	0	0	0	0	1	1	0	1	1
PLEVA‡	0	1	1	0	0	0	0	0	0	0	1	1
Psoriasis	0	3	3	0	1	1	1	9	10	1	13	14
Seborrheic dermatitis	0	0	0	0	0	0	0	1	1	0	1	1
Hypopigmentary conditions												
Vitiligo	10	23	33	0	3	3	98	157	255	108	183	291
IGH§	0	0	0	0	0	0	0	1	1	0	1	1
Hyperpigmentary conditions												
Melasma	0	13	13	0	2	2	6	37	43	6	52	58
LPP¶	0	4	4	0	1	1	0	15	15	0	20	20
Macular amyloidosis	0	1	1	0	0	0	1	2	3	1	3	4
Acral pigmentation	0	0	0	0	0	0	0	2	2	0	2	2
Acanthosis nigricans	0	0	0	0	0	0	1	12	13	1	12	13
Generalized pigmentation	0	0	0	0	0	0	0	1	1	0	1	1
Miscellaneous												
Acne	0	0	0	0	0	0	0	8	8	0	8	8
Acrochordon	0	0	0	0	0	0	2	2	4	2	2	4
Actinic prurigo	0	1	1	0	0	0	1	2	3	1	3	4
Dry skin	0	3	3	0	0	0	0	2	2	0	5	5
Erythema annulare	0	0	0	0	0	0	1	1	2	1	1	2
Erythema nodosum	0	0	0	0	0	0	0	2	2	0	2	2
Generalized pruritus	0	0	0	0	0	0	0	13	13	0	13	13
Granuloma annulare	0	1	1	0	0	0	1	0	1	1	1	2
Ichthyosis	0	0	0	0	1	1	0	0	0	0	1	1
LSA#	0	0	0	0	0	0	0	2	2	0	2	2
Nail dystrophy and pigmentation	0	4	4	0	1	1	0	11	11	0	16	16
Pedal edema	0	1	1	0	0	0	0	1	1	0	2	2
Perniosis	0	0	0	0	0	0	0	3	3	0	3	3
Pseudoxanthoma elasticum	0	0	0	0	0	0	0	2	2	0	2	2
Schamberg disease	0	0	0	0	0	0	0	1	1	0	1	1
Steroid rosacea	0	0	0	0	0	0	0	1	1	0	1	1
Urticaria	2	4	6	1	2	3	16	80	96	19	95	114
Xanthelasma	0	0	0	0	0	0	0	2	2	0	2	2
Total	**13**	**86**	**99**	**1**	**15**	**16**	**166**	**524**	**690**	**180**	**625**	**805**

M: male, F: female, T: total
* Discoid lupus erythematosus
† Lichen Simplex chronicus
‡ Pityriasis lichenoides et varioliformis acuta
§ Idiopathic guttate hypomelanosis
¶ Lichen planus pigmentosus
# Lichen sclerosus et atrophicus

25.9% of melasma cases showed thyroid dysfunction. However, there are few controlled studies on melasma and thyroid disorders [9,11]. Therefore, more studies are required to determine the association between

Table 2: Dermatoses with overt hypothyroidism and hyperthyroidism

Dermatosis	Overt Hypothyroidism	Overt Hypothyroidism	Total
Alopecia areata	2	1	3
Diffuse hair loss	0	1	1
Xerosis	3	0	3
Eczema	1	1	2
Ichthyosis	0	1	1
Lichen planus	2	1	3
Lichen planus pigmentosus	1	0	1
Melasma	2	2	4
Nail dystrophy	2	0	2
Nail pigmentation	0	1	1
Psoriasis	1	1	2
Scleroderma	1	0	1
Urticaria	1	3	4
Vitiligo	6	3	9
Total	22	15	37

melasma and thyroid disorders. Both melasma and thyroid diseases are highly common in young females, hence this may lead to the incidental finding of thyroid dysfunction in melasma patients [12].

In the present study, 25% of LPP patients had hypothyroidism, which is comparable to a study by Karn et al. in which 31.7% of patients with LPP had hypothyroidism and three had hyperthyroidism. Studies with a larger number of patients are required to substantiate a significant association between the two conditions [13].

Among the 60 patients with AA in this study, nine had thyroid dysfunction, among which eight were hypothyroidism cases and one was a hyperthyroidism case. Earlier studies revealed a significant association between AA and thyroid disorders [14,15]. Similar findings were also observed in a study by Ijas et al. [16]. All these findings suggest that, for patients with AA, testing for thyroid function should be mandatory. Other authors have reported a similar association [17-19].

Premature graying of the hair, or canities, is a common hair condition of unknown etiology. In this study, only three cases were evaluated and all had normal thyroid function. A study by Daulatabad et al. also failed to identify any significant correlation between canities and thyroid status [20].

A significant association between chronic urticaria and thyroid disorders was reported in previous studies [21-24]. In this study also, 7.9% of the patients with chronic spontaneous urticaria exhibited thyroid dysfunction.

Among the 14 psoriatic patients, four revealed abnormal thyroid function in this study. However, other studies reported no significant association [25-27].

Other dermatological conditions, especially of autoimmune origin, have also been reported to have associated thyroid disorders, such as morphea, lupus erythematosus, scleroderma, dermatitis herpetiformis, erythema annulare centrifugum, generalized granuloma annulare, reticular erythematous mucinosis, pseudoxanthoma elasticum, and palmoplantar pustulosis [28].

Cutaneous manifestations may serve as an early indicator of thyroid disorders. Also, a high prevalence of subclinical hypothyroidism in many patients with various cutaneous disorders may indicate that subclinical hypothyroidism may be an important unrecognized association with numerous cutaneous disorders. Subclinical hypothyroidism was the most prevalent thyroid gland disease in one study [29].

The limitation of the present study was that tests such as antithyroid antibodies or a radioactive thyroid scan were not performed to determine the etiological nature of thyroid dysfunction in the cases of hypothyroidism and hyperthyroidism. Moreover, as all types of dermatological disorders were included in the study, it was impractical to find an equally matched control group from an outpatient set-up to be able to conduct a case-control study.

CONCLUSION

Thyroid disorders are often observed in numerous dermatological conditions, such as vitiligo, alopecia areata, diffuse hair loss, dry skin, chronic urticaria, and melasma. This suggests the inclusion of thyroid function tests in the routine investigations of these conditions. Cutaneous manifestations may also be

the only symptom or the earliest symptom of thyroid disorders. Therefore, a periodic assessment of thyroid function is necessary for the early diagnosis and management of the underlying thyroid dysfunction.

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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Our Dermatology Online

Brief Report

COVID-19 and pemphigus: A descriptive series of twelve cases

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ABSTRACT

Background: Patients with pemphigus receiving immunosuppressive therapy are considered at risk of developing severe forms of COVID-19. We aimed to analyze the clinical and evolutionary characteristics of COVID-19 infection in patients with pemphigus receiving general corticosteroid therapy by a retrospective descriptive study of twelve cases. **Patients and Methods:** We identified pemphigus cases that developed a COVID-19 infection. The data collected included the characteristics and treatment of pemphigus and the features and course of COVID-19 infection. **Results:** Twelve patients were followed at our department for pemphigus and a developed COVID-19 infection. Nine patients had a severe form of pemphigus, and three were in clinical remission. The infection was severe in three patients. The evolution was good in all patients. **Discussion:** Our study suggests that systemic corticosteroid therapy in patients with severe forms of pemphigus may be a protective factor against severe forms of SARS-CoV-2 infection. This theory should be evaluated by a larger study.

Key words: COVID-19; Corticosteroid Therapy; Pemphigus; Rabat; Morocco

INTRODUCTION

COVID-19, a disease resulting from infection by the virus SARS-CoV-2, was first described in late December 2019, in Wuhan, China. On March 11, 2020, the World Health Organization (WHO) declared the disease a pandemic responsible for more than one million deaths worldwide [1].

The severity of coronavirus disease-2019 (COVID-19) is related to age, the male sex, and the presence of comorbidities: obesity, pulmonary and cardiovascular pathologies, diabetes, and cancers [2].

For nearly a year, numerous studies have been published to provide a better understanding of the virus, its management, and its consequences, including in patients with pemphigus. Indeed, patients suffering from pemphigus, especially its severe form, and receiving immunosuppressive treatment are considered at risk of developing severe forms of COVID-19.

We evaluated the risk of COVID-19 and its severe forms in these patients by a retrospective, descriptive study of twelve cases of pemphigus followed at our department.

Our objective was to analyze the clinical and evolutionary characteristics of COVID-19 infection in patients with pemphigus receiving immunosuppressive therapy.

MATERIALS AND METHODS

This was a retrospective, descriptive study including all cases of pemphigus followed at the dermatology department of Ibn Sina Rabat Hospital and having developed a COVID-19 infection confirmed by a positive SARS-CoV-2 PCR test over a period of eleven months (between March 2020 and February 2021).

RESULTS

Twelve patients followed at the dermatology department of Ibn Sina Rabat Hospital for pemphigus (six cases of

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superficial pemphigus, six cases of deep pemphigus, one of which was vegetative) developed a COVID-19 infection between March 2020 and February 2021.

Table 1 details the clinical characteristics of these twelve patients.

There were ten females and two males, with a sex ratio of 0.2. The mean age of the patients on diagnosis was 50.9 years (25 to 68 years).

Four patients were diabetic, three were moderately to severely obese, and one had ischemic heart disease under treatment. One patient was hypertensive and another was followed for rheumatoid arthritis.

Nine had a severe form of pemphigus, with a PDAI between 21 and 98. These nine patients had been receiving a high dose of general corticosteroid therapy between 60 and 140 mg/day. Two were on 150 mg of azathioprine in combination. One patient had received rituximab D1 D15 (2 g).

Three cases were in clinical remission under low-dose corticosteroid therapy (5 to 20 mg/day), among which one received its M6 dose of rituximab (1 g) three months previously.

Nine of the twelve cases were in contact with suspected or confirmed cases of COVID-19, while no exposure to risk was noted for the remaining three cases.

A SARS-CoV-2 PCR test was positive by a nasopharyngeal swab in all twelve patients. Regarding the clinical features of COVID-19 infection:

The infection was considered severe in three patients. These patients presented hypoxia, dyspnea, and a CT scan > 50% with a biological inflammatory syndrome. These three patients were hospitalized in an intensive care unit and received oxygen therapy, curative anticoagulation, and antibiotic therapy.

Among these 3 patients, one had a significant inflammatory syndrome and received tocilizumab (Note

Table 1: Characteristics of the patients with pemphigus and COVID-19 infection.

No.	Sex/ Age	History and Comorbidities	Type of Pemphigus	PDAI	Treatment in Progress	Symptoms	SARS-CoV-2 Nasopharyngeal PCR	CT Signs of COVID-19	Severity of COVID-19
1	M/67	0	Superficial pemphigus	37	Prednisone 140 mg/day + Azathioprine 150 mg/day	NO	Positive	N/A	Benign
2	F/45	Moderate obesity	Pemphigus vulgaris	Remission	Prednisone 45 mg/day + Rituximab D1 and D15 (after six months)	YES	Positive	NO	Benign
3	F/68	0	Pemphigus vulgaris	27	Prednisone 100 mg/day	YES	Positive	NO	Benign
4	F/60	Type 2 diabetes on insulin	Superficial pemphigus	Remission	Prednisone 30 mg/day	YES	Positive	YES (25–50% lung parenchyma involvement)	Severe
5	M/58	Ischemic heart disease Diabetes type 2	Superficial pemphigus	Remission	Prednisone 20 mg/day	YES	Positive	YES (severe damage 50–75%)	Severe
6	F/25	0	Pemphigus vulgaris	79	Prednisone 80 mg/day	NO	Positive	N/A	Benign
7	F/37	0	Pemphigus vulgaris	30	Prednisone 60 mg/day	NO	Positive	N/A	Benign
8	F/39	Rheumatoid arthritis	Superficial pemphigus	28	Prednisone 110 mg/day	YES	Positive	N/A	Benign
9	F/58	0	Superficial pemphigus	21	Prednisone 60 mg/day	NO	Positive	N/A	Benign
10	F/57	Osteoporosis Diabetes type 2	Pemphigus vulgaris	Remission	Prednisone 5 mg/day + 3 months after sixth course of rituximab	YES	Positive	YES (severe damage > 70%)	Severe

M: male; F: female; PDAI: pemphigus disease area index; N/A: not available

that this patient had comorbidities such as diabetes and severe obesity. This patient was in complete remission of her pemphigus and was, therefore, only receiving 5 mg of prednisone and received an M6 dose of rituximab three months previously.)

Four of the twelve cases were symptomatic with mild symptoms of flu-like illness and anosmia. Five were asymptomatic.

No systemic treatment for pemphigus was withheld in these twelve patients. All patients had a favorable outcome and no deaths were reported.

Moreover, we noted no clinical cutaneous aggravation of pemphigus in our patients.

DISCUSSION

This was a retrospective, descriptive study of twelve patients followed for pemphigus, who developed a COVID-19 infection during the previous eleven months. Among these twelve patients, nine had a severe form of pemphigus and had been receiving a high dose of systemic corticosteroid therapy (between 60 and 140 mg/day) and had developed a mild form of SARS-CoV-2 infection. The three of the twelve patients who had a severe COVID-19 infection were on low doses of corticosteroid therapy (between 5 and 20 mg/day), yet had mainly comorbidities such as diabetes and severe obesity. This suggests that high-dose systemic corticosteroid therapy had had a protective role and had improved the prognosis of COVID-19 infection in our series.

The literature has not yet reported that patients with autoimmune bullous disease have a higher risk of being infected with SARS-CoV-2 compared to healthy individuals. However, this seems possible due to the immunosuppressive context of the autoimmune disease itself and its treatment [3].

There is a limited number of series studying the course of COVID-19 in patients with pemphigus. In an Italian series including 31 patients with pemphigus, seven patients (one male, six female; mean age: 68.3 ± 9.7) presented with symptoms suspected of COVID-19, six patients (19.4%) with mild to moderate symptoms, and one (3.2%) with severe symptoms requiring hospitalization

In contrast to our series, all patients were in remission and had, therefore, been on low-dose systemic corticosteroid therapy with a mean dose of 5.9 ± 6.2 mg/day. This ongoing treatment was only interrupted for the hospitalized patient [4].

In an Italian series including nine patients with pemphigus, only one patient tested positive for SARS-CoV-2. The patient was a 65-year-old female with pemphigus lasting for more than three years and on mycophenolate mofetil for 38 months. The patient presented with severe nausea, fever, anorexia, asthenia, and the next day tested positive for SARS-CoV-2. She stopped treatment two days after the diagnosis of COVID-19. She gradually improved and was completely free of symptoms twelve days after diagnosis [5,6].

In an Iranian study, a total of 45 pemphigus patients who underwent rituximab treatment between 2014 and 2020 were included. The authors identified five cases (four female, one male; mean age: 41.8 ± 9.6 years) of confirmed COVID-19. Among these five patients, four had mild symptoms related to COVID-19. Only one incidentally diagnosed patient was asymptomatic All patients were on prednisolone therapy at a dose of 5–10 mg/day. Two patients had additionally received pulsed therapy with methylprednisolone and azathioprine. None received rituximab during the year preceding the pandemic [6].

Despite concerns that corticosteroids induce the inhibition of antiviral immunity and, thus, may disrupt the viral load, low-dose systemic corticosteroids appear to play a role in treating severe COVID-19 infections [7]. Our study confirms this hypothesis and suggests that high-dose systemic corticosteroids had a protective role and improved the outcome of severe COVID-19.

In their expert recommendations for the management of autoimmune bullous diseases during the COVID-19 pandemic, Kasperkiewicz et al. suggested that immunomodulatory therapies, including systemic corticosteroids, should be continued if necessary, as unwarranted withdrawal may cause disease exacerbation associated with high morbidity and mortality [8].

For rituximab, Shakshouk et al. advocated temporarily deferring rituximab therapy to delay the peak of immunosuppression in patients during the peak incidence of COVID-19 [6].

They also suggested that topical corticosteroids and prednis(ol)one ≤ 10 mg/day may be continued in patients infected with SARS-CoV-2, while prednis(ol) one > 10 mg/day may be reduced, taking into account the disease activity and severity, comorbidities, age, and severity of COVID-19, and therefore a withdrawal or significant reduction in the dose of systemic corticosteroids should be avoided, especially in patients with severe forms of autoimmune bullous diseases [9].

Moreover, the hospital management of severe and critical forms of COVID-19 relies mainly on two possibly associated strategies: decreasing viral replication and preventing an exacerbated inflammatory response. Corticosteroids are the only treatment at present to have demonstrated a benefit in reducing the risk of mortality in oxygen-dependent patients with a critical form of COVID-19 [10]. However, several prospective trials have been conducted to evaluate the efficacy of corticosteroid therapy in the management of severe forms of COVID-19. The RECOVERY Trial randomized the use of dexamethasone (6 mg/day for ten days) in addition to standard therapy in patients hospitalized with COVID-19 infection. In patients treated with corticosteroids (2104 vs. 4321), there was a decrease in 28-day mortality (the primary objective of the trial) for ventilated or oxygen-requiring patients, and a decrease in the risk of mechanical ventilation for patients on oxygen. This effect was absent in patients not requiring oxygen. A possible deleterious effect has been suggested in this population [10].

In fact, the WHO and several learned societies do not contraindicate the use of corticosteroids in cases in which their benefits are well established and recommend that they be continued as background treatment [11].

CONCLUSION

Our study has certain limitations. The analysis of the records was retrospective and not all data was always known. The number of patients was low making it difficult to interpret some data.

Despite these biases, the study provides insight into some aspects of COVID-19 in patients with severe pemphigus receiving high doses of systemic corticosteroid therapy and suggests the impact of this treatment on the successful outcome of SARS-CoV-2 infection despite the presence of comorbidities.

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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Our Dermatology Online

Case Report

Neutrophilic urticaria with systemic inflammation (NUSI) following Pfizer–BioNTech COVID-19 vaccine

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ABSTRACT

The Pfizer–BioNTech mRNA vaccine has shown excellent protection against the severity of COVID-19, yet adequate research on rare adverse events is lacking. Herein, we discuss the case of a 36-year-old female who had developed an urticarial polymorphous eruption, episcleritis, and inflammatory oligo-arthritis, in keeping with neutrophilic urticaria with systemic inflammation (NUSI), following the administration of Pfizer COVID-19 vaccine. Investigations for other dermatological and rheumatological conditions were unremarkable, while multiple skin biopsies were highly suggestive of a neutrophilic drug reaction. To gain symptom control, our patient required multiple weeks off from work and was treated with several immunosuppressive, anti-inflammatory, and analgesic agents. Further research with larger numbers is needed to identify adverse events more accurately, which will aid both in early diagnosis and prompt treatment for patients.

Key words: Urticaria; Rash; Arthritis; COVID-19; Vaccination

INTRODUCTION

The Pfizer–BioNTech BNT162b2 mRNA vaccine has shown 95% protection against COVID-19 in adults in phase III clinical trials [1]. However, a systematic review of the adverse events reported revealed that they usually resolved within four days and included pain or redness on the injection site, fever, fatigue, myalgia, and arthralgia [2]. A subsequent registry-based study focusing on the cutaneous manifestations of mRNA COVID-19 vaccines further highlighted delayed cutaneous reactions, urticarial eruptions, and morbilliform eruptions, also resolving within several days and only requiring simple treatment, if any [3].

Herein, we present a case of generalized polymorphous eruption, episcleritis, and inflammatory oligo-arthritis following the administration of the second dose of Pfizer–BioNTech COVID-19 vaccine. The clinical picture presented similarly to the reported entity of NUSI, an inflammatory disorder with cutaneous involvement [4].

CASE REPORT

A 36-year-old, female art therapist presented with a generalized polymorphous eruption three days after the second dose of Pfizer–BioNTech COVID-19 vaccine. The medical history consisted of vitiligo, seasonal asthma, and hypothyroidism during pregnancy. The patient's only long-standing medication was the combined oral contraceptive pill (COCP) and inhaled salbutamol as needed. She denied any new prescribed or over-the-counter medication in the preceding three months. Although she reported no previous drug allergies, a previous reaction to morphine included nausea and pruritis.

The rash first appeared as a polymorphous eruption, consisting of erythematous, indurated plaques on the

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shoulder and upper arms (Fig. 1a) and a morbilliform eruption on the face, lower arms, legs, and torso (Fig. 1b). Interestingly, all patches of vitiligo remained unaffected by the eruption, which was fiercely pruritic and significantly affected the patient's quality of life. She also reported conjunctival injection, grittiness of the ocular mucosa, and blurring of vision. She was admitted to her local tertiary hospital, in which skin biopsies were performed and she was initiated on high-dose oral corticosteroids, oral anti-histamines, wet dressings with potent topical corticosteroids, and lubricating eye drops as per opthalmology advice. Blood tests revealed a raised white cell count (WCC) at 15.6 × 10^9/L (4.0–11.0), neutrophils at 14.0 × 10^9/L (2.0–7.5), C-reactive protein (CRP) at 25 mg/L (0.0–5.0), and an erythrocyte sedimentation rate (ESR) at 8 mm/h (1–29). Skin biopsies were most consistent with a drug eruption, showing a very mildly spongiotic epidermis with occasional apoptotic keratinocytes and underlying dermal inflammation containing some neutrophils, perivascular lymphocytes, and rarely eosinophils (Figs. 2a and 2b). After the rash and ocular symptoms subsided, corticosteroids were slowly weaned. However, her eruption and ocular symptoms returned once the dose of prednisolone reached 25 mg daily. Subsequent attempts to reduce prednisolone resulted in the same eruption, Therefore, cyclosporine was initiated at a dose of 4 mg/kg daily. During this period, the patient's eruption appeared more urticarial, yet was not evanescent. Additional skin biopsies were performed at this time, further supporting the diagnosis of a drug reaction. These revealed a similar picture, with a mild spongiotic reaction, dyskeratotic keratinocytes, and mixed dermal inflammation.

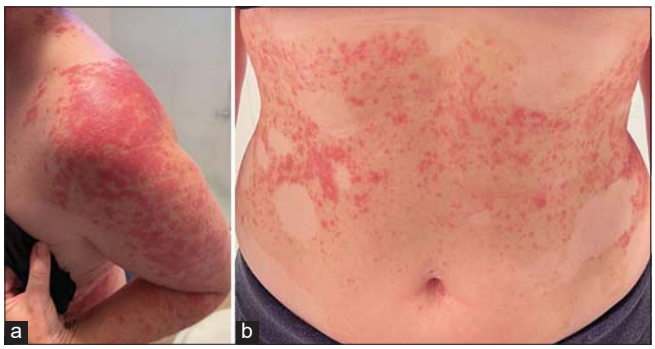

Figure 1: (a) Erythematous plaques on the shoulders. (b) Morbilliform eruption on the abdomen, notably sparing patches of vitiligo.

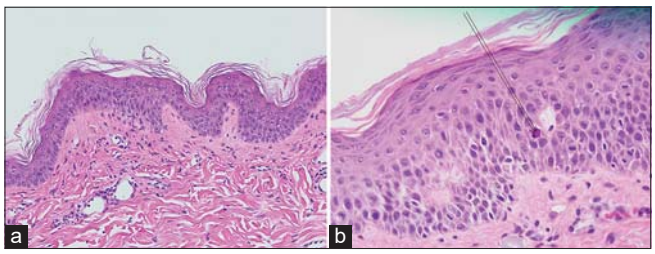

Figure 2: (a) The initial skin biopsy revealing a mildly spongiotic epidermis and mild upper dermal inflammation. (b) The initial skin biopsy revealing a mild spongiotic epidermis and a dyskeratotic cell.

Ten weeks after the initial presentation, our patient approached the emergency department with an acutely tender left elbow associated with swelling and a reduced range of motion. Further investigations revealed CRP at 10^4 mg/L and the ESR at 21 mm/h. A joint aspirate showed the WCC at 35,000 × 10^6/L (composed of 95% polymorphs, with no crystals under the microscope and no bacterial growth on culture). Anti-nuclear antibody (ANA), rheumatoid factor (RF), cyclic citrullinated peptide (CCP), HLA-B27, anti-neutrophil cytoplasmic antibody (ANCA), double-stranded DNA (ds-DNA), extractable nuclear antigen (ENA), ferritin levels, liver enzymes, and complement levels were all unremarkable. Conditions such as adult-onset Still's disease, systemic lupus erythematosus, and Schnitzler syndrome were considered and excluded. Due to her predominant joint symptoms, cyclosporine was switched to methotrexate 10 mg weekly. She was also initiated on naproxen 750 mg twice daily and colchicine 50 mg twice daily. Nonetheless, the patient developed further joint effusions in both knees, with synovial fluid aspirates showing a similar inflammatory picture to previous. Our patient's fixed urticarial eruption with neutrophilic infiltrate and inflammatory joint symptoms were consistent with the presentation of NUSI, which is presumably mediated by interleukin-1 (IL-1). Anakinra, an IL-1 inhibitor, was subsequently administered at 100 mg daily. While this did not show the dramatic resolution of the symptoms seen in the previous case series [4], there was a notable improvement in inflammatory markers (CRP at 36 mg/L and ESR at 10 mm/h), steady improvement in the joint disease, and no flares of cutaneous involvement on the gradual weaning of corticosteroids.

DISCUSSION

Herein, we are reporting a case of widespread, polymorphous eruption and inflammatory oligo-arthritis, in keeping with NUSI, three days following the second dose of Pfizer–BioNTech COVID-19 vaccine. In this case, the patient had a history of autoimmune conditions, yet had never reported similar skin symptoms or joint disease. It was most likely

that the temporal relationship between vaccination and the disease onset was causal. Repeated biopsies were consistent with a neutrophilic drug reaction and our patient was not on any new prescription or over-the-counter medications. It is also worth noting that she was successful in gaining injury compensation from the workplace, which had mandated COVID-19 vaccinations for the employees.

The original phase III trial for the Pfizer–BioNTech vaccine acknowledged that it was "not large enough to detect less common adverse events reliably" [1]. Undoubtedly, more research is vital before we may have sufficient evidence to attribute rare adverse effects to these COVID-19 vaccines. This will not only optimize informed consent for patients, yet also aid clinicians in early recognition and treatment.

CONCLUSION

Herein, we have reported a case of NUSI with a widespread, urticarial eruption, episcleritis, and inflammatory oligo-arthritis, following the second dose of Pfizer–BioNTech COVID-19 vaccine. While it cannot be stated with certainty whether the vaccination was the cause of the patient's symptoms, multiple skin biopsies were strongly suggestive of a neutrophilic drug reaction and the patient had not been given any other new medication in the preceding three months. This highlights the need for further research on COVID-19 vaccines to identify rare adverse events. Nonetheless, the safety data for the approved COVID-19 vaccines is reassuring and the overall benefit of vaccination is clear.

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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Our Dermatology Online

Case Report

Metastasis of a widespread malignant melanoma in the bladder and the upper urinary tract: A case report

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ABSTRACT

The urinary tract is an uncommon site of metastatic melanoma. Herein, we discuss a rare case of melanoma with metastatic involvement of the bladder and upper urinary tract and review its surgical management based on prognosis. We report the case of a 38-year-old male with biopsy-proven ureteral and bladder metastasis of cutaneous melanoma. The management of these metastases is challenging. Endoscopic treatments allowed to control local symptoms without associated serious adverse events. Radical surgical operations such as nephroureterectomy could be envisaged for completely resectable tumors in a patient responding well to systemic therapies.

Key words: Melanoma; Metastasis; Bladder; Upper urinary tract

INTRODUCTION

Cutaneous melanoma has the potential to spread to distant organs, causing more than 60,000 deaths annually worldwide [1]. The most common clinically apparent sites of distant metastases in melanoma patients are the skin, lungs, brain, liver, bones, and intestines [2-4]. Herein, we discuss a rare case of melanoma with metastatic involvement of the bladder and upper urinary tract and review its surgical management based on prognosis.

CASE REPORT

A 38-year-old male with multi-organ metastatic melanoma was referred to our department for gross hematuria and right renal colic. A CT scan revealed a large, circumferential tumor of the right ureteropelvic junction and right lumbar ureter (Fig. 1). Flexible cystoscopy was then performed, which found a small synchronous bladder localization.

The patient subsequently underwent a transurethral resection to remove the tumor in the bladder and right ureteroscopy with a biopsy of the tumor in the upper urinary tract. Each sample was sent to an experienced pathologist. Retrograde ureteral stenting was employed due to the dilatation of the upper urinary tract.

Pathological findings confirmed metastasis of melanoma in the urinary tract. Fig. 3 shows bladder resection specimens with an ulcerative lesion and tumor sheets next to a dystrophic urothelium (Fig. 2a). Some tumor cells were highly pigmented (Fig. 2b). Immunohistochemistry confirmed melanoma cells with SOX10 antibody (Fig. 2c) and positive BRAF V600E staining (Fig. 2d).

Due to the unresectability of multiple secondary lesions, no intention-to-treat surgery was considered for the tumor in the upper urinary tract. The patient was a poor responder to immunotherapy and had a disease progression. However, the patient was treated with conservative management by resection and

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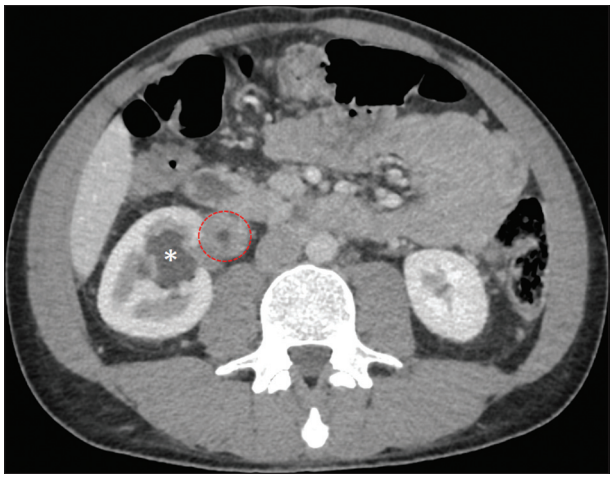

Figure 1: CT scan: The dotted line shows the circumferential tumor of the ureteropelvic junction. The asterisk corresponds to the dilatation of the upper urinary tract prior to the tumor.

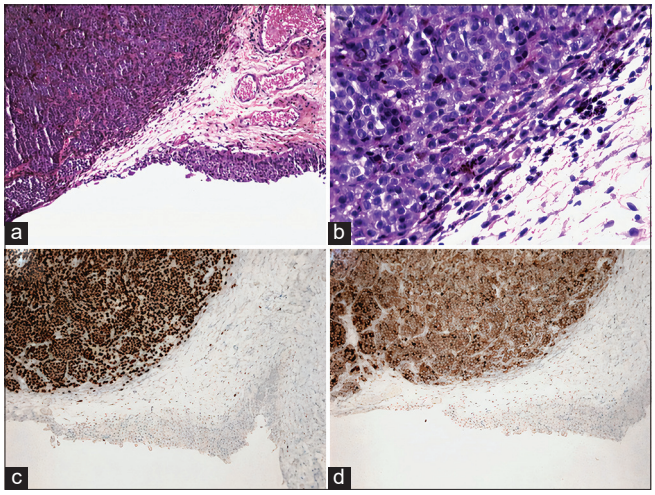

Figure 2: Pathological findings: a) Bladder resection specimens show an ulcerative lesion with tumoral sheets next to a dystrophic urothelium (H&E, 100×). b) Some tumor cells were highly pigmented (H&E, 400×). c) Immunohistochemistry confirmed melanoma cells with SOX10 antibody (100×), d) with positive BRAF V600E staining (100×).

coagulation with holmium laser, and neither hematuria nor renal colic was reported after three months of follow-up.

DISCUSSION

Historically, systemic therapy for metastatic melanoma was associated with poor response rates, yet the last decade has seen the development of multiple targeted and immune therapies that have shown a survival benefit. The surgical management of the metastatic site could be envisaged for completely resectable tumors. These stage IV patients exhibit improved survival, regardless of the site and the number of metastases [5,6].

The genitourinary tract is an uncommon site of metastatic melanoma. The treatment of genitourinary metastases is challenging and relies primarily on prognosis. Metastasectomy should be considered for local control in oligometastatic disease if a complete macroscopic resection may be obtained while any remaining distant disease is stable on immunotherapy. Transurethral resection of tumors in the bladder and nephroureterectomy provide the best local control of lower and upper urinary tract involvement, respectively [7]. In patients with a poor response to immunotherapy, palliative nephroureterectomy should be considered with caution. However, retrograde ureteral stenting and transurethral resection allowed local control of symptoms, in particular, gross hematuria, which may interrupt the administration of necessary systemic therapies and lead to more hospital admissions [7].

CONCLUSION

The treatment of metastatic melanoma is challenging. Although the genitourinary tract is a rare site of metastasis, early detection is important as effective therapies are available, improving control of local symptoms and the potential disease progression.

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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Our Dermatology Online

Case Report

Pyoderma gangrenosum mimicking a Buruli's ulcer in an HIV-positive patient from Ivory Coast

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ABSTRACT

A lower limb ulcer is a disabling disease with significant functional impact and difficulties to manage. Ulcers, due to infectious agents, an inflammatory etiology, or microvascular occlusion are particularly challenging in terms of diagnosis and treatment. The management of such ulcers requires proper clinical examination as well as oriented biological and histological assessments. Herein, we report the case of a 39-year-old female from Ivory Coast with an extensive bilateral lower limb ulcer evoking a Buruli's ulcer. Investigations, however, revealed a severe case of pyoderma gangrenosum in an HIV-positive patient. Our case report demonstrates the difficulties in the diagnosis of leg ulcers, especially in immunosuppressed patients. Confusing pyoderma gangrenosum with a Buruli's ulcer may lead to extensive surgery or the use of long-term steroids with multiple iatrogenic complications, hence the importance of a skin biopsy and biological assessments in establishing a correct diagnosis.

Key words: Ulcer; Lower limb; Pyoderma gangrenosum; Buruli's ulcer; HIV

INTRODUCTION

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis characterized by chronic ulcers due to an abnormal immune response. Five clinical subtypes of PG exist: ulcerative, bullous, pustular, and vegetative. In the case of ulcerative PG, skin and soft tissue bacterial and non-bacterial infections, such as cutaneous tuberculosis, leishmaniasis, and Buruli's ulcers, are common mimickers. Workup, including a biopsy, are required in all patients suspected of having pyoderma gangrenosum in order to exclude these differential diagnoses.

CASE REPORT

A 39-year-old female from Ivory Coast was admitted to our department for the management of multiple, non-healing, painful ulcers in the lower extremities. The skin ulcers developed six weeks earlier after the appearance of a nodule and a painful edema in the legs. There was no history of trauma. The patient took no regular medications and denied fever, chills, diarrhea, abdominal pain, or arthralgia. On admission, the vital parameters were as follows: blood pressure at 128/60 mmHg, pulse rate at 70 beats per minute, respiratory rate at 14/min, and body temperature at 37.2°C. A physical examination revealed an erythematous ulceration 15 × 10 cm in size on the anterior side of the right leg, with irregular borders a central blackish crust on the posterolateral side of the left leg, three ulcerations, with the largest 3 × 1 cm in size (Figs. 1a and 1b), a prurigo eruption on the trunk (Fig. 2), and multiple lymphadenopathies in the inguinal and cervical regions. In terms of our examination, we evoked a Buruli's ulcer, cutaneous tuberculosis, leishmaniasis, cryptococcosis in a patient with HIV, and a pyoderma gangrenosum. Laboratory results yielded a positive HIV serology confirmed by

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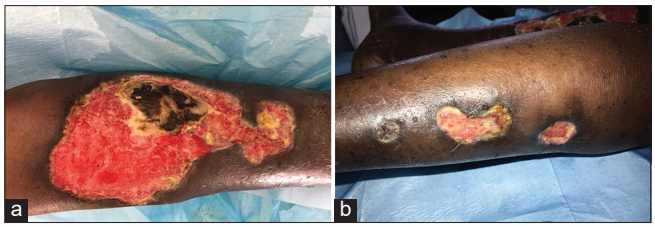

Figure 1: (a-b) Ulcerative pyoderma gangrenosum in a 39-year-old African female.

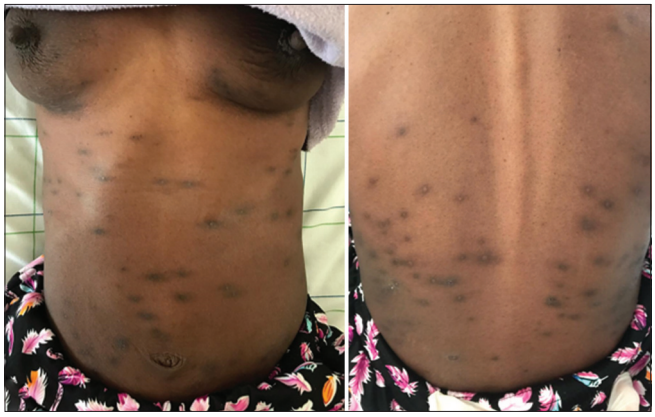

Figure 2: HIV prurigo eruption of the trunk.

a Western blot test. Her CD4 cell count and HIV RNA level were 92 cells/mL and 419 302 copies/mL, respectively. She had elevated C-reactive protein and an elevated erythrocyte sedimentation rate without an increase in the white cell count and a decreased hemoglobin level. She tested negative for hepatitis B, hepatitis C, and syphilis. A skin biopsy was performed on the second day of hospitalization. A histopathological examination revealed an infiltration of inflammatory cells, predominately neutrophils, extending from the dermis to the subcutis on hematoxylin and eosin staining (Figs. 3a and 3b). Special staining (Gram stain, Grocott stain, PAS stain) revealed no microorganisms. The culture of a biopsy specimen taken from the edge of the ulcer was negative for bacteria, fungi (cryptococcosis), and atypical mycobacteria (*Mycobacterium ulcerans*). A chest X-ray was normal, with no osteomyelitis in the lower leg X-ray. A polymerase chain reaction assay to detect *Mycobacterium tuberculosis* was also negative. The pathologists concluded that the histopathological findings were compatible with the diagnosis of pyoderma gangrenosum. On the day of hospitalization, the patient presented with headaches. An extensive workup for HIV (lumbar puncture, brain scan, serum electrolytes) was negative. Subsequently, an antiretroviral therapy including tenofovir disoproxil fumarate, emtricitabine, and efavirenz was started on the twentieth day of hospitalization. Local treatment

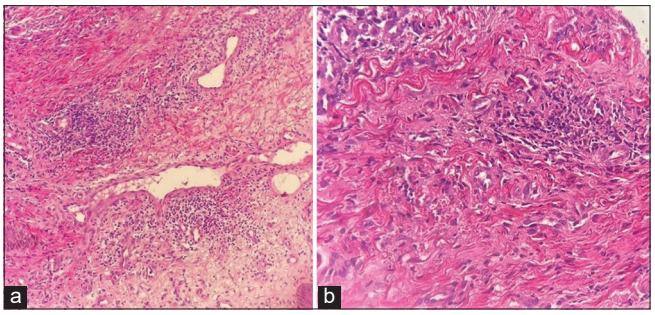

Figure 3: (a-b) Dense dermal inflammatory infiltrate consisting of lymphocytes, histiocytes, and mainly neutrophils (H&E).

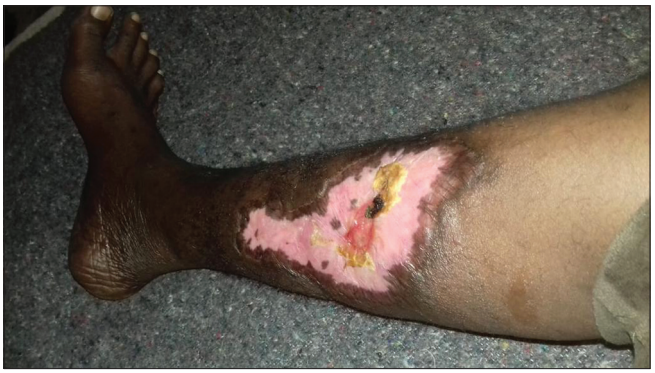

Figure 4: Complete healing of the ulcer two months after the antiretroviral therapy alone.

consisted of vaseline tulles and hyaluronic acid cream. Within two months, the ulcers became progressively smaller and less painful and reached complete healing (Fig. 4). No other immunosuppressive therapy was added, including oral prednisone.

DISCUSSION

A Buruli's ulcer (BU), also classified as neglected tropical disease by the WHO, is a disabling skin infection caused by *Mycobacterium ulcerans*. It has been reported in around 33 (mostly tropical) countries, with the greatest frequency in Africa, particularly in the West African countries of Ivory Coast, Ghana, and Benin (20 to 158 cases per 100,000) [1]. BUs preferentially affect children from two years of age without a predilection for sex. It affects females more often than males in adulthood, probably due to direct transcutaneous transmission from water. Similarly to pyoderma gangrenosum, BUs often affect the legs. However, they often begin with a painless indurated nodule or plaque, sometimes edema of a limb with local inflammatory symptoms, then appear as a profound dermoepidermal ulceration with a yellowish necrotic background. They evolve very slowly (for several months) with spontaneous scarring at the cost

of irreversible sequelae (retraction, ankylosis), which differentiates them from PG (rapid evolution, painful character). The main complication of a BU is osteitis, that is why an X-ray of the limbs is mandatory. When the ulcers are multifocal and extensive, it is necessary to search for an association with an HIV infection, which is considered the main risk factor for a BU [2,3].

The clinical aspect of PG and a BU may be identical and it may be difficult to diagnose a BU. The culture of *M. ulcerans* on a Loewenstein–Jensen medium requires a low ambient temperature (32°C) and the growth is very slow (6–8 weeks). Acid-fast bacilli may be found in biopsy specimens (with a sensitivity of 90%) in actively ulcerating cases, yet otherwise the diagnostic yield is fairly low. Histology of a cutaneous biopsy shows necrosis of dermal collagen and subcutaneous adipose tissue with a minimal inflammatory reaction and typically the presence of more or less frequent large acid-fast bacilli. The confirmation diagnosis is based on the DNA amplification technique (PCR) of *M. ulcerans*.

The standard of care remains surgical excision and skin grafting, if in primary closure, is not feasible. A mistaken treatment of a BU as pyoderma gangrenosum with high-dose corticosteroids has been reported. This underlines the clinical similarity of these two entities. BUs should, therefore, be considered a differential diagnosis of pyoderma gangrenosum in any patient from an African country with lower limb ulcers [4].

CONCLUSION

To conclude, the diagnosis of leg ulcers is based on a set of arguments: the epidemiological situation of the patient completed by a biological and X-ray assessments guided by a clinical examination. An extensive ulcer of pyoderma gangrenosum may be confused with a Buruli's ulcer, especially in an HIV-positive patient, hence the interest in skin biopsies and bacteriological samples to avoid any invasive or extensive surgery.

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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Our Dermatology Online

Case Report

Bullous lupus erythematosus with basement membrane deposits of IgD

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ABSTRACT

Bullous lupus erythematosus is an uncommon blistering subepidermal autoimmune disease with characteristic immunopathological nosologic features. A 67-year-old female presented with the sudden appearance of blisters in the upper area of the right chest. Skin biopsies stained with H&E favored the diagnosis of blistering lupus erythematous with a decrease in dermal sebaceous and eccrine glands. Direct immunofluorescence revealed deposits of IgG, complement C3, fibrinogen, IgM, and IgD in the epidermal corneal layer and the basement membrane zone. Reactivity to some dermal endothelial cell junctions and neural receptors was also noted. Also, complement C4 was positive against upper and middle dermal thin fibers. Complement D2 was positive around some enlarged dermal vessels, colocalizing with factor XIIIa. Our case highlights the complex and previously unreported immunologic response features associated with bullous lupus erythematosus.

Keywords: Bullous lupus; IgD; Sebaceous glands; CD2

INTRODUCTION

As with systemic lupus erythematosus (SLE), bullous SLE has often been encountered in young adult females of African descent. In fact, bullous SLE may occur in all ages, sexes, and ethnicities, yet it tends to affect younger females [1,2]. Lupus nephritis has quite often been associated with bullous lupus, and this disease is rare in minors [3]. The lesions vary from blisters, to vesicles, to urticarial lesions, most often seen on the face or in other sun-exposed areas. In several cases, mucous membrane involvement has been reported. In general, skin biopsies with hematoxylin and eosin (H&E) staining show subepidermal detachment and dermal infiltration of neutrophils (often visualized near the epidermal-dermal junction) [1,2]. The clinicopathologic diagnostic criteria for bullous SLE include 1) a diagnosis of systemic lupus erythematosus (SLE) by the American College of Rheumatology (ARA) criteria; 2) a clinical blistering/vesicular eruption, and 3) histologic evidence of subepidermal blistering and a neutrophil-predominant dermal infiltrate. Oral and esophageal lesions have been described in bullous SLE [3]. Direct immunofluorescence (DIF) staining classically demonstrates linear and/or granular deposits of immunoglobulin IgG, IgM, and, frequently, IgA in the BMZ. A serrated pattern is not seen by DIF. These patterns assist in differentiating bullous lupus (with tissue-bound auto-antibodies against type VII collagen) from many other anti-BMZ disease antibodies (in which a non-serrated pattern is seen) [1]. Some reports have shown bullous SLE antibodies to bullous pemphigoid antigens (BP 230; BP 180) and laminins 5 or 6 with immunoblotting [4]; however, the supporting literature is not extensive enough to definitively correlate with the disease. Some researchers have attempted to differentiate types I and II of bullous SLE, yet the classification is not completely accepted. One proposal would subclassify bullous SLE as type I or II depending on whether the antigens

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are directed against type VII collagen (type I bullous SLE) versus against bullous pemphigoid antigens (BP 230, 180) or laminin 5 or 6 antigens (type II bullous SLE). Dapsone at a dose of 1.0–1.5 mg/kg/day is the treatment of choice. It is effective in most patients, leading to swift clinical improvement within days or several weeks [4]. In some cases in which dapsone is ineffective, prednisolone, rituximab, methotrexate, or azathioprine are utilized [4-6].

CASE REPORT

A 67-year-old black female with a forty-year history of systemic lupus erythematosus (SLE) diagnosed with the criteria by the American College of Rheumatology (ARA) presented to the dermatologist regarding the sudden presentation of blisters, dense vesicles, bullae, and erosions. These lesions were present both on normal and erythematous skin in sun-exposed sites (Fig. 1a). Skin biopsies of perilesional areas were taken and evaluated with H&E, as well as with immunohistochemistry (IHC) and direct immunofluorescence (DIF) as previously described [7]. A diagnosis of bullous SLE was established based on the clinical presentation and the histologic findings. H&E staining demonstrated a subepidermal blister with a heavy neutrophilic infiltrate in 1) the blister lumen; and 2) the upper dermis, mainly present in the papillary tips with additional fibrin and neutrophilic debris. Notably, sebaceous glands were decreased in the dermis. Dapsone at a dose of 1.0–1.5 mg/kg/day was administered and the lesions resolved.

To better study this case, we employed both single- and double-color IHC staining, performed with the Leica Bond MAX automated system (Buffalo Grove, Illinois, U.S.) with Novolink™ detection and Compact Polymer™ technology as previously described [7]. Specifically, for primary staining, we used Bond Max refined red detection DS9390, alkaline phosphatase linker polymer, and fast red chromogen (red staining). For secondary staining, we used bond polymer refined detection DS9800, horseradish peroxidase linker polymer, and DAB chromogen (brown staining). Positive and negative controls were consistently performed. The following antibodies were used for the IHC: mouse anti-human monoclonal antibodies 1) Clone F7.2.38, Complement C4 (C4) Cat. No. F0169, 2) IgD Cat. No IR517, 3) factor XIIIa, 4) CD2 (LFA-2) Cat No: PA0271, all from Leica/Novocastra. For DIF staining, we used antibodies and techniques as previously described [7]. It is generally accepted that bullous systemic lupus erythematosus is transient in most cases and usually reverts with no further flares, sometimes leaving hypo- or hyper-pigmentation. Our patient had no pigment alterations after recovery.

Fig. 1a shows multiple blisters some with hemorrhagic contents. Fig. 1b shows some mucin deposition in the dermis on H&E. The histologic features were representative of bullous SLE. IHC staining for IgD revealed linear staining along the basement membrane zone (BMZ) (Fig. 1c).

Using IHC, Complement C4 was positive in the extracellular matrix of the upper dermis as well in the middle and deep dermis, with positive individual elongated cells resembling the shape of fibroblasts

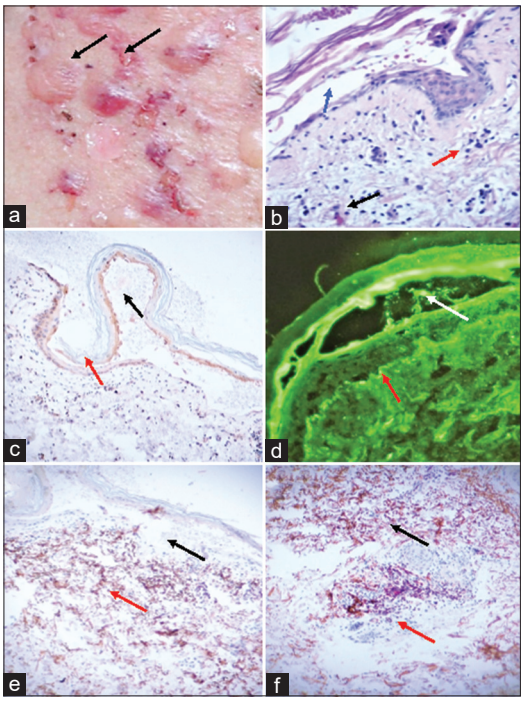

Figure 1: a: Clinical blisters and hemorrhagic blisters on the upper chest (black arrows). **b:** H&E staining displaying a partially re-epithelialized subepidermal blister (blue arrow) (200×). The black arrow highlights mucin in the dermis and the red arrow shows neutrophils around dermal blood vessels. **c:** IHC staining using IgD revealing a linear deposit along the base of the epidermis (brown staining; black arrow) as well as a lack of staining in the epidermal stratum spinosum (red arrow) (100×). **d:** DIF showing a positive blister lumen with positive staining with FITC conjugated anti-human IgM (white arrow), as well as positive non-serrated BMZ staining (red arrow) (400×). **e:** IHC staining with complement C4 showing positive staining in the extracellular matrix of the upper dermis (brown staining; black arrow), as well in the middle dermis (brown staining; red arrow) and positive staining elongated cells resembling the shape of fibroblasts (100×). **f:** IHC positive red staining on a cluster of cells using complement D2 (black arrow) (200×). The brown staining is dermal fiber structures staining for complement C4.

(Fig. 1e). Complement D2 was positive in a cluster in the dermis around the remnants of a sebaceous gland and in some vascular bundles between the middle and deep dermis (Fig. 1f). Factor XIIIa was also positive in these areas (Fig. 1f).

DIF staining displayed the following results: kappa light chains (+++, epidermal stratum corneum); lambda light chains (+++, epidermal stratum corneum); IgG (++, patchy and serrated in the BMZ); (-); complement C1q (+/-, linear BMZ); complement C3 (++, dotted in the BMZ, dotted in the epidermal and the mesenchymal endothelial cell junctions); albumin (-) and fibrinogen (++++, serrated linear BMZ, corneal layer and dermal perivascular). IgM was similar in positivity to fibrinogen, yet additional cytoid bodies were observed in the BMZ (Fig. 1d). IgD was positive (++++) in a linear fashion in the BMZ as well as in multiple small cell junctions in the upper and middle dermis. Please note that IgD was observed using both IHC and DIF in a similar pattern to that seen with fibrinogen.

DISCUSSION

Bullous systemic lupus erythematosus is also termed bullous eruption of SLE and vesiculobullous SLE. The association between collagen VII and bullous SLE was found using autoantibodies detected by indirect immunofluorescence, as well by enzyme-linked immunosorbent assays (ELISA) against type VII collagen [8]. In the current case, we clearly demonstrate positive staining in the BMZ with IgD. We also describe non-classical complement findings in the BMZ of the blisters.

The most common pattern of bullous SLE autoreactivity using DIF displays linear or granular immunoglobulins (IgG, IgM, IgA, and/or complement C3) in the dermal-epidermal junction (DEJ) along the BMZ in perilesional skin biopsies [8]. In the current case, IgD was also observed using both IHC and DIF staining in a similar pattern to that seen with fibrinogen.

Since we serve as a reference laboratory for blistering diseases, we have noted that not only bullous lupus, yet also other autoimmune blistering diseases display positivity when using IgD [9]. We have observed similar patterns of positivity across multiple disorders with IgD, IgM, and fibrinogen. Recent studies have revealed that high expression of the IgD-B-cell receptor (IgD-BCR) may help physiologically autoreactive B cells endure in peripheral lymphoid tissues owing to unresponsiveness to self-antigens; and help their entry into germinal centers to "redeem" autoreactivity via somatic hypermutation [10]. In the current case, we speculate that IgD may be helping in the attack on the self-antigen, potentiating the autoimmune response.

We also observed complement activation not usually reported in bullous lupus. In this case, complement C4 was highly positive. Interestingly, in the pathogenesis of tissue inflammation and injury in SLE, complement C4 is also higher in patients with lupus nephritis [11].

We conclude that the roles of IgD, complement C4, and other inflammatory markers may indeed play critical roles in bullous SLE and that these markers might be included in the diagnostic and research panels employed to study autoimmune diseases. Furthermore, low complement C4 levels are frequently found in systemic lupus erythematosus; patient seric levels may also fluctuate, with low levels of both often seen in disease flare-ups. In our case, the patient displayed a normal seric acid titer (< 8.3 mg/dL; normal range < 10 mg/dL) [12]. Thus, we speculate that the autoimmune response to selected structures in the dermis (demonstrated by IHC staining) may contribute to a decrease in complement C4 levels in patients with bullous SLE.

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.

ABBREVIATIONS

Hematoxylin and eosin (H&E), immunohistochemistry (IHC), direct immunofluorescence (DIF), basement membrane zone (BMZ), epidermolysis bullous acquisita (EBA), systemic lupus erythematosus (SLE), American College of Rheumatology (ARA), fluorescein isothiocyanate (FITC), 4',6-diamidino-2-phenylindole (DAPI), complement component 4 (C4)

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Conflict of Interest: None declared.

Our Dermatology Online

Case Report

Refractory pemphigus vulgaris with extrapulmonary tuberculosis: A challenging case management with rituximab

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ABSTRACT

Pemphigus vulgaris is an autoimmune acantholytic blistering disease that affects the skin and mucous membranes and that is due to IgG autoantibodies targeted against adhesion molecules such as desmoglein 1 and 3 in the epidermis. It follows a chronic course with remissions and exacerbations affecting the patient's quality of life. Since the advent of immunosuppressants, the prognosis of pemphigus has improved but mortality still persists. Long-term use of high-dose corticosteroids and immunosuppressants leads to serious adverse events. Recently, rituximab, a chimeric anti-CD20 monoclonal antibody, which causes B-cell depletion, has been shown to improve disease remission rates with faster tapering of steroids compared to the conventional treatment. Herein, we present a case of refractory pemphigus vulgaris with extrapulmonary tuberculosis and myelosuppression, focusing on unmet challenges due to high-dose systemic steroids, azathioprine, and successful management of the case with rituximab.

Keywords: Pemphigus vulgaris; Rituximab; Extrapulmonary tuberculosis

INTRODUCTION

Pemphigus vulgaris (PV) is an autoimmune bullous disorder caused by circulating autoantibodies directed against desmogleins, resulting in the loss of cell–cell adhesion characterized by blistering of the skin and mucosa. The therapeutic armamentarium includes immunosuppressants such as corticosteroids, azathioprine, mycophenolates, and immunomodulators such as dapsone and tetracyclines. Prolonged and high-dose administration of immunosuppressants is often required to control PV [1].

Some immunocompromised patients are at risk of acquiring primary tuberculosis (TB) or the reactivation of non-active tuberculosis [1]. It is the second leading cause of death from an infectious disease (after HIV infection) [2]. According to the WHO classification, extrapulmonary tuberculosis is an infection caused by *Mycobacterium tuberculosis*, which affects tissues and organs outside the pulmonary parenchyma. It represents between 20% and 25% of all cases of TB and the subsequent dissemination of the infection [3]. It affects various organs, such as the lungs, GI tract, skin, bones, and joints [1]. Herein, we present a case of rapidly progressive PV with coexisting extrapulmonary TB and myelosuppression refractory to conventional management treated successfully with rituximab.

CASE REPORT

A 47-year-old female presented with erosions and crusted lesions on the body and oral mucosa. The diagnosis of PV was histologically confirmed. She was treated with prednisone gradually increased to 120 mg/day for one month. After a brief period of improvement new lesions appeared; we, then, combined prednisone with azathioprine. The patient developed

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a psoas abscess secondary to tuberculosis and was started on extrapulmonary tuberculosis treatment. She also developed steroid-induced idiosyncratic avascular necrosis of the right femur. Hence, steroids were tapered and the dose of azathioprine was increased to 100 mg/day. Again, there was an improvement for a brief period but the disease regressed rapidly, with severe worsening of PV after four weeks (Fig. 1). This time, the patient presented with myelosuppression and a relapse of PV. At this point, we stopped azathioprine and myelosuppression was corrected by three packed cell transfusions at frequent intervals. After the correction of blood counts, 1000 mg of rituximab (RTX) infusion at two-week intervals was initiated, maintaining oral prednisone at 60 mg/day. There was a gradual improvement of the lesions on the trunk in two weeks (Fig. 2). Steroids were gradually tapered and discharged after two months. The patient has been in remission for the last one year after the first cycle of RTX.

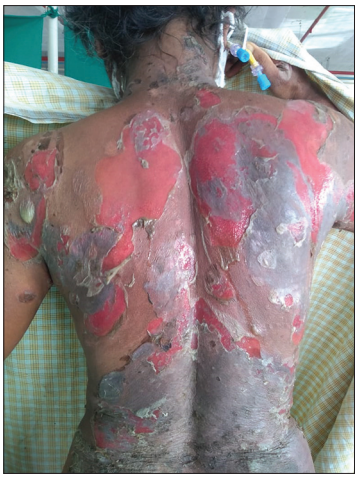

Figure 1: Extensive erosions with oozing seen on the back before the infusion of rituximab.

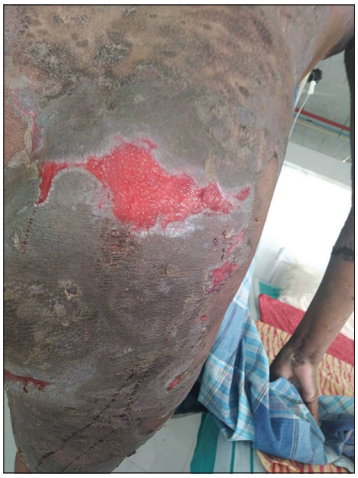

Figure 2: Epithelization of the erosions seen two weeks after the infusion of rituximab.

DISCUSSION

Every patient with PV poses a unique challenge in terms of disease control and adverse events. Diabetes, hypertension, infections, myelosuppression, and other associated complications restrict treatment options. The patient's quality of life will be compromised with recurrent or recalcitrant disease [4].

The main objective in the management of PV is rapid control of the progression of the disease, healing the lesions, and minimizing the associated morbidity. Subsequently, the aim is to achieve long-term remission and avoid adverse effects associated with prolonged use of immunosuppressants. The real challenge in our case was that the patient had severe PV with extra pulmonary TB and myelosuppression secondary to steroids and azathioprine (AZA). Due to long-term steroid-induced complications such as hypertension, diabetes, and osteoporosis, AZA was started. However, on adding AZA, the patient developed myelosuppression, which was managed by stopping AZA and packed cells transfusions. Extrapulmonary tuberculosis treatment was started for the psoas abscess. The above complications are expected in long-term use (after more than four months) of the immunosuppressant.

Prolonged and high-dose administration of steroids is often needed to control certain autoimmune diseases. Immunosuppression masks signs and symptoms of tuberculosis leading to a delay in diagnosis but also predisposes to more severe variants of tuberculosis. Previous studies have concluded that systemic steroid therapy in the long term causes a significant increase in the incidence of tuberculosis [5]. Numerous mechanisms exist: Steroids through their immunosuppressive and anti-inflammatory effects impair antibody formation and cell-mediated immunity. These effects are most evident if steroid doses exceed 0.03 mg/kg/day of prednisolone or an equivalent. At doses higher than 1 mg/kg/day, a marked increase in susceptibility to a wide variety of infections is experienced after several weeks. Continuous therapy produces longer and more profound immunosuppressive effects when compared with intermittent steroid therapy [5]. In a study conducted on patients with dermatomyositis, taking steroids and azathioprine increased the risk of developing TB [6].

AZA is a cytotoxic drug used in autoimmune diseases, which antagonizes purine metabolism and inhibits the

synthesis of DNA, RNA, and proteins. The efficacy of AZA as a corticosteroid-sparing agent in PV is a well-documented and the most often prescribed immunosuppressant. The recommended dose in PV is 1–3 mg/kg/day orally in two separate doses. Its major side effects are pancytopenia, hepatotoxicity, an increased risk of infections, and neoplasms [7].

Rituximab (RTX) is indicated mainly for patients with PV refractory to at least two therapeutic modalities [8]. It is a murine/human chimeric monoclonal antibody against CD20 that induces the depletion of B-cells *in vivo*. RTX binds human complement, affecting complement-dependent cell lysis, and antibody-dependent cellular cytotoxicity disrupts the signaling pathway and triggers apoptosis [9]. There are two officially approved regimes. The lymphoma regime involves 375 mg/m^2 of RTX IV infusion weekly once for 4–8 consecutive weeks. In the rheumatoid arthritis regime, two IV infusions of 1000 mg of RTX are given two weeks apart [9].

In June 2018, the U.S. FDA approved RTX for PV [7]. Schmidt et al. reported a complete remission in 77% and a partial remission in 21% of patients [8]. Serious adverse reactions include angina, adverse drug reactions, intestinal obstruction, lymphocytopenia, anemia, recurrent hepatitis B, progressive multifocal leukoencephalopathy are rare with RTX. The most common adverse effects are fever, chills, bronchospasm, pruritus, hypotension, often related to the rate of infusion and immune hypersensitivity [10,11]. We minimized infusion reactions with prior administration of analgesics, antihistamines, and corticosteroids.

In our case, the patient developed tuberculosis after being treated with prednisolone and myelosuppression with azathioprine for more than a year, and was later was successfully treated with RTX. Such patients should be screened for pulmonary tuberculosis and myelosuppression before and at three-month intervals after the commencement of immunosuppressants and provided with appropriate treatment if needed. There is limited literature on RTX infused in PV with coexisting extrapulmonary TB.

CONCLUSION

Systemic steroids and immunosuppressants used in combination or rotation are the mainstay of management in PV. However, the adverse effects from long-term therapy contribute to morbidity and mortality. In our refractory and clinical rapidly progressive case, RTX led to a longer remission with a faster clinical improvement. RTX is an emerging therapy for numerous autoimmune diseases, especially for recalcitrant and rapidly progressive PV. Further studies are required to determine the dose needed to achieve a long-term clinical remission and cost-effective management.

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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Our Dermatology Online

Case Report

Chronic scrotal erythredema revealing lupus in a sixteen-year-old male

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ABSTRACT

The literature insufficiently describes the etiologies of chronic penoscrotal edema, and even more so those of chronic permanent scrotal erythredema. Herein, we report the case of a sixteen-year-old male who presented, in addition to permanent and chronic scrotal erythredema, classical cutaneous manifestations of systemic lupus. The patient had received systemic corticosteroid therapy combined with hydroxychloroquine. The evolution was good, without new outbreaks or recurrences of penoscrotal edema. Apart from the usual urological emergencies, systemic diseases may be involved in scrotal erythredema, which requires long-term medical management.

Key words: Scrotal erythredema; Systemic lupus erythematosus; Male genitalia

INTRODUCTION

Penoscrotal edema is a frequent pediatric emergency associated with multiple etiologies. Urological emergencies predominate and should always be investigated. However, some scrotal edemas may be of systemic origin. Herein, we report the case of a sixteen-year-old male who presented classic cutaneous–systemic manifestations of systemic lupus associated with permanent and chronic scrotal erythredema. The latter is an uncommon manifestation of cutaneous lupus.

CASE REPORT

A sixteen-year-old male presented with permanent scrotal erythredema persistent for three months. The patient presented himself six months earlier with painful nasal ulcerations, alopecic scalp lesions, and photosensitivity. The symptomatologic evolution was marked three months later by the sudden onset of inflammatory polyarthralgia and painless scrotal erythredema, which gradually worsened and was associated with maculopapular face lesions, fever, and weakness. A physical examination revealed a fever at 39°C and purplish scrotal erythredema, which extended to the perineal and inguinal areas (Fig. 1a). Testicular bursa palpation revealed no evidence of isolated scrotal lymphedema. The patient showed a maculopapular erythematous malar rash with a butterfly distribution extending to the forehead and respecting the nasolabial folds (Fig. 1b). Several discoid lesions were present in the arms with small alopecic scalp plaques. The patient also had a permanent reticular livedo of the lower limbs (Fig. 1a) with multiple cervical and inguinal lymphadenopathy.

Doppler ultrasound of the scrotum highlighted scrotal wall thickening and subcutaneous tissue edema with normal testicles and epididymis. Laboratory data included normochromic normocytic anemia with the hemoglobin level at 6.9 g/dL (12–18) and the rate of erythrocyte sedimentation slightly increased, at 40 mm (N < 20). Immunological samples revealed a speckled antinuclear antibody (ANA) pattern at a titer > 1.280 and positive anti-Sm antibodies with negative anti-DNA. The direct Coombs test was positive. C3 and C4 complement levels were within normal values. There was no hematuria or proteinuria. An infectious disease workup for syphilis, HIV, hepatitis B and C, and tuberculosis was negative. A chest x-ray, abdominopelvic

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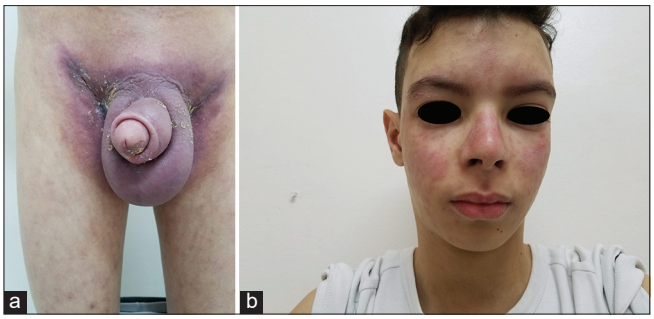

Figure 1: (a) A purplish scrotal erythredema extending to the perineal and inguinal areas associated with a permanent reticular livedo of the lower limbs and (b) an erythematous maculopapular malar rash with a butterfly distribution extending to the forehead and respecting the nasolabial folds.

ultrasound, and transthoracic echocardiography were normal. On histological examination of a perineal fragment, the epidermis was hyperacanthotic, papillomatous, and hyperorthokeratotic without interface involvement. The dermis was edematous with ectatic vessels in the superficial and middle dermis. Perivascular lymphocytic infiltration was minimal. Histology of the inguinal lymph nodes suggested a reactive infiltrate without signs of malignancy.

The mucocutaneous manifestations, the cervical and inguinal lymphadenopathy with fever, the hematological manifestations, and the high titers of ANA and SM antibody associated with a positive direct Coombs test were all consistent with the diagnosis of SLE. The patient received pulsed steroid treatment for three days, followed by oral prednisolone (2 mg/kg/day) and hydroxychloroquine (4 mg/kg/day) with external photoprotection.

The short-term outcome was favorable, characterized by a general clinical improvement and decreased clinical and laboratory signs, including scrotal erythredema. The systemic corticosteroid therapy was gradually reduced after two years, without any new relapse or recurrence of penoscrotal edema. Regular systematization assessments were always negative (Fig. 2).

DISCUSSION

Scrotal edema may affect the dermis and/or subcutaneous tissue as well as the contents of the scrotum [1]. The origin of the scrotal edema may easily be elucidated by well-performed clinical and paraclinical examinations [2]. Its management is most often surgical. However, in some situations, diagnosis is not evident. Chronic penoscrotal edema etiologies

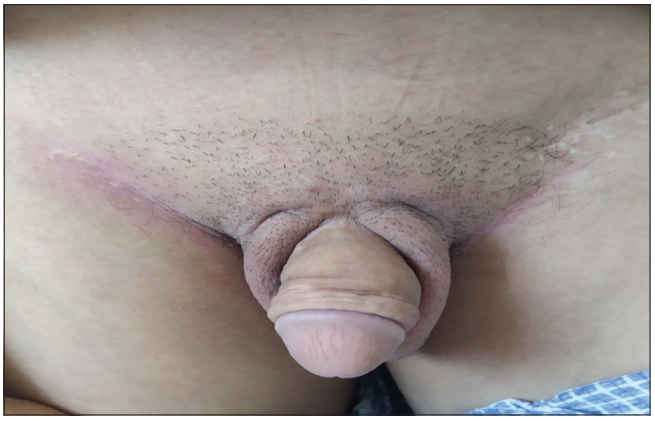

Figure 2: Clinical improvement with the disappearance of the scrotal erythredema.

and chronic permanent scrotal erythredema have insufficiently been reviewed in the literature [3].

A wide range of etiologies are associated with chronic scrotal edema. They may be general (heart failure, kidney disease, and ascites), obstructive (abdominal neoplasms, inguinal hernias, and spermatic vein thrombosis), infectious (filarial elephantiasis), iatrogenic (radiotherapy, lymph node dissection), and traumatic [1,4]. Inflammatory affection may be secondary to these situations and, therefore, be responsible for scrotal erythematous edema [5]. In addition, various inflammatory pathologies may affect skin coating and be responsible for scrotal edema. Among these etiologies, we find fungal skin infections, hidradenitis suppurativa, reverse psoriasis, Behçet's disease, and extramammary Paget disease [5]. In our patient, a clinical examination of the container and scrotal contents, combined with the results of scrotal imaging and histology, allowed us to exclude all the aforementioned etiologies.

Erythematous scrotal edema or scrotal erythredema is an infrequently described entity. Few cases of scrotal erythredema associated with systemic diseases have been reported in the literature, particularly with Crohn's disease [6], Henoch–Schönlein purpura, sarcoidosis [7], rheumatoid arthritis [8], juvenile dermatomyositis [9], testicular vasculitis [10], non-Hodgkin's lymphoma, and Kaposi's sarcoma [8]. However, our patient's clinical status did not meet any of the above-mentioned etiologies. In contrast, apart from scrotal erythredema, all of our patient's clinical, biological, and immunological manifestations met the SLICC criteria for systemic lupus erythematosus (SLE) [11,12].

15% to 20% of patients with SLE develop signs and symptoms during childhood and adolescence [11].

Juvenile systemic lupus erythematosus (JSL) is suggested if SLE develops before the age of eighteen [13]. Mucocutaneous manifestations are the second most frequent affection in SLE-J after hematological affection [14]. Several types of skin lesions are noticed during the course of SLE. Lupus lesions are found, defined by their clinical, histological, and progressive appearance, and non-lupus, vascular or non-vascular manifestations, are mainly present in systemic forms [15,16]. Also, atypical and infrequent skin show have been reported [17,18]. Systemic lupus skin lesions usually occur in light-exposed areas. On the other hand, genital localization is rare and is poorly documented in the literature, hence the interest of our case [19,20].

Inuzuka et al. reported the case of a 71-year-old Japanese female who had infiltrated erythematous patches on the eyelids and subcutaneous nodules on the hands, thigh, and leg. She also suffered from mouth ulcers, arthralgias, and fever. Laboratory tests revealed elevated antinuclear antibodies, an increased rate of erythrocyte sedimentation, and anemia. Skin biopsies from the hand and thigh showed perivascular lymphocytic infiltrates as well as vacuolar changes in the basement membrane of the appendices. In addition, there was a dense lymphocytic infiltrate in the dermis with extension into the subcutaneous fat, which was consistent with the diagnosis of deep lupus erythematosus. Although a biopsy from an eyelid lesion does not contain subcutaneous fat, the changes in the dermis are essentially the same as those in the hand and thigh. The rash and other symptoms disappeared quickly with oral prednisolone [17]. In our patient, except for the genital localization and unspecific histological results, the clinical–biological status was superimposable. Other similar cases have been reported in a systematic review by Mullaaziz et al., with systemic signs such as arthritis and fever and with abnormal biological and immunological assessments, as in our patient [18]. By analogy with this association, "palpebral edema and systemic lupus," we linked our patient's scrotal edema to systemic lupus. This was based on clinical, biological, and especially evolutionary arguments in the face of the disappearance of the scrotal erythredema after treating the lupus with a two-year follow-up.

CONCLUSION

Scrotal erythredema is rarely described. Apart from the usual urological emergencies, systemic diseases may be responsible for this genital manifestation. The knowledge of this origin is important because the treatment is medical and involves long-term care.

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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Our Dermatology Online

Case Report

Hidradenitis suppurativa and bilateral interstitial keratitis: A case report

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ABSTRACT

Hidradenitis Suppurativa (HS) is a chronic inflammatory disease that cause painful abscess and nodules in skin that contain apocrine glands. While HS has known associations with several inflammatory disorders, a rare association is interstitial keratitis. We present a case of bilateral interstitial keratitis attributed to a severe flare of HS disease resulting in systemic inflammation. Other case reports have established that bilateral interstitial keratitis can be attributed to HS, as well as other eye symptoms and diseases. Despite the rarity of keratitis in patients with HS, clinicians should be aware that this association does exist when their HS patient presents with severe or atypical eye symptoms.

Key words: Keratitis; Hidradenitis Suppurativa; Inflammatory Disease; Autoimmunity

INTRODUCTION

Hidradenitis Suppurativa (HS) is a chronic, inflammatory disease resulting in panful abscesses in skin bearing apocrine glands. This disease more often affects women beginning in their second or third decade of life [1, 2]. Interstitial Keratitis (IK) is characterized by nonulcerative and nonsuppurative inflammation of the corneal stroma [3]. While inflammatory disorders such as inflammatory bowel disease, spondyloarthropathy, and other autoimmune disease are commonly associated with HS, IK is described as an association that is uncommon in daily clinical practice [1,4]. Here we describe a patient with a history of Hidradenitis Suppurativa presenting with bilateral interstitial keratitis.

CASE REPORT

A 34-year-old female with a 15-year history of Hurley Stage 3 Hidradenitis suppurativa (HS) with draining sinuses on her left buttock and right axilla (Fig. 1) presented to the clinic with bilateral eye pain, decreased vision, and redness (Fig. 2). Her disease is severe with poor response to typical HS treatments. She began Adalimumab in November 2019 with relief but was discontinued. Nine months later, the patient presented to an acute care center with a white spot on her right eye with erythema, pain and pruritis that progressed over 10 days to include her left eye. She was prescribed prednisolone drops and showed improvement within a day.

Ophthalmology diagnosed her with bilateral peripheral interstitial keratitis and continued prednisolone eye drops with oral steroids and cyclosporine on reserve. They gathered ANA titers, ANCA, RF, CCP, CMP, CBC, CRP/ESR and syphilis titers. She had an ANA titer of 1:160 with a negative reflex, positive c-ANCA, and slightly elevated CRP/ESR. Suspicion for Granulomatosis Polyangiitis was low due to a negative MPO/PR3, low ANA titers without negative reflex, and lack of other autoimmune symptoms. Coogan's Syndrome was considered but ruled out due to no hearing loss. Her keratitis and elevated inflammatory markers were ultimately attributed to severe HS disease resulting in systemic inflammation. They recommended restarting Adalimumab, but she did not due to insurance reasons. Currently, her HS

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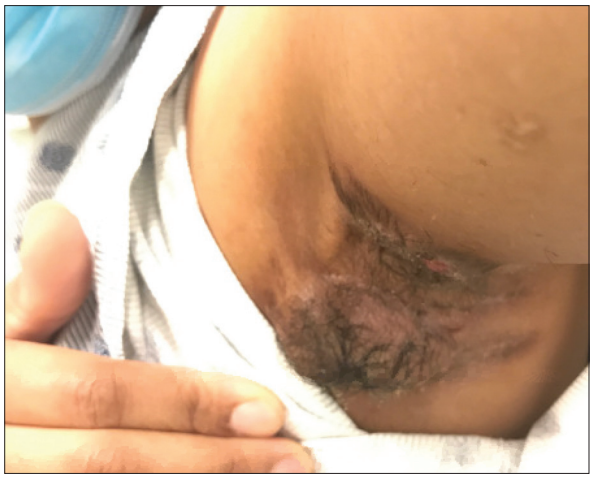

Figure 1: Axillary HS with nodules forming sinus tracts.

Figure 2: Bilateral eye erythema.

disease is stable without recent flares and her keratitis has resolved.

DISCUSSION

Although bilateral interstitial keratitis is a rather rare complication of HS, it may be important to screen these patients for this complication along with other immune dysregulation phenomena such as acne conglobata, spondyloarthropathies, pyoderma gangrenosum, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome, Dowling-Degos disease, fox den disease, florid steatocystoma multiplex, pyoderma vegetans, and pityriasis rubra pilaris.[3] Prevalence and incidence data is limited for the association of HS and keratitis, but there are at least 10 cases in which the two entities were linked to one another [4].

One of these case reports is a similar presentation of another young Black female with severe HS that presented with bilateral interstitial keratitis that initially responded well to topical steroids, as our patient did [5]. One month following discontinuation of topical steroids, she had a flare of her HS disease that coincided with another flare of keratitis. Both conditions responded to Adalimumab and remained in remission for 7 months. Although we cannot associate a response of our patient's keratitis to Adalimumab, we also saw that there was a temporal association with the activity of our patient's HS disease and her keratitis. Her keratitis initially presented when her HS disease was flaring and remained stable when her HS symptoms were minimal.

Another study investigated the associated of HS with any type of inflammatory eye disease (IED). They found 20 patients with concomitant HS and IED, though the association between the two could not be determined as causal [3]. The majority were, similar to our patient, African American and female with 35% of patients without another autoimmune/inflammatory disease to explain the IED. Despite topical steroids being considered first line therapy, most patients with HS required systemic immunosuppression to alleviate symptoms [3].

CONCLUSION

Despite this being a rare phenomenon, it is valuable to be watchful of any HS patients with any eye discomfort, pain, change in vision, or change in appearance of the eyes, and consider urgent referral to ophthalmology. Alongside referral, prompt escalation of therapy to systemic immunosuppressive agents is necessary in over 70% of HS cases complicated by inflammatory eye disease and results in significant improvement [1,3]. Although our patient did not require any systemic therapy, coordination between ophthalmology, rheumatology, and dermatology resulted in the appropriate ruling out of any other autoimmune conditions, and attribution of her keratitis symptoms to her HS disease.

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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Our Dermatology Online

Case Report

Necrobiosis lipoidica in a non-diabetic female with extensive vitiligo: An uncommon association

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ABSTRACT

Necrobiosis lipoidica diabeticorum (NLD) is a chronic non-infectious granulomatous disease characterized by sclerodermiform plaques, papules, or inflammatory nodules. NLD may be associated with diabetes mellitus (DM), sarcoidosis, rheumatoid arthritis, and inflammatory bowel disease. While reports of patients having NLD, DM, and vitiligo at the same time exist, there are, to the best of our knowledge, no reports of the cooccurrence of NLD and vitiligo in the absence of evidence of DM. Herein, we report a 57-year-old, non-diabetic vitiligo patient, who had developed yellowish-brown plaques over bilateral shins with central scarring and atrophy. Histopathology was compatible with NLD. While there is a case report of a patient having psoriasis, NLD, DM, and vitiligo concurrently, this case, having NLD and vitiligo without clinically evident DM, is prominent. Since around 20–40% of cases of vitiligo may have metabolic syndrome, this case draws attention to the possible overlap in pathogeneses and the need for the intensive monitoring of such patients.

Key words: Necrobiosis lipoidica; Vitiligo; Metabolic syndrome; Dermatology

INTRODUCTION

Necrobiosis lipoidica (NL) is a chronic, non-infectious granulomatous disease characterized by sclerodermiform plaques, papules, or inflammatory nodules, which typically affect the shins. Around 12.5–70% of cases of NL have been reported to be associated with diabetes mellitus (DM) [1]. NL is also known to be associated with a myriad of dermatoses, including sarcoidosis, rheumatoid arthritis, autoimmune thyroid disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), and post-jejunal bypass operations [2,3].

Vitiligo is an acquired, idiopathic, depigmenting skin disease characterized by the progressive loss of dihydroxyphenylalanine-positive melanocytes in the basal layer of the epidermis. Recently, vitiligo has been reclassified as a systemic disease rather than a depigmenting disorder [1].

While there exists a report of a patient suffering from NL, DM, and vitiligo at the same time [4], there are, to the best of our knowledge, no reports of the cooccurrence of NL and vitiligo in the absence of evidence of DM. Herein, we report such a case and further discuss the implications and conclusions that we may derive therefrom.

CASE REPORT

A 57-years-old female reported to the dermatology OPD with asymptomatic, gradually enlarging, red, and raised lesions and yellowish areas of discoloration over bilateral lower limbs present for the past six months. The patient had been a known case of hypertension for the past one year, controlled with enalapril 5 mg OD. There was no overt history of DM or thyroid disorders in the patient's or the patient's family.

A general examination revealed vitals in the normal range. The waist circumference was 92 cm (normal: < 88 cm). The patient also had extensive generalized vitiligo.

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A local examination revealed a single reddish-brown, well to ill-defined, annular plaque, around 9 × 3 cm in size, present over the right shin with sharply demarcated, irregular, elevated borders with slight induration. Central scarring and atrophy were noted along with superficial, fine, adherent scales. Telangiectasias were also noted. Patchy areas of yellowish-brown discoloration were present over the bilateral shin, some coalescing over the left shin (Fig. 1). No hair loss over the lesions was noted. Cutaneous sensations were intact.

A dermoscopic examination further revealed telangiectasias, white areas of collagen degeneration, and yellowish-brown patches of inflammation (Fig. 2).

Hemogram was suggestive of iron deficiency anemia. A slightly raised eosinophil count and ESR were noted. Blood sugar, HbA1c levels, and urine routine microscopy were normal. A lipid profile revealed a mild increase in LDL (108.8; normal: < 100). Electrolytes, liver and kidney function tests, serum protein levels, and a thyroid function test were within normal ranges (Table 1).

A histopathological examination revealed mild hyperkeratosis in the epidermis (Figs. 3a and 3b). The upper dermis, lower dermis, and subcutaneous tissue showed perivascular lymphoplasmacytic infiltrate with occasional eosinophils. The infiltrate was more pronounced in the deeper layers. Mild septal panniculitis was present. Upon clinicopathological correlation, a diagnosis of NLD was established.

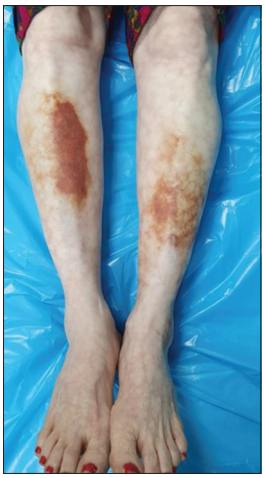

Figure 1: Yellowish-brown, well to ill-defined, annular plaques over the bilateral shin with central scarring and atrophy.

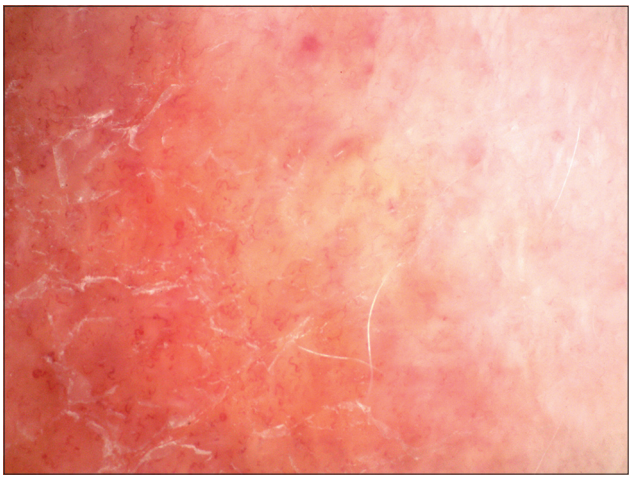

Figure 2: Dermoscopy revealing telangiectasias, white areas of collagen degeneration, and yellowish-brown patches of granulomatous inflammation.

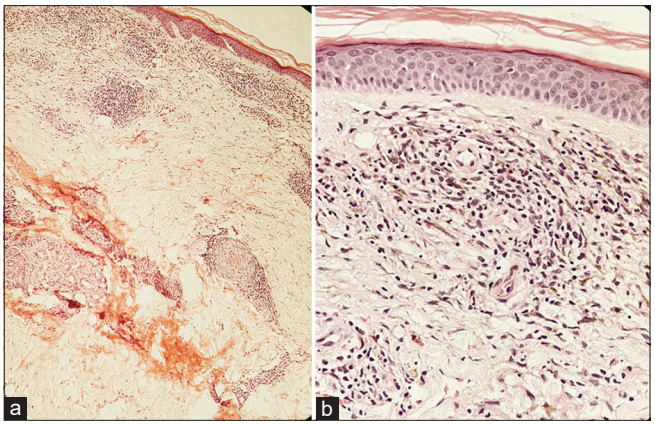

Figure 3: (a and b) Upper dermis, lower dermis, and subcutaneous tissue showing perivascular lymphoplasmacytic infiltrate with occasional eosinophils on histopathology (10× and 40×).

DISCUSSION

NL was first described by Oppenheim [5] in 1929, naming it *dermatitis atrophicans diabetica*, which was later renamed as NLD (necrobiosis lipoidica diabeticorum) by Urbach [6].

The first case of NL in a non-diabetic patient was reported by Goldsmith in 1935 [7].

The average age of onset of NL is thirty years, with a female-to-male ratio of 3:1. It is widely recognized for its association with diabetes mellitus, occurring in around 0.3–1% of cases of the same [8,9]. As high as 65% of NL patients are clinically diabetic while the remaining have a high likelihood of demonstrating abnormal glucose tolerance or a positive family history of DM. DM is usually moderately severe or severe, with 50% of cases reporting diabetic angiopathic stigmata of end-organ damage, such as retinopathy, nephropathy,

Table 1: Lab investigations.

PARAMETER	VALUE
Haemoglobin	9.6 (Normal= 12- 15)
Total Leucocyte Count	10, 600
MCV	78.4 (Normal= 83- 101)
MCH	24.1 (Normal= 27- 32)
MCHC	30.7
RDW	15 (Normal= 11.6-14)
Platelet count	3.56 lakhs
Differential Eosinophil count	8.0 (Normal 0-6)
ESR	25 mm at 1 hour (Normal 0-20)
Fasting blood sugar	84
Post prandial blood sugar	142
HbA1C (Glycated Haemoglobin)	5.3
Urine routine profile	Within normal limits
Cholesterol/ Triglycerides/ HDL/ VLDL	169/ 71/ 46/ 14
LDL	108.8 (Normal <100)
LDL/ HDL Ratio	2.37
Cholesterol/ HDL Ratio	3.67
Free T3, Free T4, TSH (Thyroid Stimulating Hormone)	1.9/126/3.71
Sodium/ Potassium	139/ 4.36
S.Bilirubin/SGOT/SGPT/ALP	0.2/22/36/143
S. protein/ albumin	6.8/ 3.8
S. Urea/ S. Creatinine/ S. Uric acid	20/ 1.03/ 5.0

MCV= Mean Corpuscular Volume, MCH= Mean Corpuscular Haemoglobin, MCHC= Mean Corpuscular Haemoglobin Concentration, RDW= Red cell distribution width, ESR=Erythrocyte Sedimentation rate, HDL= High density lipoprotein, LDL= Low density Lipoprotein, VLDL= Very Low density Lipoprotein, SGOT= Serum glutamic oxaloacetic transaminase, SGPT= Serum glutamic pyruvic transaminase, ALP= Alkaline Phosphatase

and neuropathy. These complications, along with the relatively earlier age of onset of NL in diabetics than their non-diabetic counterparts, highlight the accelerated diabetogenic forces operative in patients with NL [9].

Though NL presents a strong association with DM, it is not directly related to hyperglycemia, glucosuria, or control of DM (including HbA1c levels), but its onset prior to the occurrence of detectable carbohydrate abnormalities makes it an important clinical marker of prediabetes [9,10].

Among several dermatological associations of DM, vitiligo is reported to account for around 5.7–10% of cases [11,12].

Vitiligo has a three-pronged pathomechanism that eventually triggers insulin resistance [1]:

1. The presence of pro-inflammatory cytokines (IL-1, IL-6, TNFα);
2. Autoimmune dysfunction and lipid peroxidation, leading to the deterioration of reactive oxygen species, which reduces melanocytes in adipose tissue;
3. Elevated homocysteine levels.

Further, vitiligo patients have been reported to have a deranged lipid profile (increased LDL and decreased HDL). The above features highlight the higher risk of metabolic syndrome that these patients might face [1].

Metabolic syndrome is a composite of risk factors: abdominal obesity, dyslipidemia, glucose intolerance, and hypertension. Around 25% of the world's population is affected by metabolic syndrome, with a significant subpopulation linked to inflammatory skin diseases, such as vitiligo, scleredema, Behçet's disease, rosacea, NL, granuloma annulare, skin tags, knuckle pads, and eruptive xanthomas [1,13].

Abraham et al. previously reported a case of a diabetic patient having psoriasis, NL, GA, vitiligo, and skin infections (recurrent erysipelas and mycotic infections) [4]. Our case, having NLD and vitiligo without clinically evident DM, is prominent, being different from those previously reported in the literature.

It is, hereby, being highlighted that NL and vitiligo have certain similar underlying pathomechanisms and there is a possibility of an overlap wherein both diseases might present with the partial manifestation of DM or metabolic syndrome, that is, when the patient meets only some of the diagnostic criteria, yet not enough to be labeled as the above case. While our patient had no overt DM, she did have some features that could have predisposed her to frank metabolic syndrome in the future, that is, hypertension, an increased waist circumference, and raised LDL. Since vitiligo also has an association with DM, this patient should be under observation for the future development of DM. Hence, the presence of NL in vitiligo should make the dermatologist more watchful.

CONCLUSION

It is recommended that all cases of NL without DM should be evaluated for possible underlying causes, including metabolic syndrome, which should be excluded. These patients should also be regularly followed up for yearly diabetes screening. Patients with vitiligo having risk factors for metabolic syndrome, such as an increased waist circumference, should also undergo evaluation for the same. At this stage, where the disease is still in evolution, counseling regarding behavioral and lifestyle changes is imperative. Intervention at this stage could substantially decrease the risk of developing undetected, uncontrolled DM later in life, complications of end-organ damage of

DM, and complications of metabolic syndrome, such as hypertension and coronary artery disease.

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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Our Dermatology Online

Case Report

Endometrial cancer in neurofibromatosis type I (von Recklinghausen's disease): A case report and literature review

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ABSTRACT

Neurofibromatosis type I is a complex, multisystem cancer predisposition syndrome of a number of tumors, which commonly arise in the central and peripheral nervous system, the gastrointestinal tract (GIT), and breast and soft tissues, yet the association with endometrial cancer is rare. Herein, we report the case of a 67-year-old female, never married, who had been followed since puberty for neurofibromatosis type I clinically manifested by pigmentary abnormalities such as café-au-lait macules, neurofibromas, and Lisch nodules with various comorbidities, such as diabetes type I, hypertension, renal failure, and ophthalmic disorders (poor vision). One year earlier, she developed a locally advanced endometrial cancer, for which chemotherapy would not have been optimal because of these comorbidities; due to the pathology of neurofibromatosis, the lifespan of such individuals is typically around fifteen years shorter than that of the general population and it negatively impacts their quality of life.

Key words: Neurofibromatosis type I; Cutaneous neurofibroma; Endometrial cancer

INTRODUCTION

Neurofibromatosis type I (NF-1), also known as von Recklinghausen's disease, is a complex, multisystem cancer predisposition syndrome, with a birth incidence falling between 1 in 2500 and 1 in 3000 individuals worldwide [1]. The syndrome is caused by autosomal dominant inheritance or the loss of function by *de novo* mutations in the NF-1 tumor suppressor gene located on chromosome 17 (17q11.2) [2]. The diagnosis of NF-1 is based on clinical manifestations, including pigmentary abnormalities, peripheral and central nervous tumors, bone abnormalities, vasculopathy, and other cancers [3]. The lifespan of individuals with NF-1 is typically around fifteen years shorter than that of the general population [4]. In large part, this shortened lifespan reflects the fact that patients with NF-1 are at an increased risk of developing several types of benign and malignant neoplasms. Although a number of these tumors arise in the central nervous system and the peripheral nervous system (PNS), several types of NF-1-associated neoplasms occur elsewhere, including the skin, the gastrointestinal tract, bone marrow, the breasts, and soft tissues [5]. Gynecological cancers, such as endometrial adenocarcinoma, are not commonly encountered in NF-1.

CASE REPORT

Herein, we report the case of a 67-year-old female, never married, who had, since puberty, presented a neurofibromatosis (NF1) manifested by pigmentary abnormalities such as café-au-lait macules and various sizes of cutaneous neurofibromas (Figs. 1a and 1b). The patient had been treated for diabetes and hypertension for more than fifteen years. There was no family history of the same clinical case.

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She had been followed at the oncology department since July 2020 for well-differentiated, infiltrating endometrioid adenocarcinoma diagnosed at the gynecology department because of heavy postmenopausal bleeding.

A thoracic and abdominopelvic CT (TAP-CT) scan performed on August 18, 2020, revealed a well-limited, hypodense tumor of the uterine cavity, measuring 88 × 108 × 123 mm (AP × T × CC) in size, enhanced heterogeneously after the injection of a contrast product, locally infiltrating the posterior face of the bladder, coming into contact with the lower rectum and the recto-sigmoid hinge with the loss of the fatty separation border in places behind, and arriving in contact with the slender handles with the loss of the fatty separation border above and internal bilateral and external right iliac lymphadenopathy. The tumor has been classified as cT4N2M1, stage IVA (Figs. 2 and 3).

She received chemotherapy treatment based on the combination of paclitaxel 175 mg/m^2 and carboplatin AUC5 (day 1 = day 21). An evaluation after three cycles of chemotherapy found a progression in the size of the tumor. She benefited from a second line of chemotherapy based on doxorubicin 60 mg/m^2 and carboplatin AUC4. She was unfit on cisplatin due to a renal insufficiency, with clearance on creatinine at 47.6 ml/min and received a partial radiological response during an evaluation after four cycles of chemotherapy.

DISCUSSION

The diagnosis of neurofibromatosis type I is commonly based on clinical assessment according to the diagnostic criteria formulated by the National Institutes of Health Consensus Development Conference [6], underlining skin manifestations and the bone and nervous system. (Table1). Occasionally, other signs of NF-1 may not develop until the late teens or early twenties, and slit-lamp examination against Lisch nodules may be helpful in these patients. NF-1 mutational analysis clarifies the diagnosis in some uncertain cases. However, genetic testing is not advocated routinely and expert consultation is advised before it is undertaken. Furthermore, a biopsy of asymptomatic cutaneous neurofibromas should not be undertaken for diagnostic purposes in individuals with clear-cut NF-1 [7]. Cutaneous neurofibromas (cNFs) are among the most common manifestations of NF-1, affecting around 99% of patients with NF-1 [7]. They are unlikely to undergo

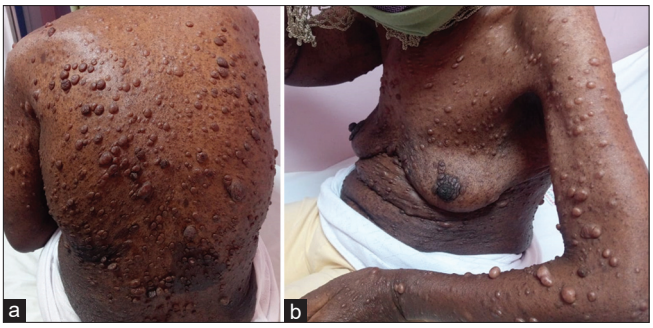

Figure 1: (a and b) Clinical manifestations by pigmentary abnormalities such as café-au-lait macules and various sizes of cutaneous neurofibromas in an adult with von Recklinghausen's disease.

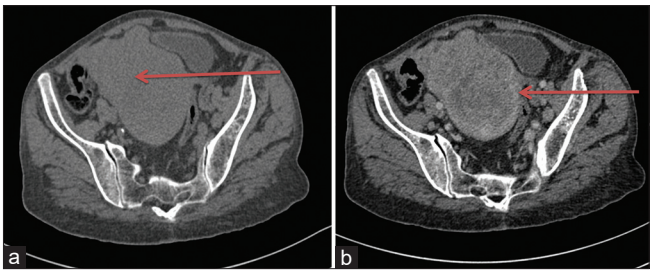

Figure 2: (a and b) Axial CT scan section showing a tumor of the uterine body, well-limited, spontaneously isodense, and enhancing heterogeneously after the injection of a contrast product.

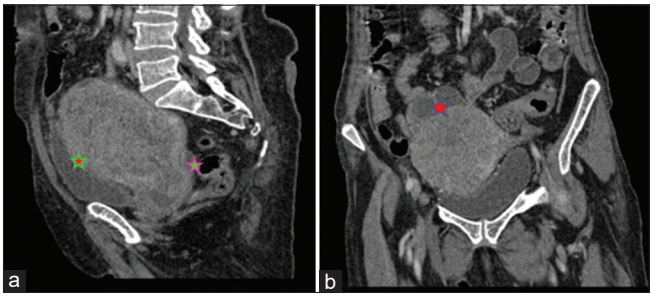

Figure 3: (a and b) Sagittal and coronal CT scan sections showing that the tumor came into contact with the bladder in the front and the lower rectum behind (a), and into contact with the slender handles above (b).

malignant transformation or to cause severe neurologic disabilities or fatal complications. Nevertheless, cNFs are considered one of the greatest concerns in patients with NF-1, especially adults. These concerns are mainly due to disfigurement and dysesthesia, causing substantial psychological distress and negative body image perception [8]. In our case, the patient was 67-year-old, never married, did not continue her studies as her generation, which negatively impacted her quality of life (Table 1).

The treatment of cNFs involves monitoring or procedure-based therapy. Although surgical resection allows the complete removal of the lesion, there are obstacles, including a limited number of lesions

Table 1: Diagnostic criteria for neurofibromatosis type I (NF-1).

National Institutes of Health Consensus Development Conference (1988)[6]
• Six or more café-au-lait macules (> 0.5 cm in children and > 1.5 cm in adults),
• Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma,
• Axillary or groin freckling,
• Optic pathway glioma,
• Two or more Lisch nodules (iris hamartomas seen on slit-lamp examination),
• Bony dysplasia (sphenoid wing dysplasia, bowing of the long bone±pseudarthrosis),
• First-degree relative with NF1.

that may be treated in one session and possible scars. Other alternatives include electrodessication, which removes cNFs through dehydration and denaturation [9]. This allows for the removal of large numbers of cNFs in a single session, yet requires general anesthesia and may cause scarring and pigmentation changes. Other procedure-based therapies for cNFs are laser photocoagulation [10] and radiofrequency ablation [11]. Another approach uses a local drug in photodynamic therapy, which is being tested for different cancers [12]. The use of ketotifen is one of the first managed efforts for the treatment of cNFs and their associated symptoms [13]. Ketotifen is used to block the histamine 1 receptor, which helps to stabilize mast cells; its use in NF-1 is based mostly on the finding of abundant mast cells in neurofibromas. A significant improvement in pain and pruritus has been reported, but an objective tumor reduction has not been documented [14]. As for the local therapeutic approaches, some drugs have been tested for cNFs with promising results, such as ranibizumab, which is a vascular endothelial growth factor monoclonal antibody injected intralesionally, imiquimod, which shows minimal efficacy in tumor shrinkage compared to the baseline volume, and topical rapamycin, an mTOR inhibitor [14]. The safety profile of these tested drugs remains a major concern for physicians, regulators, patients, and their caregivers. Because of our patient's poor financial situation, she had no chance to benefit from these emergent treatments for her cutaneous neurofibromas, which had impacted the quality of her life.

The NF-1 gene encodes neurofibromin, which has been shown to control cell growth through two major intracellular pathways. First, neurofibromin regulates negatively RAS pathway signaling through its action on GTPase-activating protein (GAP), stimulating the conversion of GTP-bound RAS to its GDP-bound form [15]. Increased RAS activity leads to the downstream activity of the MEK/ERK pathway as well as the PI3K/AKT/mTOR pathway [16]. This genetic deregulation in females with neurofibromatosis type I may explain the exceptionally high risk of developing endometrial cancer, in which the PI3K/AKT/mTOR pathway is the most frequently deregulated pathway via mutations in PTEN and/or PIK3CA [17].

NF-1 associated with an endometrial cancer is poorly documented in the literature. Optimal oncological management by chemotherapy is often compromised following the coexistence of various comorbidities in NF-1, as in our case, which was diabetic and hypertensive, had a renal insufficiency, and had repetitive episodes of neutropenia and anemia that required multiple blood transfusions.

CONCLUSION

In conclusion, neurofibromatosis type I is inherited in an autosomal dominant manner. Around half of individuals with NF-1 have been found to have an affected parent, and more than 50% have an altered gene as a result of *de novo* mutation. With NF-1 is suspected in a child, its parents should have medical histories, physical examinations, and ophthalmological slit-lamp examinations performed with particular attention to the features of NF-1. In females older than 60 years, the annual performance of endovaginal ultrasound would allow the diagnosis and early management of an associated endometrial cancer. A diagnosis of NF-1 in a family member may permit an unequivocal diagnosis of NF-1 in a child; it is essential and highly important for genetic counseling and in medical implications for the affected parent.

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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Our Dermatology Online

Case Report

Intracerebral hemorrhage as a rare manifestation in a patient with neurofibromatosis-1 and quasi-Moyamoya disease

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ABSTRACT

Neurofibromatosis-1 (NF-1) is an autosomal dominant neurocutaneous syndrome with incomplete penetrance and variable phenotypic expressivity. Although it may affect any system of the body, the disease remains generally innocuous. NF-1 has been commonly linked to neurological symptoms, including headaches, seizures, cognitive deficits, and learning disabilities, and others. While optic glioma is the most common CNS complication, vasculopathy and cerebrovascular anomalies have also been rarely reported. Specifically, intracerebral hemorrhage with vascular stenosis in NF-1 is an extremely rare manifestation. Herein, we report a patient with NF-1 presenting with stroke secondary to intracranial hemorrhage and underlying quasi-Moyamoya disease. Since the cutaneous features of NF-1 appear early in life and are striking, dermatologists might be the first contact for such patients with the medical system, and consequently play an important role in the diagnosis, evaluation, and prevention of complications.

Key words: Neurofibromatosis-1; Genodermatoses; Stroke; Cerebrovascular anomalies; Moyamoya disease

INTRODUCTION

Neurofibromatosis-1 (NF-1) is a neurocutaneous syndrome affecting multiple systems, especially the skin, the eye, and the musculoskeletal, cardiovascular, and nervous systems. It is inherited in an autosomal dominant manner and the responsible gene is located on chromosome 17. As the skin lesions appear early and are conspicuous, patients usually present to the dermatologist. Diagnosis is based on the National Institute of Health (NIH) Consensus Development Conference diagnostic criteria [1]. A thorough workup for possible systemic involvement is imperative. Among the systemic features of involvement, cerebrovascular anomalies, including vascular stenoses and aneurysms, are rare yet recognized entities [2]. However, intracerebral hemorrhage with vascular stenosis in NF-1 is extremely unusual and of uncertain etiopathogenesis with only several cases published in the literature [3,4]. An interesting case of initially undiagnosed NF-1 presenting as an acute neurological emergency is being reported and its possible causes discussed.

CASE REPORT

A 44-year-old male presented to casualty with sudden weakness in the right upper and lower limbs persistent for one day, slurring of speech for four to six hours, and transient lateral deviation of the right side of the mouth. There was no history of trauma, loss of consciousness, an altered sensorium, headaches, seizures, blurring of vision, shortness of breath, palpitations, loss of bladder and bowel control, or any sensory deficit except a mild tingling sensation in the right foot. There was no history of a similar episode of sudden-onset weakness in the

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past. There was no history of hypertension, diabetes, or a chronic illness, including tuberculosis.

On admission, a general physical examination was normal. A neurological examination revealed a power grade of 4/5 in the flexor and extensor muscles of the right upper and lower limbs tested at the elbow, wrist, hip, knee, and ankle. Owing to a number of the cutaneous manifestations, a dermatology referral was sought, which revealed multiple (70–80 in number) soft papules and nodules present over the neck, trunk, and upper and lower limbs. They were well-defined, non-tender, and mobile and some showed buttonholing (Figs. 1a and 1b). Multiple (8–10) café-au-lait macules (CALMs), ranging from 1 × 0.5 cm to 3 × 2.5 cm in size, were scattered over the trunk and upper limbs. Several brownish-black freckles, 1–2 mm in size, were present over the trunk and the axillary (Fig. 2a) and inguinal regions. On ophthalmic evaluation, the patient had several Lisch nodules in the iris of both eyes (Fig. 2b).

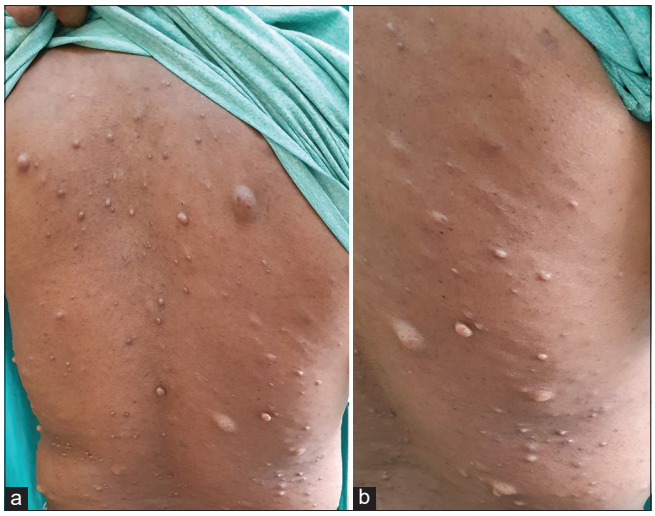

Figure 1: (a-b) Multiple soft, skin-colored papules and nodules on the trunk.

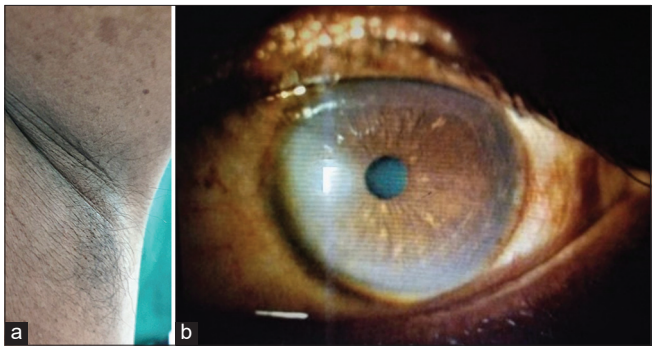

Figure 2: (a) Axillary freckling and b) classical Lisch nodules in the iris of the right eye.

A routine hemogram and biochemical investigations, including blood sugar, a lipid profile, and liver, renal, and thyroid function tests, were normal. A skin biopsy from the nodule on the trunk was compatible with neurofibromatosis. Chest radiograph and ultrasound of the abdomen were unremarkable. NCCY (non-contrast CT) of the head revealed a hyperdense parenchymal lesion in the left basal ganglia, thalamus, and internal capsule, suggestive of hemorrhage with perilesional edema (Fig. 3a). MRI of the brain confirmed the above finding (Fig. 3b). 3D TOF (time of flight) MR angiography revealed stenosis of the cavernous segment of the left internal carotid artery (ICA) with non-visualization of the left middle and anterior cerebral artery with the presence of multiple collateral channels (Fig. 3c).

Based on history taking, the clinical examination, and investigations, a diagnosis of NF-1 with right hemiparesis secondary to intracerebral hemorrhage and underlying quasi-Moyamoya disease was reached. The patient was given injections of dexamethasone and mannitol for five days and was subsequently started on citicoline (a neuroprotective agent). His speech showed signs of improvement by the fourth day and muscle power slowly returned to normal after three months.

DISCUSSION

NF-1 is an autosomal dominant disease with an incidence of 1 in 2500–3300 [5]. Its cutaneous features include CALMs, intertriginous freckling, and discrete cutaneous and subcutaneous neurofibromas, all of which were present in our patient and which are usually sufficient to make the diagnosis based on the NIH criteria [1]. Neurological and cardiovascular involvement may be disabling and sometimes fatal. The most frequent NF-1 complication of the central nervous system is optic glioma, occurring in 5–15% of individuals and is often the first the physician considers in a patient with neurological symptoms [5]. However, a constellation of cerebrovascular lesions has also been reported, including narrowed or ectatic vessels, vascular stenoses, aneurysm, pseudoaneurysm, fistula, and Moyamoya disease [2]. In a study on 353 children with NF-1, cerebrovascular abnormalities were found in 2.5% of the cases [6].

It has been proposed that NF-1-related vasculopathy is secondary to abnormal neurofibromin function and may affect anterior cerebral, and less commonly

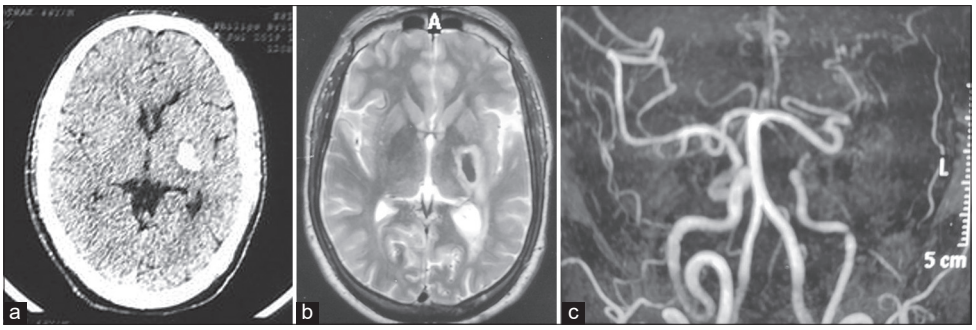

Figure 3: a) Axial non-contrast CT image showing a hyperdense hematoma with surrounding hypodense perilesional edema in the left basal ganglia region extending into the internal capsule and thalamus. b) Axial T2 W MR image showing a hypointense hematoma with surrounding hyperintense edema in the left basal ganglia region extending into the internal capsule and thalamus. c) Coronal MR angiography image showing stenosis of the cavernous segment of the left internal carotid artery with non-visualization of the left middle and anterior cerebral artery with the presence of multiple collateral channels.

the posterior cerebral, circulation [2]. The common clinical manifestations include headaches, seizures, and acute neurological deficits secondary to ischemia, due to thrombus or embolization, or intracranial hemorrhage [7]. Moyamoya disease, or more appropriately quasi-Moyamoya disease, with the occlusion of ICA or its branches and numerous resultant collateral channels has also been described [3].

A large case-control study analyzing data from patients with NF-1 between 1998 to 2009 revealed that odds of stroke are significantly increased in patients with NF-1 and may present at a younger age. Adult patients with NF-1 and stroke had a lower prevalence of stroke risk factors, including diabetes, atherosclerosis, and atrial fibrillation [8].

Occlusive cerebrovascular disease presenting with intracranial hemorrhage is a highly rare entity in NF-1, with only several cases reported. A case of a 49-year-old female with NF-1 presenting with intracerebral hemorrhage along with severe ICA stenosis with a fine telangiectatic network of collaterals was reported [4]. Another reported case was of a 39-year-old female with NF-1 presenting with intracerebral hemorrhage secondary to ICA occlusion and numerous collateral channels seen as flow voids on MRI, suggestive of quasi-Moyamoya disease [3]. In the present case, the patient presented *de novo* with sudden-onset neurological symptoms suggestive of a stroke before he was diagnosed with NF-1. The diagnosis of NF-1 was established only after a cutaneous examination done by the dermatologist. Imaging studies revealing the presence of a ganglio-thalamic bleed with left ICA stenosis and multiple collateral channels pointing toward the rare quasi-Moyamoya disease as the underlying etiology. Had a timely diagnosis of NF-1 and the associated quasi-Moyamoya been made before our patient landed with this complication, interventions, including revascularization surgery, which has been proven to be effective in hemorrhagic MMD, could have been instituted [9].

CONCLUSION

Although rare, physicians should be aware of the increased risk of stroke in NF-1 and evaluate it for the potential causes mentioned above. Screening patients with NF-1 who usually present first to the dermatologist with MRI and MRA to exclude uncommon yet potentially fatal cerebrovascular lesions could facilitate the institution of timely interventions and improve the overall outcome.

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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Our Dermatology Online

Case Report

Autoeczematization Id reaction following candidal diaper dermatitis

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ABSTRACT

Id reactions are secondary inflammatory reactions that develop from a remote, localized immunological insult. They may be caused by various fungal, bacterial, viral, and parasitic infections. Diaper dermatitis with psoriasiform Id eruptions is a rarely reported phenomenon. Herein, we report the case of an infant who developed candidal diaper dermatitis followed by generalized psoriasiform Id eruptions. Most authors report the resolution of diaper area lesions with topical antifungals with or without steroids and Id eruptions with topical steroids alone. Our patient showed complete resolution of all lesions with oral fluconazole alone.

Key words: Id reaction; Candidal rash; Diaper dermatitis; Psoriasiform ID; Fluconazole

INTRODUCTION

Id reactions exhibit multiple clinical presentations, including localized or widespread vesicular lesions, maculopapular or scarlatiniform eruptions, erythema nodosum, erythema multiforme, erythema annulare centrifugum, Sweet's syndrome, guttate psoriasis, and autoimmune bullous disease. The mechanisms underlying **Id** reactions vary depending on the type of clinical presentation. Fergusson et al. studied 52 cases of diaper dermatitis with psoriasiform **Id** eruptions and found *Candida albicans* to be a causative agent [1]. Other causes include infantile seborrheic eczema, psoriasis, atopic dermatitis, and ammoniacal diaper dermatitis [2]. The patient initially presents with intensely erythematous, papulo-squamous eruption with satellite lesions and pustules. A secondary generalized psoriasiform eruption occurs days to weeks later.

CASE REPORT

A six-month-old infant presented with a one-week history of multiple reddish, scaly skin lesions in the trunk area. An inspection of the diaper area revealed multiple reddish, moist, elevated skin lesions. No history of atopy or psoriasis was present in the family members. An examination revealed a well-defined area of intense erythema and papules with some satellite papules around the larger lesion in the diaper area also involving the groin folds (Fig. 1a). Similar lesions were also present in the neck fold area. Multiple well-defined erythematous plaques with loosely adherent white scales were seen in the trunk area (Figs. 1b and 1c). A potassium hydroxide (KOH) examination of the diaper and neck fold area revealed budding yeast cells suggestive of *Candida albicans*, whereas the trunk lesions showed no fungal elements (Fig. 2).

Routine blood investigations were done and returned normal. The patient was treated with oral fluconazole at a dose of 6 mg/kg of body weight for ten days. The lesions in the diaper area, neck folds, and trunk resolved completely with post-inflammatory hypopigmentation in ten days with no subsequent reoccurrence (Figs. 3a and 3b).

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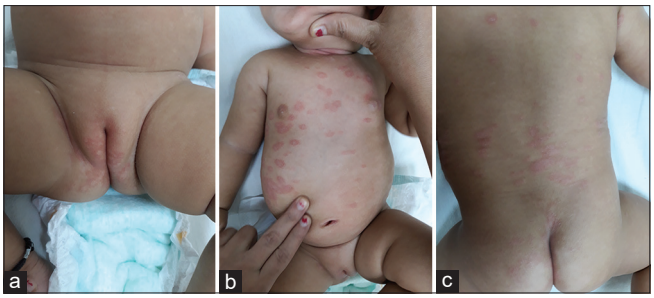

Figure 1: (a-c) Multiple well-defined, erythematous plaques with loosely adherent white scales present in the anterior and posterior trunk. Involvement of the neck fold and diaper area with erythema.

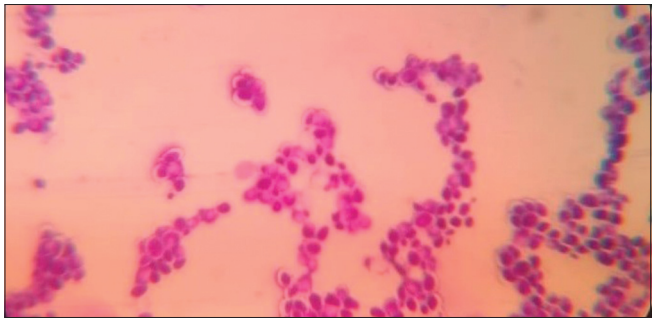

Figure 2: Potassium hydroxide (KOH) examination of the diaper and neck fold areas revealing budding yeast cells suggestive of *Candida albicans*.

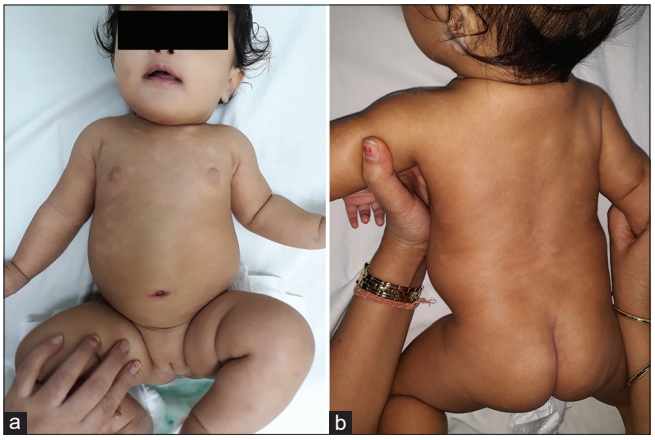

Figure 3: (a and b) Post-treatment pictures of the complete resolution of the psoriasiform lesions leaving post-inflammatory hypopigmentation

DISCUSSION

Diaper dermatitis is a common condition, especially among newborns and infants. It is an irritating and inflammatory acute dermatitis of the perineal and perianal areas resulting from occlusion and irritation caused by diapers. Diapers create particular conditions of moisture and friction, and with urine and feces come increased pH and irritating enzymes (lipases and proteases) [3]. Fungi may take advantage of all these factors to cause infection. *Candida* yeasts, especially *Candida albicans*, are responsible for the most frequent secondary infections.

Early irritant dermatitis is characterized by erythema, mild maceration, and edema, while *Candida* diaper dermatitis (CDD) is characterized by erythematous and scaly plaques with maceration and edema, sometimes with satellite pustules or papules, the latter being the most characteristic feature of *Candida* infection [4]. Erosion and ulceration may occur in severe cases.

Id reaction is also known as an *auto eczematous response*, as there must be an identifiable initial inflammatory or infectious skin problem that leads to generalized eczema. Josef Jadassohn, a German dermatologist who coined the term **Id**, observed a dermatophytosis infection causing secondary allergic skin dermatitis [5]. Alex et al. observed infants who developed erythema multiforme and psoriasiform-type **Id** reactions due to a *Candida spp.* infection in the diaper area [6]. Fergusson et al. studied 52 cases of diaper dermatitis and napkin dermatitis that later evolved into disseminated psoriasiform **Id** eruptions [1]. One of the definite causes was attributed to *Candida albicans* in these cases. Other causes included infantile seborrheic eczema, psoriasis, atopic dermatitis, and ammoniacal diaper dermatitis.

Rattet et al. studied two cases of diaper dermatitis with the subsequent presence of generalized, papulosquamous, scaly lesions. Biopsies from these lesions showed psoriasis-like histological features [2]. Another such case was studied by Balasubramanian et al., in which a post-ureterostomy infant on prolonged antibiotic therapy developed candidal diaper dermatitis followed by generalized psoriasiform **Id** eruptions [7].

Due to paucity of literature on the topic, we report a case of an infant who presented with generalized skin lesions resembling psoriasis clinically, with the simultaneous presentation of candidal diaper dermatitis. Most authors report the resolution of diaper area lesions with topical antifungals with or without steroids and **Id** eruptions with topical steroids alone [8]. Our patient showed complete resolution of all lesions with oral fluconazole alone.

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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Our Dermatology Online

Case Report

Idiopathic unilateral facial hirsutism

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ABSTRACT

Hirsutism is the growth of terminal hair in a female in a male-like distribution. Idiopathic hirsutism (IH) is when there is no increase in circulating androgens or ovarian hormones. IH usually involves multiple sites with variable densities. Localized and unilateral dermatomal hirsutism has been rarely described. We report a forty-year-old female with a history of terminal hair growth on the left side of the chin. There was no associated biochemical or ultrasonic evidence of hyperandrogenism suggesting it to be idiopathic.

Key words: Idiopathic Hirsutism; Unilateral; Localized

INTRODUCTION

Hypertrichosis is a term that refers to excessive hair growth on any part of the body or the entire body as compared to individuals of the same age, sex, and race [1]. The term *hirsutism* is applied to the androgen-induced growth of terminal hair in women and children in a male-like distribution [2]. Polycystic ovary syndrome (PCOS), androgen-secreting tumors, non-classic adrenal hyperplasia (NCAH), or syndromes of severe insulin resistance are the known causes of hirsutism. Idiopathic hirsutism is an unknown cause of terminal hair in an androgenic distribution. Hair growth secondary to any systemic cause such as other normal cutaneous processes shows bilateral symmetry. Terminal facial hair growth in a unilateral distribution is unusual. Herein, we report the case of a forty-year-old female with a history of unilateral facial hirsutism persistent for the last five to six years.

CASE REPORT

A forty-year-old female presented with a history of facial hair growth localized on the left side of the face persistent for the last five to six years. She denied any history of topical application, irritants, any medicine taken in the last three months, trauma, or surgery on the site affected. She had normal menstrual cycles and had no family history of hirsutism. She had three children, with the youngest fourteen years old. On physical examination, she had dense terminal hair growth on the left side of the chin that extended exactly to the midline of the chin without any hair growth on the other side of the chin (Figs. 1 and 2). The skin on both sides of the face was of normal texture and pigmentation. The vellus hair growth in the rest of the face was normal for her age. There was no other evidence of virilism. Routine laboratory investigations (complete hemogram, liver and renal function tests, serum electrolytes, a lipid profile, thyroid function tests, fasting blood sugar) were done and found to be within normal limits. In addition, serum follicular stimulating hormone, luteinizing hormone (and their ratio), serum testosterone levels, serum prolactin, and serum dehydroepiandrosterone and 17-hydroxyprogesterone were also within normal limits. Insulin resistance was calculated with the homeostasis model assessment of insulin resistance (HOMA-IR) and was found to be normal. Ultrasound for the pelvic organs and adrenals was normal. The patient was hence diagnosed to have idiopathic hirsutism in a unilateral distribution.

DISCUSSION

Terminal hair growth is associated with androgenetic hormonal influences, both internal and external

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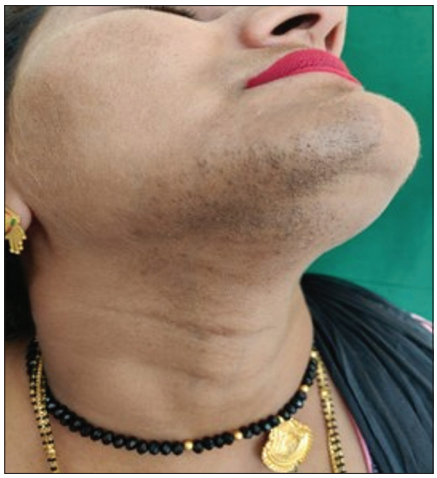

Figure 1: Terminal hair on the chin, mandible, and neck on the right side.

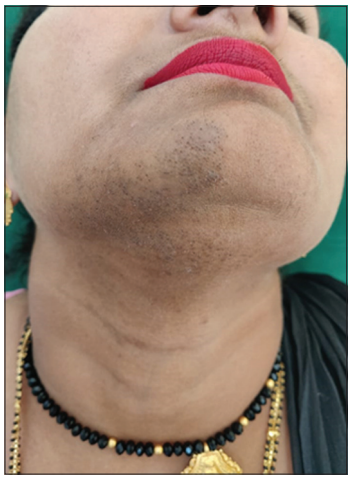

Figure 2: Sharp demarcation of terminal hair growth on the midline.

to the follicle, external stimuli, and congenital anomalies [3]. Idiopathic hirsutism (IH) is also known as simple or peripheral hirsutism. IH is the diagnostic label given to those hirsute females in whom no overt underlying endocrine disorder (ovarian function and circulating androgens) could be detected [2]. Less than 20% of females with hirsutism are diagnosed as idiopathic [4]. A history of regular menstrual cycles does not rule out ovulatory dysfunction and polycystic ovarian syndrome. The primary pathology in IH is unknown but, as the name suggests, the alteration is somewhere in the periphery or in the target area. There may be an increase in skin 5-alpha-reductase levels. The level of DHT may be normal despite an increase in 5-alpha-reductase activity due to its quick metabolism in the skin, hence leading to local action only. Treatment with 5-alpha-reductase inhibitors is helpful while reducing androgen secretion with the help of oral contraceptive pills (OCPs) is of limited value in IH. Other proposed pathogenetic mechanisms of IH are androgen receptor gene polymorphism and increased sensitivity of hair follicles to androgens. Various growth factors, for instance, transforming growth factor-β and epidermal growth factor, and cytokines have been observed to affect hair growth [5]. It has been suggested that these factors operate by increasing the synthesis of stromelysin, a matrix metalloproteinase that acts on the dermal papilla to accelerate growth.

A dermatomal pattern of hair growth is unusual, as seen in our case. No congenital abnormality or history of external stimuli to the area were noted. She may have had relative hyperresponsiveness to circulating androgens on the terminal hairside or hyporesponsiveness on the vellus hairside.

Ellis reported a female with unilateral hirsutism involving the entire right side of the body and associated with polydactyly, premature fusion of the epiphyses of the right leg, and myasthenia gravis [6]. Androgen metabolic activity in the skin on both sides in this case was in the low normal range, while plasma testosterone values were in the normal female range. In 1886, Humphry reported a twelve-year-old girl with unilateral facial hirsutism associated with ipsilateral gingival hyperplasia [7].

Local determinants of hair growth play an important role in IH. In our case, the response to the same systemic hormonal stimuli to the individual follicles on one side of the face was different than on the other side.

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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Our Dermatology Online

Case Report

Becker's nevus syndrome: A new case series

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ABSTRACT

Becker's nevus syndrome (BNS) is a rare epidermal nevus syndrome characterized by Becker's nevi and other, often unobtrusive, systemic symptoms and/or skin lesions, often ipsilateral. A Becker's nevus (BN) is a hamartoma that is unilateral, hyperpigmented, and often hairy. Systemic symptoms typically involve breast gland hypoplasia and skeletal and muscular disorders. Herein, we describe three rare cases of Becker's nevus syndrome. In the first case, the BN coexisted with ipsilateral breast gland hypoplasia; in the second case, the BN coexisted on both sides with breast gland hypoplasia and keratosis pilaris only in the left antecubital region and with scoliosis; in the third case, we found two Becker's nevi in the left and right hip area associated with hypoplasia of the third canine tooth on the right side and with scoliosis. Our three cases were sporadic and all occurred in males. Coexisting symptoms of BN were found accidentally. We describe two new coexisting symptoms: atypical keratosis pilaris and hypoplasia of the canine teeth.

Key words: Becker's nevus; Becker's nevus syndrome; Ipsilateral Breast Hypoplasia; Hamartoma; Epidermal Nevus

INTRODUCTION

Becker's nevus syndrome (BNS) is a rare epidermal nevus syndrome characterized by the presence of Becker's nevi (BN) and other systemic and/or skin symptoms [1].

A Becker's nevus (BN) is an epidermal cutaneous hamartoma characterized by hypertrichosis and hyperpigmentation. The nevus usually consists of a circumscribed, unilateral, irregularly shaped, hyperpigmented macule, commonly occurring around the anterior upper trunk, with or without hypertrichosis and/or acneiform lesions.

The association of a Becker's nevus with developmental abnormalities such as breast gland hypoplasia, musculoskeletal defects, scoliosis, vertebral defects, pectus excavatum, hypoplasia of the sternocleidomastoid muscle, bilateral ureteral stenosis, soft tissue hypertrophy, fused carpal bones, pigmented epithelioid melanocytoma, café-au-lait spots has been described [2]. However, Danarti et al. described more unknown symptoms belonging to the clinical spectrum of BNS [3].

The etiopathogenesis of BNS is unclear, yet androgens may play a role in the clinical manifestations of BNS [4]. BNS involves the incomplete penetrance of autosomal dominant inheritance.

Herein, we present three cases of Becker's nevus syndrome with the coexistence of ipsilateral breast gland hypoplasia, keratosis pilaris, and hypoplasia of the third canine tooth.

CASE REPORTS

Case 1

A sixteen-year-old male was initially referred to the doctor because of acne. Accidentally, a lesion on the

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right shoulder joint was found. It was brown, with a hairy surface, and was associated with hypoplasia of the ipsilateral breast. The lesion appeared spontaneously at 2–4 years of age, The patient had undergone no treatment. Detailed clinical and radiological examinations, including an X-ray of the spine, detected no other abnormalities. The Becker's nevus was recognized on a clinical basis.

Case 2

A twelve-year-old male presented with a brown lesion on the anterior aspect of the chest (Fig. 1). The brown patch had a black, hairy surface and coexisted on both sides of the breast gland, more pronounced on the left side. Atypical keratosis pilaris located only in the left antecubital region was also found. All skin lesions appeared at 2–3 years of age. An X-ray of the spinal column confirmed the presence of scoliosis.

Case 3

A fifteen-year-old male drew our attention due to the presence of two pigmented hairy areas present since early childhood, which had extended over time: one from the right lumbar area to the right side of the abdominal wall, another located along the left hip. Long, dark, asymmetric hair was spread throughout the light brown pigmented plaques. The pigmentation of the right hip area was less dark—only slightly brown—and with less asymmetric hair. (Figs. 2a and 2b). A histopathological examination of a biopsy taken from the brown patch revealed acanthosis, papillomatosis, increased melanin deposition in the basal layer, and hyperplasia of the erector pili muscle, confirming the suspicion of a Becker's nevus. Complete blood count and routine liver and kidney tests were all within normal limits. An X-ray of the entire spine evidenced scoliosis while a dental examination revealed hypoplasia of the right canine tooth (Fig. 3).

Our patients were diagnosed with Becker's nevus syndrome. Other skin areas and mucosal surfaces were unaffected. No family members or past histories had shown similar skin diseases. All patients reported that, in adolescence, the lesions spread with a concomitant increase in body hair in that region.

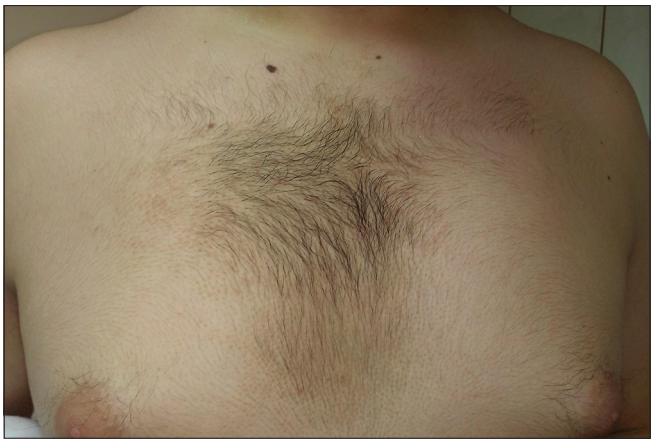

Figure 1: Hypertrichotic and hyperpigmented skin lesions on the anterior aspect of the chest and both sides of the breast gland hypoplastic with more severity on the left side (case 2).

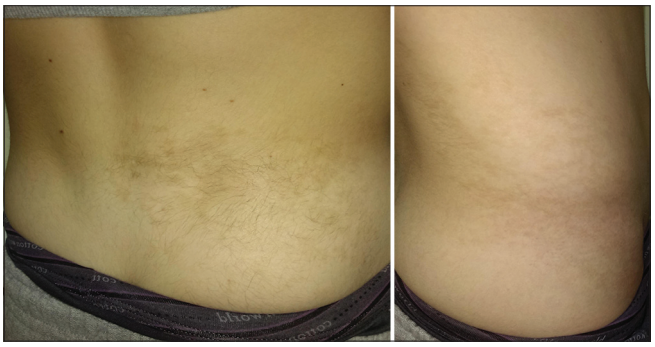

Figure 2: (a-b) Hyperpigmented skin lesions with hypertrichosis on the left hip area (case 3). Hyperpigmented, non-hairy skin lesions on the right hip area with hypertrichosis in the rip region (case 3).

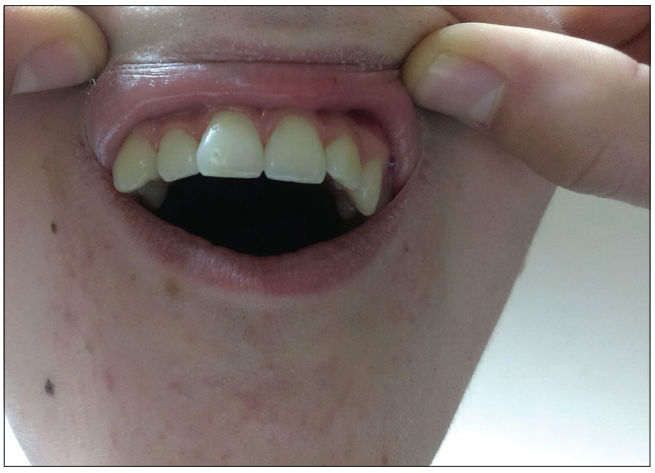

Figure 3: Hypoplasia of the third canine tooth on the right side (case).

DISCUSSION

The Becker's nevus (BN) was first described by Samuel Becker in 1949, yet it was in 1995 that the term BNS was first introduced by Happle, who found an association of BN with unilateral breast hypoplasia and muscle, skin, and/or skeletal abnormalities in 23 patients [5]. The exact etiology of the Becker's nevus remains unknown. According to Torrelo et al., the genetic mechanism of BNS is a postzygotic, autosomal, lethal mutation

that survives in a mosaic form [6]. Usually, BN lesions appear in childhood yet become evident after puberty. A hypothesis that the BN is an androgen-dependent nevus was suggested, as seen by a higher incidence in males, pubertal development, hypertrichosis, an association with intralesional acne, and an anomalous scrotum [1,7]. An increase in androgen receptors in the involved skin was also noted. Breast hypoplasia may be explained by the counterbalance effect of androgens that decrease the estrogenic action.

BNS affects males and females in equal proportion, yet some publications report a male-to-female ratio of 2 to 1 [2,7]. Others claim that it is more easily diagnosed in females due to the more visible breast hypoplasia [4].

The literature has described no more than seventy cases of BNS [4,5]. Following the observation of our cases, we believe that cases of BN/BNS may often be relatively subtle and pass undetected, and that, therefore, the syndrome could more common. The evolution of the BN is benign, the pigmentation rarely regresses, and the hair growth follows the onset of pigmentation.

A majority of publications have described BNS as a coexistence of BN and scoliosis or unilateral breast hypoplasia. We present, herein, a rare clinical presentation of BNS [3].

BNS may sometimes remain unnoticed since it usually proceeds with non-specific clinical findings [8]. All coexisting symptoms in our patients were found accidentally (scoliosis, atypical keratosis pilaris, and hypoplasia of the canine tooth).

Zawar et al. presented an interesting case of a BN coexisting with ipsilateral acanthosis nigricans (AN) [7]. The authors presented the case for the extreme rarity of a distinct morphological presentation of two different pigmentary disorders in the same patient.

Cuesta et al. reported the first case of a concurrent congenital acral BN and Kabuki-makeup syndrome [9]. The term *Kabuki-makeup syndrome* was coined after the peculiar facial features reminiscent of Japanese Kabuki theater masks.

We describe, herein, an exceedingly rare case of unilateral double Becker's naevus. There have only been several documented cases with multiple and bilaterally symmetrical Becker's nevi [6].

The treatment of BNS is difficult and may include surgical excision, Q-switched ruby laser (694 nm), Er: YAG laser, or pharmacotherapy with antiandrogen drugs, including spironolactone. At a dose of 50 mg/day, the improvement of breast hypoplasia has been reported. A satisfactory response with a significant reduction of hyperpigmentation was reported with topical flutamide. Nonsteroidal, antiandrogen, hypoplastic breast augmentation with autologous fat grafting appears promising and may be a safe treatment option with minimal side effects [10].

CONCLUSION

We report three rare cases, all males, in whom the coexisting symptoms of a BN were found accidentally. Described were new coexisting symptoms: atypical keratosis pilaris, hypoplasia of the canine tooth, and a rare unilateral asymmetrical double Becker's nevus. Becker's nevus syndrome involves extremely subtle clinical findings and, thus, many cases may remain undetected.

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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Our Dermatology Online

Case Report

Bilateral nevus of Ota with palatal involvement, unilateral nevus of Ito, and a port-wine stain: A rare presentation

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ABSTRACT

Nevus of Ota and nevus of Ito are dermal melanocytoses, usually presenting themselves as a bluish-black or grayish-brown, patchy, diffuse, or mottled pigmentation of the skin. They share a common pathogenic mechanism involving failure in the migration of melanocytes from the dermis to the epidermis and differ only in the sites of their distribution on the body. Nevus of Ota, often unilateral, may rarely be bilateral or may involve the oral mucosa. Even rarer is its association with nevus of Ito and other extracutaneous features. A port-wine stain is a form of congenital capillary malformation presenting itself as a pinkish-red to purple discoloration, most commonly of the unilateral head and neck area. Only 25% of cases occur on other sites of the body. The presence of a port-wine stain in conjunction with two different dermal nevi has been an exceedingly rarely reported entity. Herein, we report a 26-year-old male who presented himself with a bilateral nevus of Ota with oral mucosal involvement and associated with nevus of Ito and a port-wine stain.

Key words: Nevus of ota; Dermal nevi; Nevus of Ito; Palatal pigmentation; Port-wine stain

INTRODUCTION

Dermal melanocytoses comprise a broad group of congenital and acquired conditions characterized by scattered, spindle-shaped or dendritic melanocytes in the dermis resulting in a bluish-grey discoloration of the skin [1]. The various morphological forms include the Mongolian spot, blue nevus, nevus of Ota, nevus of Ito, Hori's nevus (acquired bilateral nevus of Ota such as macules), and Sun's nevus (acquired unilateral nevus of Ota such as macules) [1,2].

Nevus of Ota, first described by Masao Ota in 1939 as *nevus fuscocaeruleus ophthalmomaxillaris* [3], is usually unilateral, along the skin, and innervated by the first and second branches of the trigeminal nerve [4], with the involvement of the ipsilateral sclera in about two third of cases [5]. Other mucosal sites such as the palate and nasal mucosa may also be involved.

Nevus of Ito involves the supraclavicular, deltoid, and scapular areas and was first described by Minor Ito in 1954. The simultaneous presentation of nevus of Ota and nevus of Ito is a rarely reported entity [6].

The port-wine stain, another cause of discoloration of the skin, characterized by congenital vascular malformation due to the ectasia of the dermal capillaries, presents itself as non-involuting pinkish-red to purple macules.

Herein, we report the case of a male patient with an exceedingly rarer presentation of a bilateral nevus of Ota, a unilateral nevus of Ito, and a port-wine stain along with palatal lesions.

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CASE REPORT

A 26-year-old male patient, born out of a non-consanguineous marriage, presented himself to us with an asymptomatic, bluish-grey pigmentation around the bilateral cheeks, eyelids, and eyes since birth. The lesions had been lighter in color until childhood but had gradually progressed until puberty; they became darker and more pigmented, then becoming stable. The patient also complained of developing similar, but lightly pigmented, grayish lesions on the right shoulder present for the last ten years. The patient also complained of diffusely distributed, red reddish patches on the central part of the back present since birth, which had increased proportionately in size with the growth of the patient until puberty. The patient sought medical consultation because of a cosmetic concern. No family history of similar lesions was present.

A mucocutaneous examination revealed the presence of bluish, mottled, pigmented macules present over the dorsum of the nose (Figs. 1a and 1b). The pigmentation involved the bilateral temples, eyelids, and periorbital and malar regions. The pigmentation extended medially to the bilateral ala and laterally to bilateral earlobes and helix along with bluish discoloraltion over unilateral hard palate (Fig. 2). A diffuse, ill-defined, lightly pigmented, large, grayish macule was present over the right scapular (Fig. 3a). There was no increased hair growth over the involved areas.

Over the back, there was a large, deep, red macule with ill-defined geographical borders distrusted over the center of the upper and middle back, right side of the middle back, and almost the entire territory of the lower back, extending all the way down to the lumbosacral area. The lesion was blanchable with some areas of normal skin in between the large macule. The lesion was diagnosed clinically as a port-wine stain (Fig. 3a).

An ophthalmological examination revealed a bluish-black pigmentation in the bilateral sclera. The conjunctiva and sclera showed a bilateral inferomedial and inferolateral bluish-black pigmentation around the limbus. There were no abnormalities detected on visual acuity and indirect gonioscopy.

The remaining examination of the oral mucosa was normal. There was no discoloration of the tympanic membrane on auditory examination.

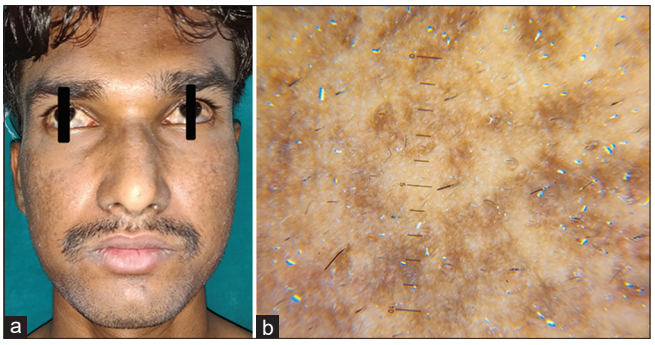

Figure 1: (a) Bluish-gray macules on the face and bluish-black discoloration of the sclera. (b) Bluish-brown, structureless areas on the dermoscopy of the facial macules.

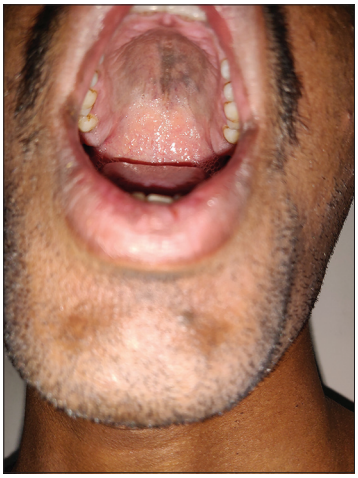

Figure 2: Bluish-gray discoloration of the hard palate crossing the midline.

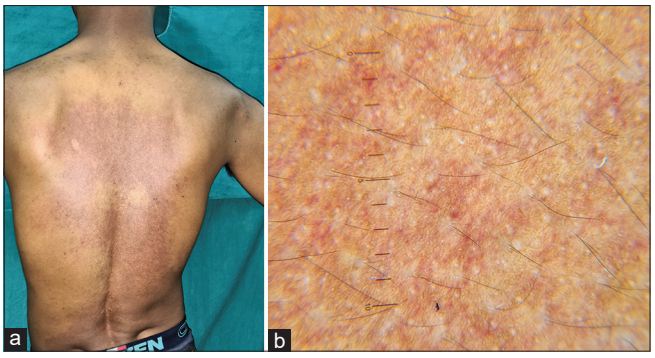

Figure 3: (a) Deep red, ill-defined macule on the upper, middle, and lower back. (b) Dotted and globular vessels, linear, dilated, and tortuous vessels, and pale, circular areas around the follicular hair openings on the dermoscopy of the port-wine stain.

The patient was clinically diagnosed as having a bilateral nevus of Ota along with a nevus of Ito with a port-wine stain.

A dermoscopic examination of the lesions on the face revealed bluish to brown, structureless areas (Fig. 1b). Similar features were seen in the macular lesions on the

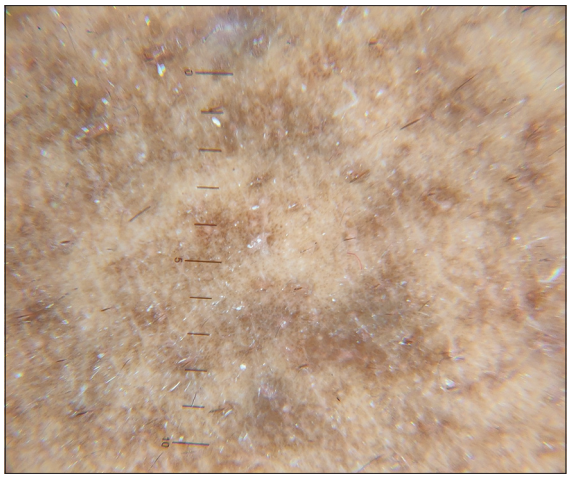

Figure 4: Bluish-gray macule on the right scapular. Light brown, structureless areas on the dermoscopy of the right scapular lesion.

helix on dermoscopy. Also, on dermoscopy of the bluish lesion, on the right scapular area, there were similar bluish to brown, speckled areas, which were lighter in color (Fig. 4). An examination of the port-wine stain on the back revealed dotted and globular vessels as well as linear, dilated, and tortuous vessels along with pale circular areas around follicular hair openings (Fig. 3b).

DISCUSSION

Nevus of Ota and nevus of Ito are forms of dermal melanocytosis having a common pathogenic mechanism of failure in the migration of melanocytes, arising from the neural crest to the epidermis. The bluish discoloration of the skin in deeper lesions seen in both of these conditions is due to an optical effect altering the perceived color of the brown pigment in the dermis. The incident visible light absorbed by the melanin in the dermis is dispersed in such a way that the diffuse reflectance in the longer (red) wavelength is reduced, leading to the appearance of the pigmented sites as bluish in color. This effect is called the Tyndall effect [6]. More superficial lesions, however, appear slate gray.

Oculodermal melanosis was first described by Hulke in 1861, followed by Masao Ota in 1939 [3]. Both nevus of Ota and nevus of Ito are much rarer in the white population than in Asians and Afro-Americans. Nevus of Ota has a prevalence falling between 0.014% and 0.034% in the Asian population [6], with a male-to-female ratio of 1:4.8. Most often, the onset is perinatal, yet it may rarely appear around puberty as well. Several factors may influence the intensity of the discoloration, such as puberty, menstruation, stress, ultraviolet light exposure, and changes in weather [7]. Nevus of Ota and nevus of Ito are typically unilateral but bilateral involvement has also been sometimes reported. In around 45% of cases, nevus of Ota occurs bilaterally [8], as in our case, where the closest differential diagnosis is Hori's nevus. The two may be differentiated clinically as given in Table 1 [9].

Table 1: Comparison of bilateral nevus of Ota and Hori's nevus

Bilateral nevus of Ota	Hori's nevus
Presents at birth or early childhood.	Presents in late adulthood.
Exact etiology unknown, genetic mutations implicated.	Acquired condition. Exact etiology unknown, but the triggering factors include cosmetics, dark and sensitive skin, estrogens, pregnancy, and ultraviolet radiation
Bilateral and asymmetrical involvement of the skin of the face, distributed along the first and second branches of the trigeminal nerve.	Bilateral and symmetrical involvement of the skin of the face, including the forehead, cheeks, temples, parotid area, parts of the nose, eyelids, and forehead.
Mucosal involvement frequent, the most common being the sclera.	Mucosal involvement extremely rare.
Speckled macules are blue to gray in color.	Macules are brown to slate gray in color.
Intense pigmentation.	Less intense pigmentation.
Histopathology showing the presence of bipolar to satellite melanocytes in both the epidermis and dermis with late-stage melanosomes.	Histopathology showing the presence of irregularly shaped, bipolar melanocytes in both the epidermis and dermis with relative sparing of the deep dermis with early-stage melanosomes.

The extracutaneous lesions involve the eye (sclera, cornea, retina), tympanum, nasal mucosa, pharynx, and palate in descending order of prevalence. The palatal lesions are highly uncommon in nevus of Ota and have been reported to occur more often with bilateral cutaneous involvement and, to the best of our knowledge, apart from ours, only fifteen cases have been reported to date [10,11].

In 1939, Tanino classified nevus of Ota into four major subtypes: type 1 (mild), type 2 (moderate), type 3 (intense), and type 4 (bilateral). A further modification has been proposed by Mukhopadhyay [6] in 2013, with a proposal of including nevus of Ito in the classification by suggesting type 5 (nevus of Ito without nevus of Ota) and type 6 (nevus of Ito with nevus of Ota). According to Tanino's classification, our case is type 4, whereas, according to the revised classification, our case should be type 6. However, in 2013, the Peking Union Medical College Hospital (PUMCH) proposed a different classification, according to which our case should be type V [12]. Patients with ocular involvement may have complications such as increased intraocular pressure with or without glaucoma, uveitis, cataracts,

orbital melanomas, and retinitis pigmentosa. Our patient had no such changes but was advised biannual ophthalmic examination to prevent the development of these complications. Although the association of these two nevi is rare, there are some reports showing their simultaneous presence. Bilateral nevus of Ota with nevus of Ito is exceptionally uncommon, with only a handful of cases having been reported to date.

Histologically, these nevi show a normal epidermis, with the presence of dendritic melanocytes in the papillary and upper reticular dermis, which are surrounded by fibrous sheaths, unlike other dermal melanocytoses, such as blue nevus or Mongolian spots. There might also be the presence of dermal melanophages. Hirayami classified it into five subtypes based on the distribution of the dermal melanocytes as superficial (type S), superficial dominant (type SD), diffuse (type Di), deep dominant (type DD), and deep (type De). They correlate with the color of the nevus: the most brownish lesions are represented by type S or type SD, while the most bluish lesions by types Di, DD, or De. Furthermore, these types strongly correlate with the location of the nevus: types S and SD are more frequent on the cheeks, whereas types Di, DD, and De more frequently occur on the eyelids, temples, and forehead. Nevus of Ota may be associated with various other cutaneous, leptomeningeal conditions and ocular disorders.

A port-wine stain is a congenital capillary vascular malformation with an incidence of around 0.3% [13]. It appears clinically as a homogenous, pinkish-red to deep-purple lesion with a geographic contour. Around 75% of these capillary malformations are present on the head and neck with the majority of cases having the involvement along the distribution of the trigeminal nerve. The remaining 25% of cases may involve other areas of the body, such as the back, as in our case. They may occur in combination with other vascular malformations as part of a syndrome, such as Sturge–Weber syndrome, phakomatosis pigmentovascularis (PPV), Klippel–Trénaunay syndrome, or Servelle–Martorell syndrome [14].

Considerable cosmetic disfigurement may be caused by nevus of Ota and nevus of Ito with occasional emotional and psychological distress. The patient should be counseled on the benign nature of the condition, apart from cosmetic camouflage makeup. Otherwise, topical therapy has no value in the treatment. The first-line management is laser surgery, with Q-switched ruby laser (694 nm) surgery being the treatment of choice. Other lasers such as Q-switched alexandrite (755 nm) and Q-switched Nd: YAG lasers (1064 nm) may also be employed. Other surgical methods include dermabrasion (with or without other modalities, such as carbon dioxide snow), autologous epithelial grafting, cryotherapy, microsurgery, dermabrasion, and sequential dry ice epidermal peeling. As far as the port-wine stain is concerned, the current modality of choice is laser photocoagulation with pulsed dye laser (PDL) [15].

Although, in the past, port-wine stains have been reported with nevus of Ota, to the best of our knowledge, no case report has highlighted the concomitant presence of these two conditions together with nevus of Ito. We are reporting this case for the rarity of the association of these three conditions in the literature.

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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Our Dermatology Online

Review Article

Cutaneous lupus: Immunofluorescence and lupus band test

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ABSTRACT

Cutaneous lupus erythematosus is an autoimmune disease with a broad range of clinical findings. There are several methods to conduct a diagnostic approach, among these stands direct immunofluorescence, in which we can find the Lupus Band Test (LBT) consisting of a band of granular deposits of immunoglobulins and complement along the dermo-epidermal junction. It can have a high sensitivity and specificity for diagnosis in some cases, according to the biopsy site, the constituents of immunorreactants found at the dermoepidermal junction, and the morphology and intensity of the immunofluorescent band. Certain limitations of the test should be considered when interpreting the results. Although useful in diagnosis, the lupus band is not considered a pathognomonic sign of erythematous lupus. About one-third of patients with positive direct immunofluorescence on a skin biopsy do not have systemic lupus erythematosus (SLE). A positive LBT in non-lesional photoprotected skin represents a criterion with high specificity to identify patients with SLE.

Key words: Direct Immunofluorescence; Lupus Erythematosus, Systemic; Lupus Erythematosus, Cutaneous; Lupus Erythematosus, Discoid; Immunoglobulins

ABBREVIATIONS

DI: Direct immunofluorescence
IA: Immunoreactive agents
LE: Lupus erythematosus
CLE: Cutaneous lupus erythematosus
SCLE: Subacute cutaneous lupus erythematosus
DLE: Discoid lupus erythematosus
SLE: Systemic lupus erythematosus
NLE: Neonatal lupus erythematosus
LBT: Lupus band test
DEJ: Dermoepidermal junction
DNA: deoxyribonucleic acid
C5b-9: Complement complex 5b-9
ESR: Erythrocyte sedimentation rate
NPV: Negative predictive value
PPV: Positive predictive value
ESJ: Epithelial-stromal junction
ANA: Antinuclear antibodies:
LET: Lupus erythematosus Tumidus

INTRODUCTION

Lupus erythematosus (LE) is an autoimmune disease associated with multisystemic inflammation. There are four main types: neonatal lupus erythematosus (NLE), cutaneous lupus erythematosus (CLE), drug-induced lupus and systemic lupus erythematosus (SLE) [1]; three types of CLE are recognized: acute, subacute and chronic [2]. All of these subtypes share clinical, histological, and immunological characteristics. Circulating autoantibodies of LE are detected with serological tests and cutaneous immune deposits by direct immunofluorescence (DI), which can be

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useful for making the diagnosis when there is clinical and/or histopathological suspicion [3,4]. Evaluation by direct immunofluorescence of lesional or non-lesional skin to search for a diffuse band of granular deposits made out of immunoreactive agents (IA) along the dermoepidermal junction (DEJ) as part of the cutaneous lupus (CL) and systemic lupus erythematosus (SLE) diagnostic approach is historically recognized as the "lupus band test" (LBT). The range of DI positivity rates is very wide, ranging from 39% for subacute cutaneous lupus erythematosus (SCLE), 55-70% for discoid lupus erythematosus (DLE), 80% for acute cutaneous lupus erythematosus (ACLE), and from 50% to 90% for SLE [5]; therefore its diagnostic value is not very clear for the diagnosis of LE. On the other hand, it has been considered that DI could be useful in distinguishing between the different subtypes of CLE since the frequency of deposits, their morphology and position vary between the different subtypes, in addition, it can be helpful to differentiate CLE from other dermatoses that may have similar clinical findings (such as rosacea, facial telangiectasias, lymphocytoma cutis, pemphigus erythematosus, lichen planopilaris (Fig. 1), pseudopelade of Brocq, drug-induced LE, pharmacodermias and cutaneous vasculitis) or overlapping histopathological findings, as in polymorphous light eruption or benign lymphocytic infiltration of the skin [2,3].

The correlation between clinical, histopathology, immunofluorescence, and serologic profiles remains crucial for accurate diagnosis of cutaneous lupus erythematosus [3]. New diagnostic methods such as ex vivo confocal laser scanning microscopy have tried to identify histopathological features and perform the lupus band test at the same time, albeit with a lower performance than conventional DI [4], making conventional DI microscopy a still one of the most accurate diagnostic tools for cutaneous inflammatory lesions.

Direct Immunofluorescence in Lupus

Throughout the DEJ in DI of patients with any type of lupus, the most frequent immune deposits are IgG and IgM (Fig. 2) [3]. Immunoreactants in the DEJ are believed not to be antibodies to the basement membrane, but to represent circulating immune complexes of DNA and antinuclear antibodies trapped in the DEJ [6]; UV-damaged keratinocyte DNA is released and can diffuse through the basement membrane to bind to type IV collagen and serve as antigen for circulating antinuclear antibodies [7].

Several fluorescence patterns have been defined, the most described being: linear and granular, which can be seen in low-power microscopy as thin or thick bands [5]. Within the granular pattern, which is the most frequent[6], when viewed with a high-powered microscope, such as confocal laser scanning microscopy other patterns can be identified: homogeneous, fibrillar, dotted, shaggy, lumpy, linear, and filiform [7], classification not widely used in clinical practice due to the lack of availability of this type of microscope. All of these usually present continuously, an interrupted form is less specific and can be seen in other dermatoses.

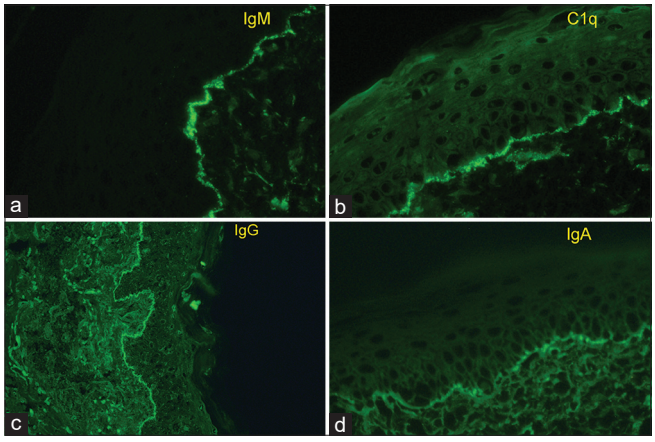

Figure 1: a and b) Clusters of cytoid bodies in the superficial dermis that label for IgA, IgM, kappa, and lambda. Consistent with lichen planus. c) Trace intercellular IgG deposition and 1+ linear basement membrane zone deposition of C3 consistent with paraneoplastic pemphigus. d) Granular deposition in the walls of superficial dermal vessels of IgA (2+), C3 (1+) lambda (1+), and kappa (trace) consistent with IgA vasculitis

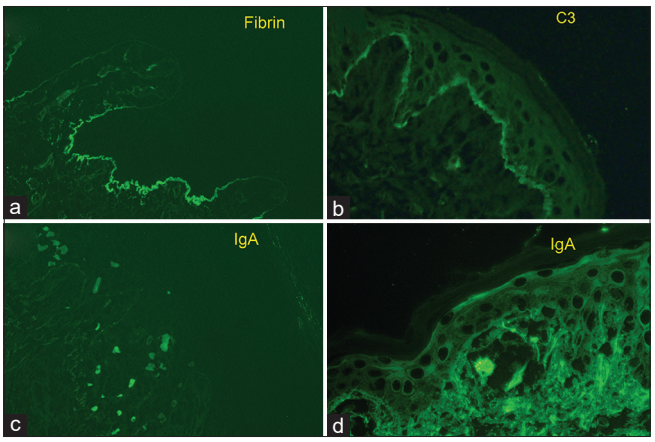

Figure 2: Granular basement membrane zone deposition of IgG (1+), IgA (trace, (C3(trace), C1q (3+) Kappa (1+), and lambda (1 to 2+) compatible with Lupus Erythematosus.

In addition to these immune deposits, cytoid bodies can also be seen in the DEJ, which represent basal keratinocytes that "fell" to the papillary dermis and adhered to immunoglobulins (most often IgM and IgA) and circulating complement [3].

Systemic immunosuppressive treatment is associated with a lower frequency of positive DI. In addition, while fluorescence intensity is related to DNA antibody titers [4], it does not correlate with the degree of inflammation in SLE lesions [5]. There is also a variation in the positivity of the lesion skin test with a cephalocaudal gradient, head lesions are more frequently positive than those of the trunk [5,7]. Unlike histopathology, DI does not reflect real time changes but displays any past insult on the structures involved [3].

The particular characteristics of DI for different types of lupus are discussed below.

Discoid Lupus Erythematosus

The possibility of finding immune deposits in DLE depends on the biopsy site, previous treatments and duration of the lesion; 60-94% of lesional skin biopsies are reported to have immune deposits. In one study, DI was positive in 96% of biopsies of facial lesions, while it was positive in only 65% of lesions in other photoexposed regions and 30% in non-photo-exposed areas [8]. The frequency of positive DI in lesions under treatment (for more than three weeks before biopsy) is lower than that found in untreated lesions, and finally, it has been seen that while the duration of the lesion increases, The frequency of positive DI also does so by up to 82% in lesions older than one year, while it has been found that only a third of lesions less than 1 month long have a positive DI [8]. To confirm the diagnosis of DLE, the most appropriate site for biopsy is the oldest, untreated lesion, preferably from an area not usually exposed to the sun [9,10].

In the immune deposits of the DEJ there is predominance of IgG (77-80%) [11,12] and intense granules of C5b-9 (60%); Both are typically absent in endothelium or keratinocytes [10]. Although these immune deposits can be seen in many other diseases (including rosacea, lichen planus, and primary biliary cirrhosis), the immunoglobulin class may be helpful in distinguishing DLE, as IgG deposits are more specific to DLE [3]

Subacute Cutaneous Lupus Erythematosus

The positivity of DI varies from 54% to 100% in the lesions of SCLE, from 18% to 100% in non-lesional skin and from 0-100% in non-lesional and non-photoexposed skin [11,12].

Unlike DLE, immune deposits are also found in basal keratinocytes and this has been reported as a more specific pattern for SCLE, consisting of granular fluorescence for IgG and C5b-9 in the cytoplasm and nucleus of basal keratinocytes [3,10], this is probably an ANA in situ phenomenon, thought to be a reflection of the binding of anti-Ro (SS-A) or anti-La (SS-B) antibodies or both to their respective keratinocyte antigen [12,13]. This pattern has been shown to be an independent factor from serological findings in patients with and without anti-Ro antibodies [10] and has also been reported in patients with anti-Ro antibodies (SS-A) who do not have SCLE [3]. The deposition of C5b-9 along the DEJ is observed in 66% of cases [10] and vascular deposits are generally absent, except in patients with drug-associated SCLE [10,13].

Systemic Lupus Erythematosus

The prevalence of immunoglobulins and complement deposition in SLE, as in DLE, depends on several factors. In SLE, immune deposits can be present in 4 sites [14,15]: in the DEJ, which is the most characteristic site, in the cytoid bodies (which represent basal keratinocytes that have suffered necrosis), in the superficial dermis vessels walls (similar to vasculitis) and finally, in the keratinocytes nuclei, a much less frequent finding reported for the first time in patients with mixed connective tissue disease and usually seen in patients with antibodies against $U1_{RNP}$, although it can be seen in patients with other antinuclear antibodies [15].

85% of patients with SLE have multiple immune deposits throughout the DEJ, the most frequently found being IgG, IgM, IgA, C1q and C3 and generally in combination; About 45% of patients demonstrate IgG and IgM with or without C3 [16]. The presence of IgG and C5b-9 deposits in the DEJ is observed in patients with SLE with anti-Ro/SSA antibodies, patients in whom there is circulating lupus anticoagulant or vasculitis demonstrated in the biopsy [14]. Intense deposition of C5b-9 granules has been observed in 80% of lesional skin [10]. Other immune deposits include IgD, IgE, and fibrin. In the

Table 1: Differential diagnoses for lupus band in other dermatoses

Dermatosis	Characteristics of the DI
Positive lupus band test	Granular or narrowly spaced band, vertically oriented fibrils in the DEJ; sometimes a homogeneous thick band.[7]
Photoexposed healthy skin	Can demonstrate positive lupus band test Usually with less intensity, focal or interrupted. Nonreactive in photoprotected skin.
Autofluorescence of dermal collagen and elastin fibers	They can simulate a lupus band. The artifact nature of this false-positive finding becomes more apparent at a greater increase.[7]
Pemphigus (Figure 3a)	Tubular band, dark and bright center. Intracellular epidermal deposits. Thinner and more homogeneous than LE.[22]
Bullous Pemphigoid (Figure 3b)	Narrow linear band defined in the DEJ. IgG and C3 more predominant than IgM.[36] The presence of circulating antibodies against the basement membrane is helpful for the correct diagnosis.[7]
Porphyria (Figure 3c)	The fluorescence of the DEJ is less intense than that found in the dermal blood vessels, exactly the opposite of what is seen in LE.[7] Homogeneous deposits. Complement is rarely found.[13]
Telangiectatic rosacea, Polymorphic light eruption.	Less intense band and frequently with a focal or interrupted pattern.[7,22]
Systemic sclerosis.	Granular deposition of IgM along the DEJ in sun-exposed skin.[29] Perivascular deposits/ vasculitis often seen
Dermatomyositis.	The intensity of the fluorescence is usually lower in dermatomyositis compared with LE.[30] Lower frequency of positive DI.
Leukocytoclastic vasculitis.	Immune deposits within postcapillary venules in the superficial dermis. Granular or fibrillary.[31] Fibrinogen deposition throughout the dermis.

cell nuclei the main immunoglobulin found is IgG (in situ ANA phenomenon) [15-17].

Nuclear and cytoplasmic granular deposits of IgG and C5b-9 have been observed in keratinocytes and blood vessels when patients present with extractable nucleus antigen (ENA) antibodies: Ro, La, Sm, or U1RN; while deposits are weak or absent when these antibodies are not present [14].

The lupus band dotted pattern, consisting of multiple small round points of fluorescence, is the most commonly type seen in clinically normal skin of SLE, and has been associated with disease of less than one year of evolution; while a filiform pattern has been associated with an evolution of more than one year [14]. In chronic atrophic, hypertrophic, hyperkeratotic, or scaly skin lesions, a well-defined homogeneous or "solid" band of bright fluorescence has been reported, while in acute erythematous and edematous lesions a fibrillar pattern consisting of short, stacked and bright fibrils has been seen [7].

The intensity of the DEJ fluorescence is related to the levels of antibodies against double-stranded DNA and therefore to disease activity [3].

Serological tests are more reliable than DI in the diagnosis of SLE, since the presence of high titres of antinuclear antibodies by immunofluorescence and antibodies specific to several nuclear antigens such as $U1_{RNP}$ and Sm are very characteristic of SLE [3].

Lupus band test in non-lesional or non-photoexposed skin in SLE

In SLE there may be alterations in DI of healthy skin, this could be useful for early diagnosis [7] and in the differential diagnosis with DLE or CLE, since skin lesions may be identical and the DI characteristics of the affected skin are similar in all these entities, but in the non-lesional skin DI of patients with DLE or SCLE there are no alterations [18]. However, the frequency of positive DI in patients with DLE is lower in healthy skin, and varies between photoexposed and non-photoexposed skin (Table 1), while in injured skin it is positive in 50-100% of the time [3].

The lupus band test in patients with SLE is positive in 70%-80% of photoexposed non-lesional skin biopsies [7], the lupus band test in fully photoprotected non-lesional skin, such as buttocks or the inner arm consisting of three or more components (IgA, IgG, IgM or complement proteins) is positive in 55% of cases [7], and appears to have the highest specificity for SLE than any other test [7,14], it can be used for diagnosis when clinical and serological criteria are insufficient [15].

A positive lupus band may also serve as a prognostic indicator in patients with an established diagnosis of LE [7]. If it is positive in non-injured photoprotected skin, it indicates less long-term survival [9,10] Some authors suggest a significant relationship between a positive lupus band in non-lesional skin and renal pathology, since 70% of these patients have active nephritis, being severe renal disease 3 times more common [12]. Patients with pure IgM deposits in non-lesional skin have anti-DNA antibodies restricted to the IgM class and tend to have a less severe course of disease. On the other hand, the deposits of C1q along the DEJ in the skin of patients with SLE may reflect the presence of DNA in the DEJ, these patients have a high rate of disease activity [7]. Also, positivity in non-lesional photoprotected skin indicates less long-term survival [9,10].

Drug-induced Lupus Erythematosus

Older age at onset and leukocytoclastic vasculitis are more commonly seen in drug-induced LE, mucin deposition and positive immunofluorescence are clues to the idiopathic form [19,20].

Neonatal Lupus Erythematosus

DI is not performed on a routine basis on NLE lesions, diagnosis is based on characteristic skin lesions with or without evidence of heart block, as well as serological markers of the disease in infants, their mothers, or both. It has been noted that immune deposits in NLE are also found throughout the DEJ [21,22],the most frequent are IgG, IgM and C3. In a clinical and histopathological analysis of 10 infants with NLE, the authors noted that only two biopsies were analysed with DI, and from them, only one case turned out positive [21]. Other authors also report that approximately 50% of the biopsies have positive DI [23].

Lupus Tumidus

Results of DI in patients with LET are mostly negative at the dermoepidermal junction or around the papillary and reticular dermal blood vessels, a study where 40 LET cases were evaluated could not found none of the 3 major immunoglobulin classes (IgG, IgM, and IgA) or complement components (C3 and C4) in any specimen, only 10% of patients were ANA positive [24].

Lupus Band Test Definition

In 1963, Burnham et al., described for the first time the deposits of immunoglobulins in the DEJ along with a thickened basement membrane in the lesional skin of patients with SLE [6]. Subsequently, Cormane demonstrated similar deposits in clinically normal skin in patients with SLE [7].

The definition of positive lupus band test is controversial, by some authors it is defined as the presence of a bright fluorescent band in the DEJ [8]; while other authors consider as criteria the presence of IgM or IgG deposition (individually or in combination with another class of immunoglobulins) in the area of the basement membrane where complement components may be present [4]. Other authors describe that, to increase the specificity of the test, the presence of IgM alone (with or without C3) should be excluded from the definition of positive lupus band, since IgM is commonly found in patients with normal skin without SLE, especially in photoexposed skin, where weak deposits are describe [5,7]. IgG is the most specific immunoglobulin for LE and the most frequently reported, followed by IgM and IgA [9]. Another criterion that has also been mentioned is that to consider a positive lupus band test, the deposit of IgM in the photoexposed skin must be a continuous band that covers at least 50% of the sample width of the biopsy and be at least of moderate intensity, since mild IgM deposition throughout the DEJ is common in patients who do not have LE, as in actinic keratosis and rosacea lesions, and in 20%-25 of normal skin samples from healthy young adults; while only 5% show the presence of IgG, IgA or C2 [7,10] In non-photoexposed skin, an interrupted band of IgM of at least moderate intensity is sufficient to designate the test as positive [7].

Clinical Use of the Lupus Band Test

The sensitivity and specificity of the test is strictly related to the body area where the biopsy is performed and the criteria by which a positive value is assigned to the test. George et al., found that in DLE the test has a sensitivity of 58%, a specificity of 87%, a positive predictive value (PPV) of 95% and a negative predictive value (NPV) of 32%; for SLE, they reported a higher sensitivity of 93%, and a specificity of 87%, a PPV of 64% and a NPV of 98%.[5] In some studies it has had a specificity of up to 100% [25].

The sensitivity of the lupus band for active disease is higher than the serum levels of C3 and C4, anti-DNA antibodies, LE cells, lymphocyte count and ESR[19], its NPV and its high specificity, allows differentiating between LE and other skin disorders that are clinically similar [17,19] (Table 1).

The PPV for the lupus band test in SLE is greater with C4 (100%), properdine (91.3%), and IgA (86.2%) than with IgM (59%). Specificity and PPV also increase with the number of immunoreactive agents detected in the DEJ [7].

In DLE, although histopathological examination (HPE) and DI have a very high specificity and PPV (100%), DI has a higher sensitivity for diagnosis compared to HPE, and a higher NPV [11].

In a study that looked for the correlation of a positive lupus band with SLE activity measured with the SLEDAI score (*Systemic Lupus Erythematosus Disease*

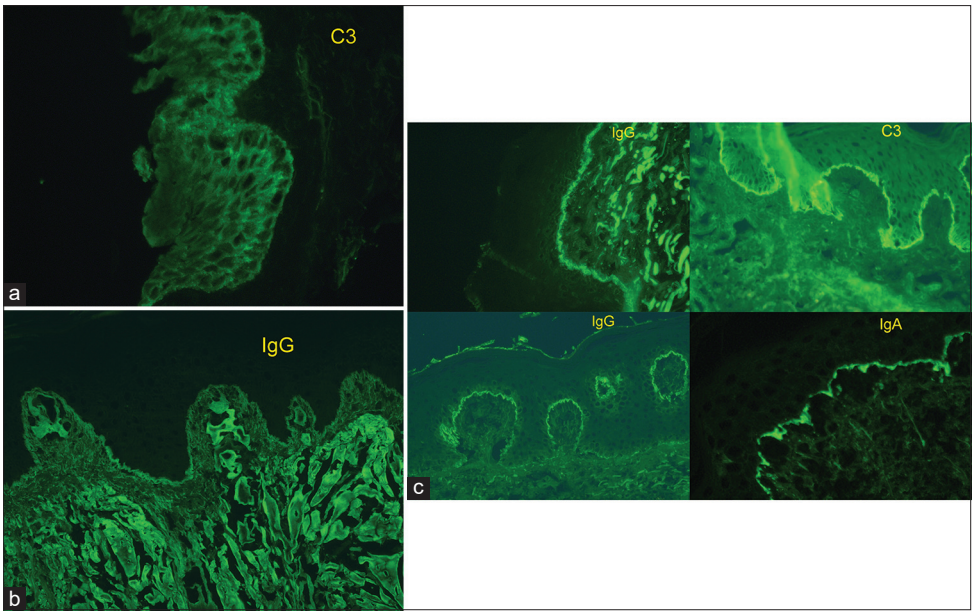

Figure 3: (a) Pemphigus Vulgaris. (b) 2+ linear IgG and C3 in an n-serrated pattern along the basement membrane zone compatible with BP. (c) Porphyria cutanea tarda.

Activity Index), the frequency of the lupus band was found to be significantly higher in patients with active disease, as well as with higher titres of anti-dsDNA antibodies, and the presence of renal involvement [19].

Another diagnostic value that the test has is in the differential diagnosis of SLE from other diseases with positive antinuclear antibodies such as drug-induced LE, rheumatoid arthritis, scleroderma, dermatomyositis and mixed connective tissue disease [14].

A study found that CLE without SLE was the only subgroup with staining of solitary immunoreactant, while multiple staining was significantly associated with internal lupus [3], multiple rather than single immunoreactant on lesional skin may likely imply systemic involvement. Patients with positive DI have severe SLE, >1 immunoreactant on lesional skin correlates to higher immunological profile and SLE disease activity [26].

A study in India found that statistically significant risk of kidney involvement was presents both when patient had bullous lesions and DI positivity of unexposed skin [6]. DI from sun protected normal skin helps in assessing the severity of the disease and correlates positively with the risk of developing nephritis [6].

Lupus Band and Other Rheumatic Diseases

Occasionally, there is the presence of a positive lupus band test in the lesional skin of patients with

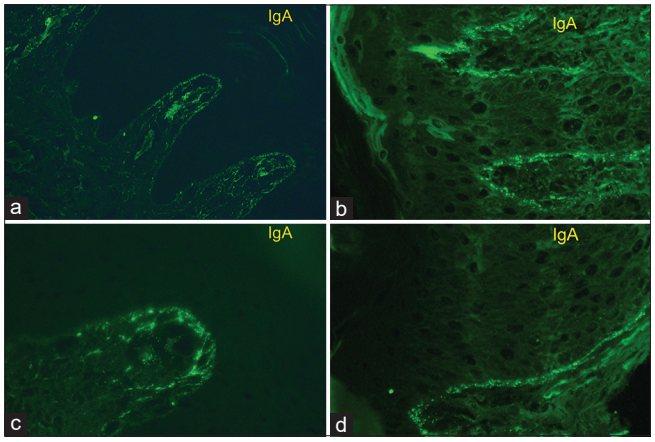

Figure 4: Granular IgA and C3 deposits at tips of papillary dermis (Dermatitis herpetiformis).

dermatomyositis or systemic sclerosis, this finding is related to a more severe course of the disease [7].

A biopsy in skin with telangiectasias in scleroderma may demonstrate the presence of a band of low-intensity immunoglobulins [2]. Also, rare cases have shown weak dermoepidermal deposits in telangiectasias of patients with dermatomyositis, mainly IgA.

In rheumatoid arthritis there may be in rare cases dermoepidermal deposition of IgM, especially in cases where there is a high serum concentration. Bright bands of IgG throughout the dermoepidermal junction are present in cases with marked vascular damage [2].

Limitations - False Negatives and False Positives

Certain limitations of the test should be considered when interpreting the results. Although useful in diagnosis, the lupus band test is not considered a pathognomonic sign of SLE [17,20]. About one-third of patients with positive DI do not have SLE [5].

False negatives are often seen when there are levels of extravascular dermal IgG [14] or if biopsy is taken from non-photo-exposed sites, where the lupus band is often absent despite SLE lesions, such as the trunk [27].)

Elbendary et al., found that IgM deposits showed greater sensitivity for the diagnosis of LE when they were found at the stromal-epithelial junction (SEJ) of the sweat glands and greater specificity when detected along the SEJ of hair follicles [28] when compared with other immune mediated diseases, also, the pattern of IgM in lupus and dermatomiositis is granular, in contrast to the linear deposition in other autoimmune disorders [28]. This may be helpful in narrowing differential diagnosis when evaluating DI specimens of immune-mediated dermatoses. Full thickness skin biopsy specimens that demonstrate adnexal structures are preferred as they are more likely to demonstrate adnexal structures [28-31].

Finally, the lupus band test can be positive in non-autoimmune diseases such as porphyria cutanea tarda, and dermatitis herpetiformis (Figs. 3 and 4)

CONCLUSION

The lupus band test is a useful diagnostic tool in patients with LE, however, the correct interpretation of the test requires detailed knowledge of the patient's context, such as the site of the biopsy, the components of the immunoreactants found in the DEJ, the morphology and intensity of the immunofluorescent band and other serological findings, as well as the response to treatment. A positive test in non-lesional photoprotected skin represents a criterion with high specificity to identify patients with SLE. The lupus band test is a procedure that can be useful in the diagnosis of LE and must be interpreted according to clinical findings, serological and immunological parameters in order to achieve a correct diagnosis.

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Clinical Image

Symmetric periorbital edema after mRNA COVID-19 vaccine

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A 42-year-old Caucasian female patient presented with symmetric, asymptomatic, periorbital angioedema (Fig. 1) that appeared 24 hours after the second dose of the Moderna mRNA COVID-19 vaccine. She was injected with the hyaluronic acid dermal filler Juvéderm Volite in the glabella and periorbital area three months earlier and underwent a botulinum toxin session in the forehead, glabella, and crow's feet with Vistabel six months earlier. No present or previous history of allergy or concomitant diseases was reported. Cetirizine dihydrochloride 3 × 10 mg and cold compresses resulted in the complete resolution of the symptoms within three days.

Reactions to the Moderna vaccine possibly related to the dermal filler placement are rare and have an unknown pathogenesis. Three out of 15,184 patients developed facial or lip swelling after mRNA vaccine [1]. These reactions may be immunologically triggered by viral or bacterial illness and vaccinations, including allergies to vaccine ingredients such as polyethylene glycol [2].

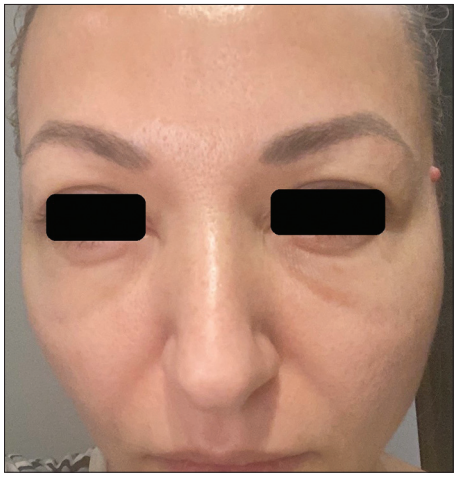

Figure 1: Symmetric periorbital edema developed 24 hours after the second dose of the Moderna mRNA COVID-19 vaccine.

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The patient described by this article gave written informed consent to the publication of their case details.

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.

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DOI: 10.7241/ourd.20222.22

Clinical Image

Hydroa vacciniforme associated with EBV infection in a Moroccan child

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Hydroa vacciniforme (HV) is a very rare photosensitivity disorder of childhood characterized by pruritic or painful vesicles in photo-distributed areas. We report a case of a seven-year-old male presenting with recurrent scars on the face with significant impact on psychological health.

The history of the patient's disease went back to when he was five years old and began to show eruptions on the face and forearms associated with a burning sensation, evolving recurrently with each exposure to the sun. Later, these lesions became confluent and crusted, then detached, leaving residual scars. A clinical examination revealed varioliform scars on the face, with scaly and crusted lesions on the nose and auricle (Figs. 1a – 1c). The rest of the examination revealed no adenopathy or organomegaly. Blood count, lymphocyte circulating levels, and immunophenotyping were normal and EBV serology was positive, with IgG+ and IgM-. The child refused to have a skin biopsy performed and did not return for another consultation.

Hydroa vacciniforme is associated with an EBV infection. This infection might be responsible, in the presence of an underlying cellular immune dysfunction, for T lymphocyte proliferation possibly evolving into a hydroa vacciniform-like lymphoma (HVLL), or even an EBV-induced malignant T lymphoma. As lymphoma progression and mortality occur not only in childhood but also in adulthood, adult-onset cases may need more careful monitoring [1,2].

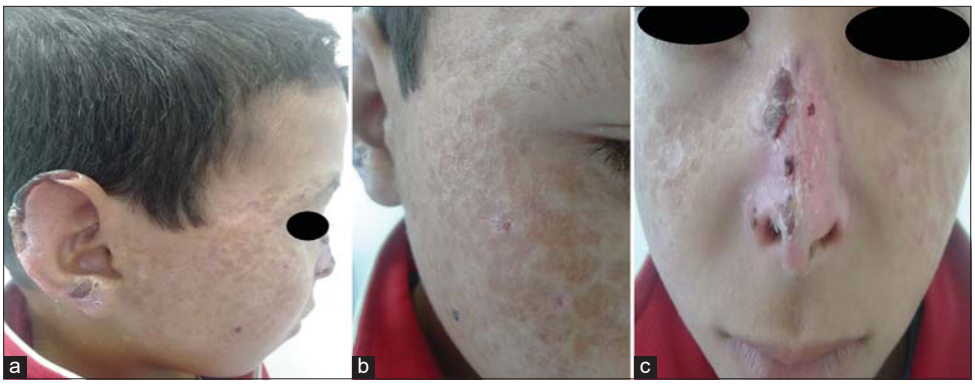

Figure 1: (a and b) Varioliform scars on the face with scaly and crusted lesions on the auricle and (c) scaly and crusted lesions on the nose.

How to cite this article: Abdelmouttalib A, Hamich S, Elghtaibi FZ, Senouci K. Hydroa vacciniforme associated with EBV infection in a Moroccan child. Our Dermatol Online. 2022;13(2):211-212.

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DOI: 10.7241/ourd.20222.23

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.

Clinical Image

Blue rubber bleb nevus syndrome

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We present an unusual case of a rare vascular disorder known as blue rubber bleb nevus syndrome (BRBNS). While many cases of BRBNS occur sporadically, some have been associated with an autosomal dominant inheritance pattern with a locus on chromosome 9p [1]. Furthermore, BRBNS causes vascular malformations to occur in the skin and the gastrointestinal (GI) tract. GI bleeding is a common cause of morbidity in these patients [2]. This syndrome affects males and females in equal numbers [3].

A nineteen-year-old male presented with several soft, blue, and easily compressible papules on the trunk (Figs. 1 – 3). These papules were painful to palpation and had been present for years. The patient was referred to a dermatologist by the pediatrician as new papules described recently appeared. Additionally, an ultrasound of the trunk interpreted the areas involved as lipomas. The pertinent history includes the diagnosis of BRBNS in the patient's uncle and diagnosed with BRBNS by the dermatologist. Finally, the patient was referred

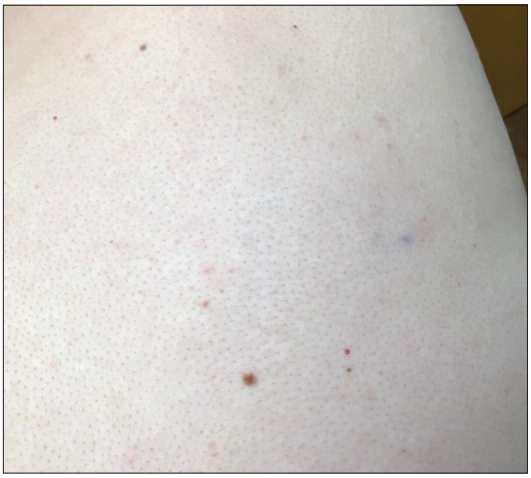

Figure 2: Soft, easily compressed, dark blue papules on the back.

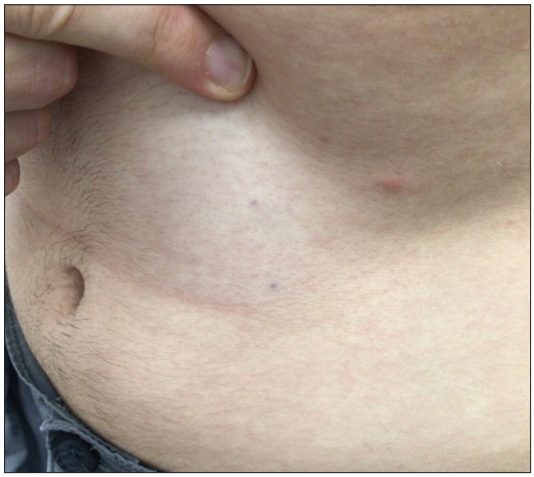

Figure 1: Soft, easily compressed, dark blue papules on the abdomen.

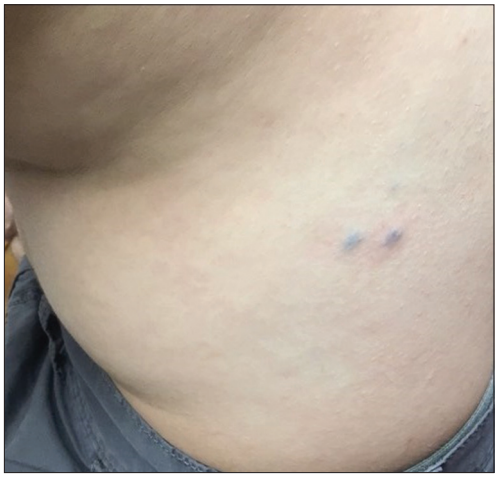

Figure 3: Dark blue papules on the flank.

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to gastroenterologist consultation for colonoscopy to evaluate possible vascular malformations in the GI tract.

Consent

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

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Clinical Image

Warty papules on the hands and feet: Acrokeratosis verruciformis of Hopf

Refka Frioui, Mariem Tabka, Sana Mokni, Azza Ghanem, Nedia Fetoui, Amina Ounallah, Colandane Belajouza, Mohamed Denguezli

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A 47-year-old female was referred to our department because of skin-colored lesions located mainly on the dorsum of the hands and feet. The patient had no diseases and had not taken continuous medication. The lesions were present at birth and had increased in number since then. Four more members of the family, including the mother and the uncle (mother's brother), had similar skin lesions. A dermatological examination revealed multiple flesh-colored, flat-topped papules, about 2–5 mm in size, which were reminiscent of flat warts on the dorsum of the hands and feet (Fig. 1). A nail examination revealed thickened nails with V-shaped nicks at their free margins on the fingers of both hands (Fig. 2). The patient declined skin biopsy. We retained the diagnosis of acrokeratosis verruciformis of Hopf (AVH).

AVH is a rare inherited disorder of keratinization caused by an abnormal ATP2A2 gene [1,2]. Familial cases indicate an autosomal dominant pattern of inheritance, yet sporadic cases of the disease have also been reported [2]. It is characterized by multiple asymptomatic, flat-topped, skin-colored papules on the dorsum of the hands and feet. Other features may include pits on the palms and soles and nail dystrophy (pearly white nails or nails with longitudinal ridges and nicks in the free edge) [3]. AVH is diagnosed clinically, which becomes easier if there are family members with similar skin findings. Sometimes, a skin biopsy is performed to assist the diagnosis. The key features on histology are hyperkeratosis, hypergranulosis, acanthosis, papillomatosis, and circumscribed epidermal elevations known as *church spires*, which are a distinctive finding [1,2].

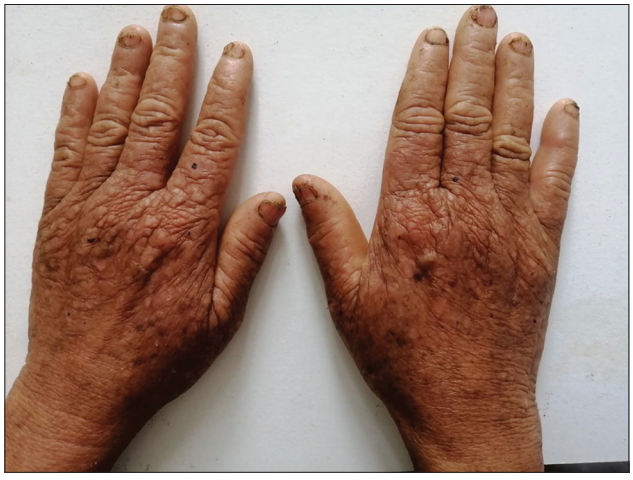

Figure 1: Skin-colored, warty, hyperkeratotic papules on the dorsum of the hands.

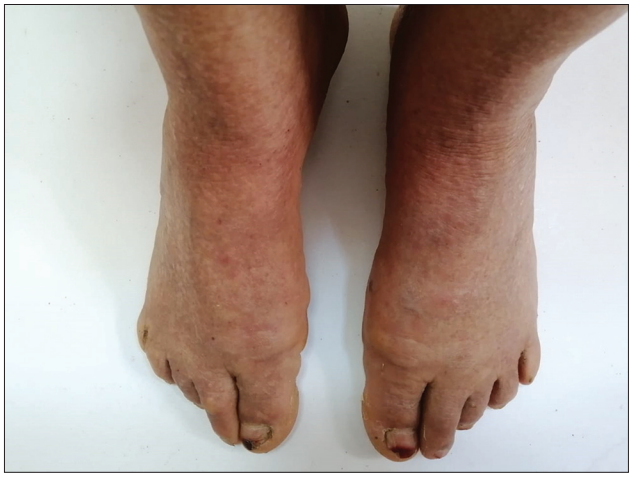

Figure 2: Skin-colored, warty, hyperkeratotic papules on the dorsum of the feet.

How to cite this article: Frioui R, Tabka M, Mokni S, Ghanem A, Fetoui N, Ounallah A, Belajouza C, Denguezli M. Warty papules on the hands and feet: Acrokeratosis verruciformis of Hopf. Our Dermatol Online. 2022;13(2):215-216.

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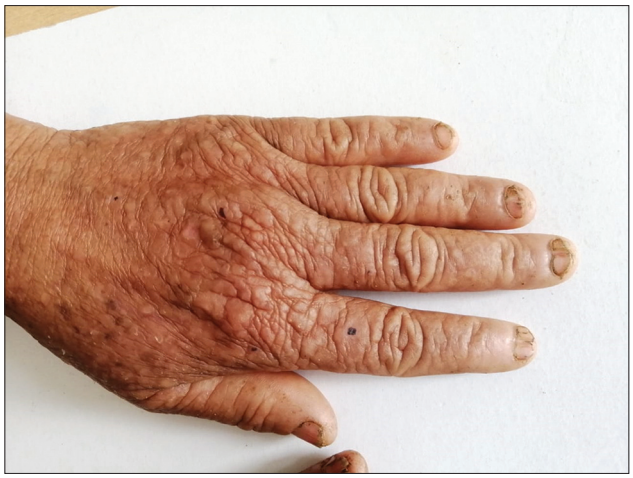

Figure 3: Thickened nails with V-shaped nicks at their free margins.

Consent

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

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

Our Dermatology Online

Study Letter

A singular emplastrum containing *Amni majus* flowers and firebird extract is able to fight the odd adverse reactions involved in the variant/subvariant Omicron of COVID-19

Lorenzo Martini[1,2], Piotr Brzeziński[3]

[1]University of Siena, Department of Pharmaceutical Biotechnologies, Via A. Moro 2, 53100 Siena, Italy, [2]C.R.I.S.M.A. Inter University Centre for Researched Advanced Medical Systems, Via A. Moro 2, 53100 Siena, Italy, [3]Department of Physiotherapy and Medical Emergency, Faculty of Health Sciences, Pomeranian Academy, Slupsk, Poland

Corresponding author: Prof. Lorenzo Martini, M.Sc., E-mail: lorenzo.martini@unisi.it

Sir,

The authors of this article desire to highlight the evidence of the insurgence 48–72 hours after the third administration of a whichever mRNA vaccine, nowadays compulsory in most of the European states and other nations of the world, of a slight flu strain tantamount to a simplest epidemical and seasonal viral occurrence from South Africa that may be treated administering as a trivial antibiotic as Tubocin (Actavis/Balkanpharma, Bulgaria) and/or a peculiar and reinforcing and immunostimulating tea based on a combination of antiviral herbs such as *uña de gato* or the firebird (a particular coneflower with the strongest antiviral potency never known hitherto); Tylenol is unnecessary.

While the corresponding authors affirm that Omicron is nothing but a variant, according to the WHO's official statement, "based on the evidence presented indicative of a detrimental change in COVID-19 epidemiology, the TAG-VE has advised WHO that this variant should be designated as a VOC, and the WHO has designated B.1.1.529 as a VOC, named Omicron."

Finally, the authors decided to treat the illness using only an emplastrum to be applied topically for ten days, abating pain and discoloration of the fingers.

At any rate, the administration of the third dose of mRNA vaccine began in many European countries some weeks ago and several cases of odd adverse reactions were reported, which have been occurring since the very first days of vaccinations, and this is suggestive that a rapid COVID-19 test may be negative or positive; symptoms are arduous to be discernable, only a prickly feeling in the throat and an evident discoloration of the extreme phalanges of the fingers of feet and hands.

This article describes the case of a 26-year-old female, a mulatta from Charleston, South Carolina who worked in the same university in which the authors co-operated. In order to work in the authors' university as cleaning staff, she had the third vaccination performed several days earlier.

Dermatologically and clinically, the following are the chief manifestations of this illness:

- a complete depigmentation of the extreme two phalanges of the fingers and toes with a severe pain whenever these upper and lower limbs hit or strike some adamantine or angulating object;
- difficulty in distinguishing savors;
- reddish eyes;
- the presence of a moderate fever only before going to bed.

The female had reddish eyes and a sort of vitiligo only in the upper limbs. She affirmed that she had felt a slight fever (37.5 °C only before going to bed, yet she used to believe it was because of the fatigue of a long

How to cite this article: Martini L, Brzeziński P. A singular emplastrum containing Amni majus flowers and firebird extract is able to fight the odd adverse reactions involved in the variant/subvariant Omicron of COVID-19. Our Dermatol Online. 2022;13(2):217-218.

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day of work in the winter). Intriguingly, while having a croissant with coffee for her coffee break, she was incapable of distinguishing the fragrance of vanilla in the croissant from the ammonia that she had used for cleaning corridors and bathrooms and, when she chewed some candy, it tasted like roast beef. She also preferred not to smoke as the flavor of tobacco was absolutely not anymore the same as before the third vaccination. Surprisingly, a rapid COVID-19 test returned negative.

The phenomenon of the depigmentation of the extremities of the limbs and the redness of the irises has already been faced and resolved by other authors [1-4] at the very beginning of the pandemic, and the explanation is now simple and clear.

Under slit-lamp biomicroscopy, the researchers revealed a prior bilateral pigment deposition on the corneal endothelium. Afterward, a pigment dispersion in the anterior chamber and a change in the color of the iris demonstrated manifold iris transillumination defects.

The patient was the volunteer who had decided to attempt all solutions to eliminate pain and the discoloration of the fingers.

She was taking a Bulgarian antibiotic with no Tylenol. (The authors deem that this was studied in order not to let her faint during work because of low blood pressure early in the morning.)

The emplastrum that the authors prepared was the recipe of the cosmetic Ceratum 500 produced by the old and reputable company Texia, Turin, Italy:

Amni majus oleolyte: 2.3 drachmas; *Spiraea ulmaria* glycolic extract: 1 drachma; *Zingiber officinalis* glycolic extract: 0.5 drachmas; *Linus usitatissimum* seed oil: 2.7 drachmas; sandarac resin (to loosen in alcohol) [5]: 1 drachma; amyl alcohol: 2 drachmas.

The emplastrum was to be applicated for ten nights to the upper and lower limbs and covered with cotton gloves.

The results were astonishing immediately after the eighth day, that is, after seven nights of applying the ointment.

The AA did not demand (or showed any interest in) the pharmaceutical approach, that was the physician's absolute demesne, as prior covenanted.

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 Letter

Active vitiligo vulgaris following the administration of the Oxford–AstraZeneca (AZD1222) vaccine against SARS-CoV-2

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Sir,

There is significant uncertainty surrounding vaccines against COVID-19. Due to the critical need, these vaccines are being developed and approved at a uniquely fast pace [1]. Currently, the approved vaccines take their action by administering the host with sequences encoding the viral spike protein. This essentially means that these gene-therapy-based vaccines, whose long-term effects remain unknown, are going to be administered globally [2]. Therefore, despite their safety and efficacy demonstrated in respective clinical trials, it is reasonable to be cautious and adopt more intensive post-marketing vigilance [3].

A forty-nine-year-old diabetic male presented with asymptomatic, rapidly growing, leukodermal patches on the scalp (Fig. 1), which began to appear suddenly fourteen days following the administration of the first dose of the Oxford–AstraZeneca (AZD1222) vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The patches were clinically consistent with vitiligo and were confirmed with their well-defined, ivory-white patches by Wood's lamp examination (Fig. 2).

There were no leucodermic patches anywhere else on the body, no family history of vitiligo, and no history of COVID-19 viral infection. After one week of reevaluation, the patch increased in size. The patient also presented with cellulitis on the right groin persistent for three days and was treated with an antibiotic with a follow-up. All baseline investigations, including a full blood count and renal and liver function tests, were normal. The patient is currently on follow-up.

Cytokines play a role in regulating the immune response and the depigmentation process in vitiligo. There is an imbalance in cytokine levels in patients with vitiligo. IFN-γ expression plays a role in the autoimmune process in vitiligo. The expression of the cytokine IFN-γ is associated with melanocyte destruction in the active phase of vitiligo lesions [4].

IFN-γ interacts with the viral receptor, resulting in the consequent reduction of several virus replicating, down-regulating genes and gene products [5]. Li et al. [6] demonstrated that IFNs are potential drug choices for SARS-CoV-2 infection.

Here, we hypothesize that patients with non-segmental vitiligo (NSV), an autoimmune skin (and mucosal) disorder, may clear SARS-CoV-2 infection more efficiently and have a lower risk of COVID-19 development. Conversely, in the case of COVID-19 development, vitiligo autoimmunity may influence the cytokine storm-related disease burden. In addition, immune activation during SARS-CoV-2 infection or COVID-19 disease may increase vitiligo disease activity. Our hypothesis is based on the shift of the immune system in NSV toward adaptive type 1 (IFNγ and CD8 T cells) and innate immune responses [7].

It is unclear whether the vitiligo in our patient was caused by vaccination, However, the temporal

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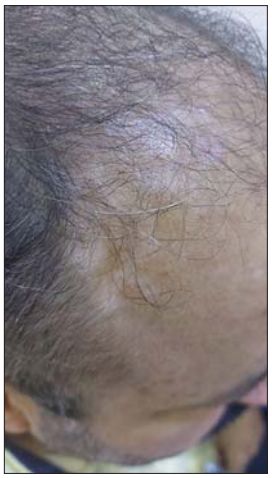

Figure 1: Vitiligo on the right side of the scalp.

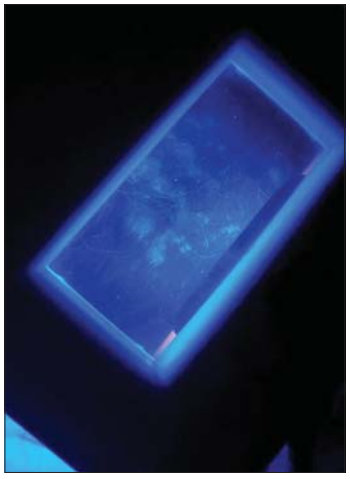

Figure 2: Vitiligo confirmed with their well-defined, ivory-white patches.

relationship between the vaccine and the development of the disease is interesting. We may, therefore, conclude that our patient had his latent vitiligo activated by the vaccine. Yet, further work is needed to demonstrate a causal relationship between vitiligo and COVID-19 vaccination.

To the best of our knowledge, this is the first reported case of vitiligo associated with the administration of the Oxford–AstraZeneca (AZD1222) vaccine.

Consent

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

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

Our Dermatology Online

Case Letter

A facial ulcer secondary to a non-invasive ventilation mask in COVID-19 pneumonia

Dassouli Ryme, Zakia Douhi, Ghita Sqalli Houssaini, Sara Elloudi, Hanane Baybay, Fatima Zahra Mernissi

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Corresponding author: Dassouli Ryme, MD, E-mail: dassouliryme@gmail.com

Sir,

An 83-year-old patient hospitalized in the intensive care unit (ICU) of the pulmonary department for chronic respiratory failure complicated by severe COVID-19 pneumonia with respiratory involvement of 50% of the lungs. The comorbidities included diabetes, uncontrolled hypertension, ischemic heart disease, Parkinson's disease, and bronchial asthma. The patient was unable to maintain adequate arterial oxygen saturation with a face mask and nasal prongs. The attending physician ordered non-invasive ventilation (NIV) and a continuous positive airway pressure (CPAP) mask was applied. On day ten of the patient's ICU stay, his attending physician noticed a grade II cheekbone ulcer.

The patient was put on a paraffin dressing. The evolution was marked five days later by a worsening in the stage of the pressure ulcer, which had become a stage III ulcer and, therefore, our opinion was requested. An examination of the patient revealed a well-adjusted, full-face mask with pressure against the zygomatic bone aggravated by the application of compresses, which further increased the aggression against the bone. A dermatological examination found two necrotic patches on both cheekbones without a peripheral detachment or inflammatory border (Fig. 1). There were no signs of bacterial infection. Upon investigation, the caregivers revealed that the CPAP mask had been left in place for nearly eighteen hours daily without formal monitoring or the inspection of the pressure areas. Fortunately, the patient's condition began to improve as did her arterial oxygen saturation. The pulmonologist was gradually attempting to remove the patient from NIV. Strict monitoring of the pressure points was recommended and the patient was put on a hydrogel dressing for five days until the necrosis was eliminated, then on a hydrocolloid dressing after the mechanical removal of the remnants of the necrosis and fibrin with good improvement of the ulcer.

The COVID-19 epidemic represents a new challenge for critical care physicians (ICU). In the context of this epidemic, the management of arterial oxygenation during critical care procedures is one of the main challenges for ICU physicians. As an effective means of ensuring satisfactory arterial oxygenation during COVID-19 pneumonia, more than 50% of patients treated in China required non-invasive ventilation (NIV) [1].

During NIV with headgear, ICU nurses should focus on interventions that help to improve the patient's comfort to maximize the acceptability of the device and minimize mask-induced skin irritability [1]. Skin pressure sores secondary to helmet application may be prevented by applying hydrocolloid dressings associated with close monitoring of the patient's tolerance to the pressure exerted by the mask [2].

The development of NIV-related pressure sores is due to a combination of pressure effects and shear forces exerted by the presence of a mask, pressure changes during the different phases of ventilation, and the tension of the mask's strap [3]. The use of oronasal masks and increased time on NIV increases the risk of

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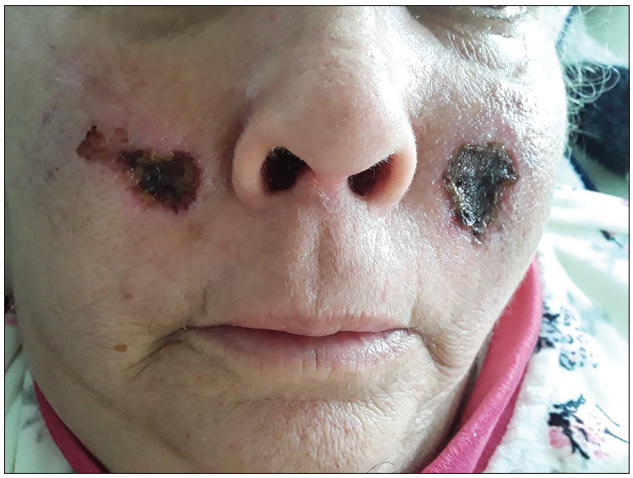

Figure 1: Necrotic eschar spots on both cheekbones without a peripheral detachment or inflammatory border.

pressure ulcer formation, as do patient factors such as age, sensory impairment, chronic skin conditions, and hypotension [4].

Oronasal masks remain the most popular interface, with a European survey revealing that they are the first choice in 70% of cases. The reasons given by respondents for their choice were the reduction of air leakage, patient comfort, and cost [5].

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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Our Dermatology Online

Case Letter

The red half-moon nail sign in a COVID-19 patient

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Sir,

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic. Several cutaneous manifestations associated with COVID-19 have been reported, including chilblains or chilblain-like lesions, erythematous rash, viral exanthem, urticaria, livedo reticularis, acral ischemia, palpable purpura, and erythema multiforme. These were thought to be useful in the early diagnosis and triage of COVID-19 patients and their risk stratification [1]. However, there are limited reports on the nail manifestations of COVID-19, including several cases of Beau lines, leukonychia, orange discoloration, and onychomadesis [2]. An exceptionally rarely reported manifestation of COVID-19 is the red half-moon-nail sign [3,4].

A 46-year-old male presented to our outpatient clinic with transversal red bands surrounding the distal margin of the nail's lunula on all of the fingernails, which the patient noticed a week previously (Fig. 1). One month before, with symptoms of fever, shortness of breath, and coughing present for three days, he had been given the diagnosis of COVID-19 following a positive nasopharyngeal swab polymerase chain reaction test. Computed tomography of the lungs revealed generalized ground-glass opacities and paraseptal emphysema in the upper lobes, and the patient was hospitalized for one week and treated with favipiravir for five days and was on oxygen therapy. He was discharged from the hospital one week later with partial remission of the respiratory symptoms. He also had hypertension, atherosclerotic heart disease, and Behçet's disease, and had been using metoprolol, amlodipine, edoxaban, irbesartan, hydrochlorothiazide, and colchicine. After two weeks of follow-up, the bands remained present and became wider (Fig. 2).

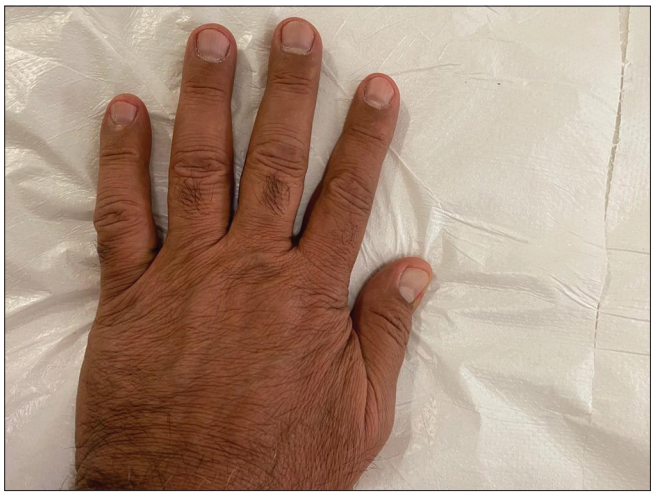

Figure 1: Transversal red bands surrounding the distal margin of the nail's lunula on the fingernails on the admission of the patients.

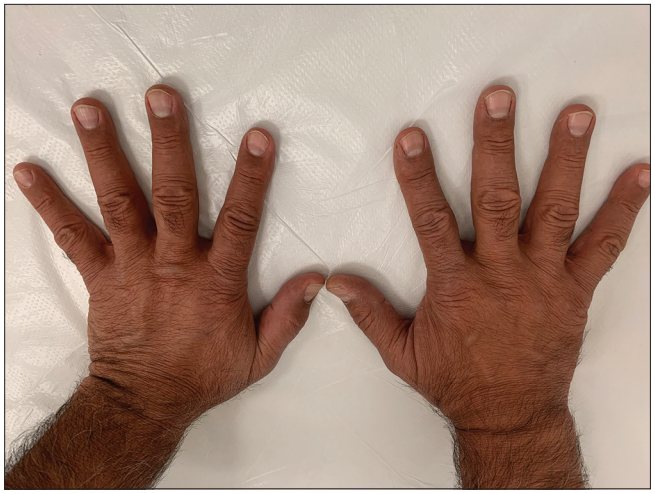

Figure 2: Two weeks later, the bands remained present and became wider.

The red-half-moon sign was first described by Neri et al. as half-moon-shaped transversal red bands after SARS-CoV-2 infection. The patient was a sixty-year-old female and the bands appeared two weeks after

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the onset of symptoms of COVID-19. The patient was hospitalized and received oxygen therapy and several other treatments, including hydroxychloroquine and lopinavir/ritonavir. As in our patient, the bands remained present and became wider after one month of follow-up [3].

Mendez-Flores et al. reported a case of the red half-moon nail sign in a 37-year-old female with COVID-19. The patient noticed the changes two days after the COVID-19 symptoms appeared, and these lasted for one week before gradually returning to normal. The patient was managed at home and required no oxygen therapy [4].

The pathogenesis of the red half-moon sign is unknown. Neri et al. proposed that localized microvascular injury secondary to an inflammatory immune response and procoagulant state may play a role. It is thought that, because of the location, the distal subungual arcade's capillary network may be affected in these cases [2,3].

We also agree that the red half-moon sign could be associated with microvascular injury or a procoagulant state connected to an inflammatory immune response. Recently, Natalello et al. reported nailfold capillaroscopy abnormalities in COVID-19 patients, including microvascular alterations in the nailfold capillary bed ranging from microthrombosis to altered capillary structures, according to the COVID-19 phase supporting this theory [5]. We also think that the persistence of the bands might be related to the severity of the disease, as both our and Neri et al.'s patients were hospitalized and had a more severe disease course than Mendez-Florez et al.'s patient.

We think that, similarly to skin findings, nail findings may be a clue in the diagnosis and prognosis of COVID-19 as well as the pathogenesis of the disease, and clinicians should search for nail findings in COVID-19 patients.

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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Our Dermatology Online

Case Letter

Kawasaki-like disease in children with COVID-19

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Sir,

In late 2019, a new type of viral infection emerged in Wuhan, China, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) and which has become the most challenging pandemic of this century.

COVID-19 has affected individuals of all ages worldwide. Epidemiological data from numerous countries show that children are a small minority of those who test positive.

Most children with COVID-19 show mild symptoms or are asymptomatic, yet new concerns have emerged, with reports on hyperinflammatory states or Kawasaki-like disease [1,2].

Kawasaki disease (KD) is a systemic vasculitis of unknown etiology that occurs mainly in children and rarely in adults [3].

Herein, we report a child with Kawasaki-like disease associated with COVID-19.

A fifteen-year-old boy presented to our department with a four-day history of high fever, vomiting, diarrhea, abdomen pain, and erythematous rash. His previous medical history was unremarkable. A physical examination revealed diffuse, erythematous, maculopapular rash, bilateral conjunctivitis, erosive hyperemia of the oral mucosa, scrotal erythema, and a deepithelialized tongue (Figs. 1 and 2).

Laboratory tests showed liver transaminases, lymphopenia, thrombocytopenia, hypoalbuminemia, and significantly increased ferritin and other inflammatory markers. A chest X-ray and ECG were normal. A nasopharyngeal swab for SARS-CoV-2 was negative. Broad-spectrum empiric antibiotics were administered.

In the meanwhile, the patient developed cardiac involvement: hypotension, tachycardia, tachypnea with oxygen desaturation, abnormal troponin T, high levels of D-dimer, and reduced systolic function on echocardiography. Treatment was switched to IG IV 2 g/kg and intravenous corticosteroid 2 mg/kg. Improvements in clinical condition, laboratory, and imaging results was noticed.

We measured anti-S-specific IgG antibodies to SARS-CoV-2 and found that the patient had high positive titers of IgG antibodies against SARS-CoV-2.

Kawasaki disease (KD) is a rare, acute pediatric vasculitis, with coronary artery aneurysms as its main complication.

Infectious triggers have been suggested in the etiology of KD due to an epidemic pattern and marked seasonality [4].

The diagnosis requires at least five days of fever and the occurrence of at least four of the five following principle clinical features [5]:

1. Extremity changes with erythema and edema of the palms and soles during the acute phase. Skin peeling may be present in the convalescent phase.
2. Diffuse polymorphic rash, including diffuse, maculopapular erythroderma or erythema multiforme-like.
3. Bilateral nonexudative bulbar conjunctivitis, typically sparing the limbus.
4. Oral mucosal changes with cracked lips, oral and pharyngeal erythema, and the “strawberry tongue” (erythema of the tongue with prominent fungiform papillae).

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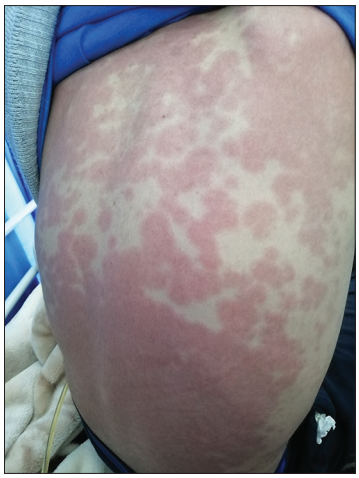

Figure 1: Diffuse, erythematous, maculopapular rash.

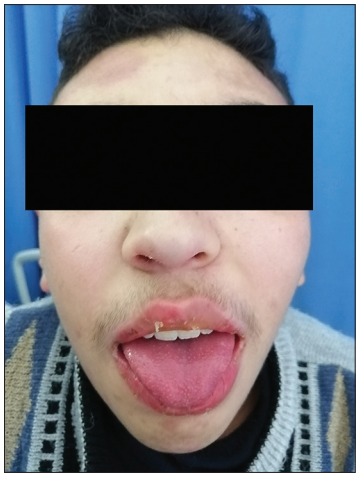

Figure 2: Erosive hyperemia of the oral mucosa.

5. Cervical lymphadenopathy, typically unilateral, at least 1.5 cm in diameter.

Recently, several cases of Kawasaki-like disease have been reported in various locations that coincide with the SARS-CoV-2 pandemic, producing concerns about the association of COVID-19 with KD.

COVID-19, caused by SARS-CoV-2, is a viral disease characterized by the inflammation and infection of endothelial cells.

The presence of viral elements and inflammatory cells within endothelial cells and the evidence of endothelial cell death suggests that SARS-CoV-2 infection facilitates endotheliitis through direct viral involvement and an inflammatory response [6].

We present our patient with KD-like disease associated with SARS-CoV-2 infection. To date, there has been no clear answer to the inquiries concerning Kawasaki-like disease in children with COVID-19. Therefore, we await further studies to explain its clinical course and pathophysiology.

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 Letter

Spinulosis revealing dermatomyositis relapse: A new description of Wong's dermatomyositis

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Sir,

Dermatomyositis (DM) is a systemic autoimmune disease affecting characteristically the skin and muscles. The typical cutaneous features include Gottron's papules, a heliotrope rash, and edema of the eyelids. Spinulosis is an unusual sign, not raising suspicion for a DM diagnosis. Herein, we report a case of DM relapsing as Wong's dermatomyositis (WDM) as an isolated spinulosic eruption.

A 42-year-old female presented with a pruritic papular eruption involving both arms and the back persistent for the last two months. An anamnesis included a history of DM diagnosed five years earlier, in complete remission under the administration of corticosteroids for three years. A physical examination revealed erythematous and violaceous scaly plaques resulting from confluent follicular papules, resembling pityriasis rubra pilaris (PRP) on the lateral sides of the arms (Fig. 1) and the upper back (Fig. 2). Muscular testing was subnormal and the general status was conserved. Laboratory findings revealed a high level of blood CPK (3×N), LDH (4×N), and ASAT (3.5×N), while electromyography displayed myogenic changes. A muscular biopsy revealed necrotic muscular cells with perifascicular atrophy and lymphocytic inflammatory infiltrate. A histological skin examination found follicular hyperkeratosis with perifollicular interface dermatitis and interstitial mucin deposits in the dermis (Fig. 3). Based on these findings, the diagnosis of WDM was retained. A malignancy workup was negative. Corticosteroid therapy was initiated with prednisone 1 mg/kg/day in combination with hydroxychloroquine 200 mg twice a day, resulting in a remarkable clinical and biological improvement.

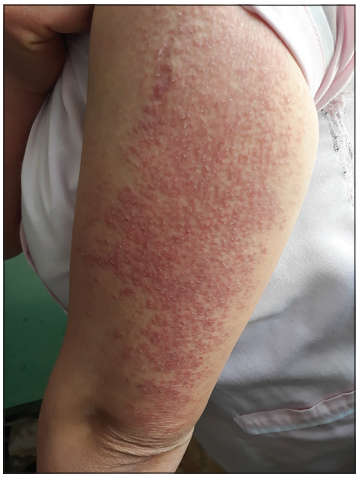

Figure 1: Confluent spinulosic scaly papules resulting in the plaque on the arm.

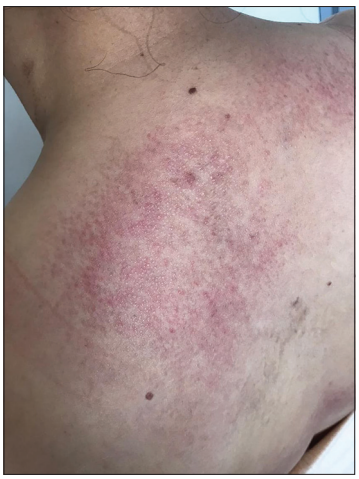

Figure 2: Violaceous plaque with follicular papules on the upper back.

WDM is characterized by the presence of PRP-like follicular papules in a patient with dermatomyositis

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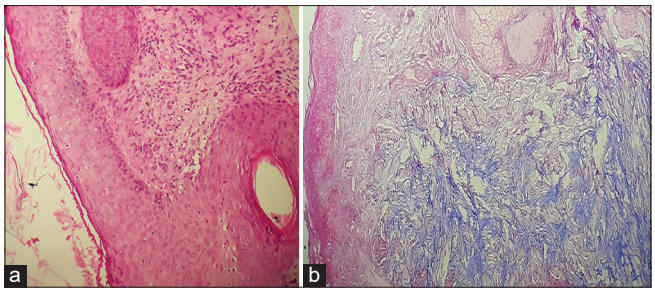

Figure 3: (a) Perifollicular interface dermatitis (b) with dermal mucin deposits (Alcian blue staining).

(DM) [1]. Some authors suggest that this exceptional presentation should be considered a true association of DM with PRP rather than a variant of DM [2]. In this rare form, spinulosic lesions are mainly located on the trunk or limbs with occasional palmoplantar keratoderma [2]. Follicular lesions are usually associated with the typical signs of DM but some cases of isolated PRP features related to WDM have been reported [3]. To our knowledge, none has been reported as a relapse of a previous classic DM. Our patient relapsed showing spinulosic lesions absent in the prior episode five years earlier, not displaying at this time any classic cutaneous signs of DM. Such puzzling presentations are very unusual and may be confusing for physicians. In our patient, the diagnosis was retained on the basis of the histopathological findings of interface dermatitis and interstitial mucin deposits in the dermis, increased serum levels of muscle enzymes with a myogenic electromyographic pattern, the typical muscular histological changes, and a medical history of DM diagnosed five years earlier. In WDM, histology usually reveals follicular hyperkeratosis with keratotic plugs filling dilated follicular infundibula, which may raise several differential diagnoses, including PRP, discoid lupus erythematosus (DLE), and, to a lesser degree, follicular psoriasis and keratosis pilaris [4]. Interface dermatitis and mucin deposits, as in our patient, are the hallmarks of distinguishing DM from PRP, follicular psoriasis, and keratosis pilaris. Although these findings may also be observed in DLE [4], in our patient, there were no clinical or histological arguments supporting DLE rather than a diagnosis of DM. Myositis as, well as interstitial lung disease, appears to be comparable to the classic variant [5]. The risk of associated internal malignancy is unknown but could be lower than in the classic form [4]. Treatment and management do not differ from classic dermatomyositis.

Consent

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

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

Our Dermatology Online

Case Letter

Unilateral bullous pemphigoid in a hemiplegic patient

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Sir,

Bullous pemphigoid (BP) is the most common autoimmune bullous dermatosis, mainly affecting the elderly. Its association with neurological diseases has been reported for several years in several studies, including with strokes.

We report a new case of unilateral BP in a hemiplegic patient.

A 78-year-old patient with a history of hypertensive and ischemic heart disease and ischemic stroke three years ago was admitted for pruriginous bullous dermatosis evolving for one month prior to admission. A general examination revealed right hemiplegia with facial involvement and aphasia. A dermatological examination found localized erosions on the paralyzed side of the body, without urticarial or bullous lesions. Nikolsky's sign was absent and the rest of the clinical examination was without abnormality (Figs. 1a – 1c). A skin biopsy revealed a skin coating widely ulcerated on the surface without eosinophilic infiltrate. Indirect immunofluorescence was positive at 1260. The diagnosis of BP was retained and the patient was started on a strong local dermocorticoid with a good evolution and the disappearance of the lesions after two months.

BP is an autoimmune bullous dermatosis clinically characterized by large, tense bubbles resting on erythematous skin and, histopathologically, by subepidermal bubbles with an eosinophilic infiltrate. Immunohistochemically, there are immunoglobulin (Ig) G and C3 deposits in the basal membrane of the epidermis. The initiating factor for the development of BP antibodies is not fully understood. Several studies have revealed the association of BP with neurological disorders such as stroke, dementia, Parkinson's disease, multiple sclerosis, and epilepsy. The risk of association is greater if the neurological disorder is in a well-developed state [1-3]. However, the exact mechanism

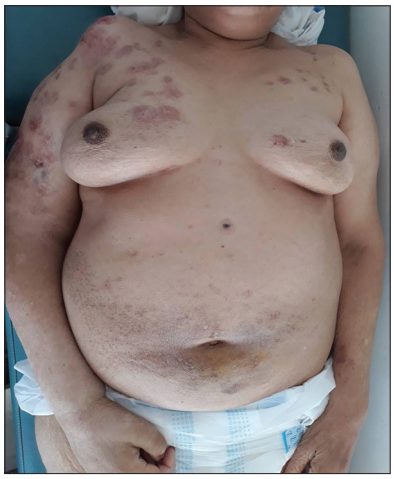

Figure 1a: Localized erosions on the paralyzed side of the body, without urticarial or bullous lesions.

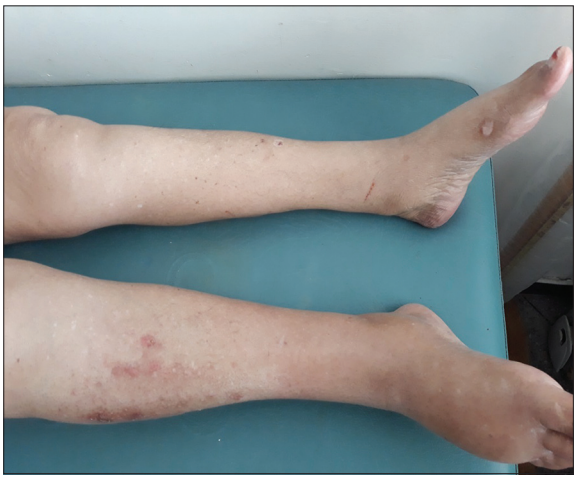

Figure 1b: Localized erosions on the paralyzed side of the body, without urticarial or bullous lesions.

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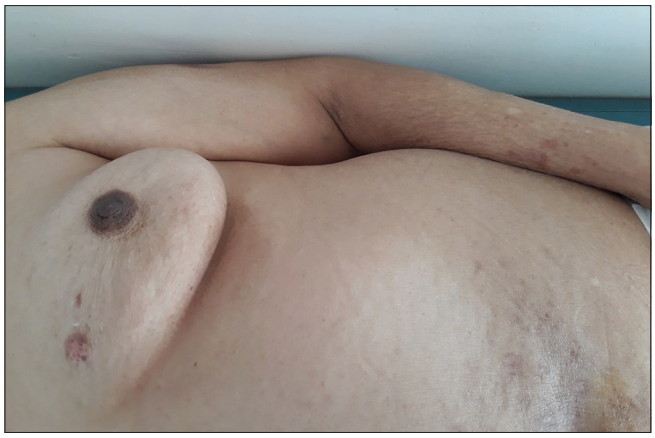

Figure 1c: Localized erosions on the paralyzed side of the body, without urticarial or bullous lesions.

of this phenomenon remains an enigma. It might be explained by a decrease in blood in the paralyzed side with altered neurological functions associated with a defect in the contraction of the muscles or it might be an adverse effect from the drugs used for neurological diseases [4]. Further studies are needed to better support this causal link.

Keep in mind the diagnosis of BP in patients with chronic neurological diseases if faced with a bubble or erosive lesion.

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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Our Dermatology Online

Case Letter

Double-branched transungual acquired fibrokeratoma

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Corresponding author: Soumaya Hamich, MD, E-mail: hamich.soumaya@gmail.com

Sir,

Acquired fibrokeratoma (AFK) is a rare benign skin tumor that usually manifests as a slow-growing solitary nodular lesion of the digit. It may appear on the fingers, toes, palms, or soles.

Herein, we report an atypical case of AK characterized by its transungual evolution and double-branched form.

A sixty-year-old male with a medical history of renal failure due to a chronic kidney disease of unknown etiology consulted for the evaluation of two lesions of the first right toenail evolving for the past one year.

The patient recalled a trauma one year before and the subsequent appearance of a cone at the proximal nail fold. Two months later, he noticed another cone emerging from the first. Both lesions were slow-growing and led to the consultation at our department.

A dermatological examination revealed two branching, longitudinal, and flesh-colored cones arising from the nail bed (Fig. 1), firm in consistency and with smooth surfaces on palpation.

Keratotic materials were observed at the tips of the cones.

Both cones seemed to have the same place of emergence and were associated with a dissection of the nail plate. No pain or other symptoms were reported by the patient. A physical examination revealed no other lesions and there were no signs of tuberous sclerosis (Bourneville syndrome).

A dermoscopic examination found two filiform structures, 2 mm thick, emerging from the nail plate, with whitish-yellow and erythematous areas (Fig. 2).

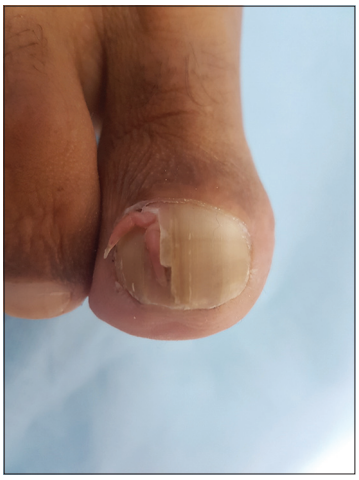

Figure 1: The two branching, longitudinal, and flesh-colored cones arising from the nail bed of the toenail.

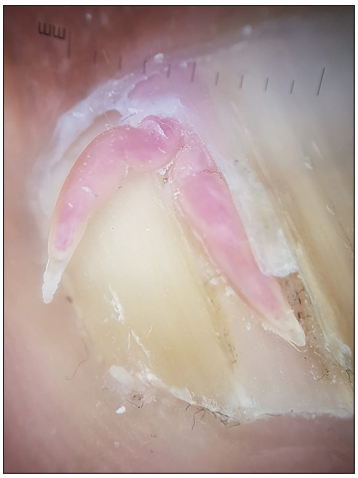

Figure 2: The two filiform structures, 2 mm thick, emerging from the nail plate with whitish-yellow and erythematous areas.

We performed a complete excision of the lesions. After retracting the proximal nail fold, we found that the two cones were fused and their basal attachment was located under the proximal matrix (Fig. 3).

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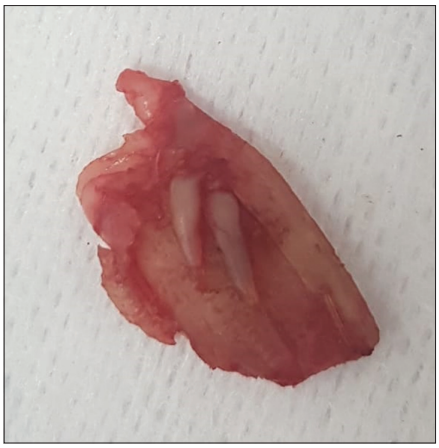

Figure 3: Surgical excision of the lesions, in which the two cones were fused and their basal attachment was located under the proximal matrix.

Histologically, an acanthotic, papillomatous epidermis was present, surmounted by orthokeratotic hyperkeratosis. The dermis was characterized by fibrosis, thick-walled capillaries, and a mononuclear inflammatory infiltrate.

AF was first described in 1968 by Bart et al. [1], initially in the fingers but also in the palms, toes, and soles. Its etiology is presumed to be trauma or repetitive irritation, as in our case. Two cases were reported after a staphylococcal infection [2]. Qiao et al. reported a case of AK associated with cyclosporin use in a renal transplant patient. The increased presence of factor-XIIIa-positive dermal dendrocytes has also been suggested as a possible causal factor [1].

Hwang et al. classified the tumor into three subtypes according to the origin: periungual, subungual, and intraungual (or "dissecting" ungual) [3]. Urbina proposed the term *transungual* as another subtype, which fits more properly our case than *intraungual* [4] as the lesions in our patient did not develop through the whole thickness of the nail along the plate.

A rare variant known as multibranched acquired periungual fibrokeratoma (APF) was first described in a case report by Moriue et al. in 2014 [5]. Two more cases of multibranched APF were described by Goktay [6], who observed 2–5 mm thick multibranched structures protruding between the cuticle and the nail plate. To our knowledge, our observation is the first case of multibranched transungual acquired fibrokeratoma.

Owing to the diversity of vascular formations and collagen fiber accumulation, dermoscopic findings may often vary in different cases [1]. A central homogeneous pale-yellow area surrounded by a white, scaly, hyperkeratotic collarette was reported. Other authors described clumps of red homogenous lacunae divided by a white meshwork-like keratotic septum [7].

Histopathologic findings are hyperkeratosis, acanthosis, focal hypergranulosis of the epidermis, and the presence of thick bundles of collagen in the dermis with dilated capillaries oriented along the longitudinal axis of the tumor.

The main differential diagnosis is common warts, superficial acral fibromyxoma, a supernumerary digit, Koenen's tumor, and cutaneous horns.

Acquired ungual fibrokeratomas do not regress spontaneously. The first-line treatment is surgical excision. The tumor has to be completely resected along with the basal attachment. Local recurrence is rare but may occur if a partial excision or curettage is performed.

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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Our Dermatology Online

Practical Issue

PowerPoint presentations (PPP): From A to Z

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ABSTRACT

PowerPoint presentations (PPPs) remain one of the most popular and efficient tools for education, teaching, and training in medicine and other sciences. Despite its widespread use, not all know its secrets and have mastered its techniques. The aim of this report is to provide an updated review for dermatologists and other healthcare providers about PowerPoint presentations.

Key words: education; dermatology; medicine; teaching; training

INTRODUCTION

In the last several decades of the twentieth century, an overhead projector was a great option for giving presentations. One could write the main points on a transparent sheet and project it onto a screen, including drawings and graphs. Alternatively, slides incorporating such information could be projected on a screen with a carousel. The limitations included carrying these and the inability to share or make changes later. The 1990s heralded the era of PowerPoint presentations (PPPs), which have relegated these to history. Toward the end of the second millennium, when the digital mode took over numerous tasks, PPPs became the *sine qua non* in almost every form of activity.

PPPs refer to presentations made with a PowerPoint slideshow projected from a computer. It allows for the systematic presentation of a clinical subject followed by structured feedback from the audience.

PPPs carry numerous advantages as it is a condensation of the source material by which the reader may assimilate information in a short time and record it through screenshots and video recording.

Some obstacles, however, may limit the delivery of an effective presentation, for instance:

- Lack of clarity;
- Not knowing the supervisor's expectations [1];
- Limited data outlining the established standards for effective presentations [2].

This article outlines key points constituting an effective PPP as an efficient mode of skills assessment to promote competency-based medical education.

Preparation

In the time allotted for a PPP, one has to condense surplus information into a format that fulfills the criteria of being appropriate, accurate, comprehensible, well-executed, interesting, and memorable [3].

Content

1. Layout

The first slide should display the title, the presenter's name, and affiliation. This should be followed by an introductory slide and one outlining the main contents [4]. The last slide should be the concluding slide.

Each slide should be self-explanatory, with a title and a uniform, dark background (blue, green, or purple) [5].

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2. Font characteristics
Size: It is preferable to use a minimum of an 18-point font for the slide text and a minimum font size of 36 points for the slide title [6] (Fig. 1).

However, this may vary depending on the place of presentation. For instance, if the presentation is shown in a large room in front of several hundred people, fonts should be extra-large to enable those in the back to read without difficulty. In a small room, medium-to-large fonts should suffice.

Character: A sans-serif font such as Arial, Helvetica, or Tahoma should be used, as Times New Roman may be hard to read [7].

Color: A contrasting color of the text as compared to the background makes the presentation more readable. The title font and the keywords or sentences should be highlighted with a different color.

Format: One must write telegraphic sentences, possibly except for the conclusions. Articles such as *a*, *an*, and *the* should be skipped. Bullets may be used to highlight different points.

One must be wary of using:
- More than two different types of fonts;
- More than four different font colors;
- More than six lines of text per slide;
- More than eight words per line of text;
- Flashy colors or templates of fonts or slide layouts [8].

3. Charts, graphs, and tables
Whenever possible, one must use graphs and charts instead of tables and simplify the presented data.

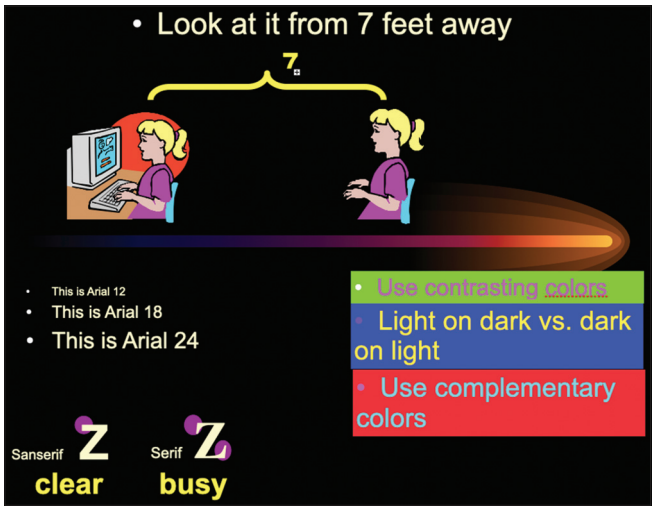

Figure 1: Important tips for slide formatting and content [11].

4. Images
Faces, if shown, should be masked to prevent identity threat. Pictures depicting treatment should show the same area before and after therapy. When scanning an image for the full screen, the image should be scanned at 480 × 640 pixels at 72 to 96 dpi in JPEG format [9].

5. Animation
An animation tool may be employed to display texts and graphics entering or exiting the slide in a lively manner. However, one must keep in mind that excessive animation may be both superfluous and distracting [10].

6. Inserting screen captures and screen recordings
PowerPoint 2013 and later versions allow for the inclusion of static screen captures or screen recordings from one's computer device, serving as a useful tool for enhancing the scope and quality of the presentation.

7. References
It is ethical to acknowledge the resources used for compiling the content and ensure no infringement of copyright laws.

ON THE DAY OF PRESENTATION

Table 1 and Table 2 contain some remarks for a better presentation.

One may arrive early on the day of presentation to test equipment to be used.

Making backup copies in at least two different places with printed handouts is helpful in the rare event of equipment failure, in which the presentation may have to be given without visual aids.

A useful tip during rehearsing is to visualize the audience sitting in front of oneself and imagining delivering the presentation with enthusiasm and

Table 1: Acceptable format of a presentation based on an original paper [14]

1.	Practicing in an environment similar to the one in which the talk will be given.
2.	Memorizing key sentences within the outline rather than learning it word for word.
3.	Ensuring to remain within the time limit, so that the time is one less thing to worry about.
4.	Wearing professional-looking and comfortable clothes, not a new outfit.
5.	Avoiding overeating and limiting coffee intake on the day of the presentation.

Table 2: Tips on remaining calm and confident on the day of the presentation [15]

Slide	Comment
Title slide	Full title, last names, and initials of all listed coauthors and affiliation (s).
Conflicts	Personal conflicts of interest.
Introduction	Brief background stated in bullet points. Clear aim of the study or research question.
Methods	Brief and one-line bullet points. No more than six lines per slide.
Results	Brief lines of numeric data. No more than six lines per slide. High-resolution graphs or images
Study limitations	Important to mention to avoid a negative discussion after the presentation.
Conclusions	Brief statements outlining the key messages.
Acknowledgements	Sources and co-authors.

leaving the room knowing that it was a first-rate presentation [12]. Practicing with a friend or family member who may provide healthy feedback is also worthwhile.

Some general principles of a systematic clinical presentation are as follows:

- Giving an outline at the beginning and having a good introductory or outline slide to grab the attention of the audience;
- Following a logical sequence: starting with broader, more general topics and going progressively deeper;
- Speaking slowly, loudly, and clearly in an engaging tone, giving appropriate pauses in between;
- Discussing only one concept per slide;
- Each slide taking around 45 to 60 seconds for discussion, with not more than fifteen slides for a ten-minute talk [9];
- Moving at appropriate times during the presentation and ensuring that gestures are natural and in sync with what is being said;
- Not apologizing for minor interruptions in the flow of the presentation;
- Maintaining good eye contact with the audience by glancing at their faces for 3–5 seconds and then moving on to the next person [12];
- Observing the audience for any lapse of attention due to excessive content and trying work on that for future presentations;
- Stories that appeal to the audience's emotions, particularly if delivering lectures for students, helping to bring the point across;
- Concluding by restating the main objective and key supporting points and prompting for questions.

When asked a question, one must first thank that member of the audience and keep answers short and succinct [13].

During conferences, short times are often allotted to the invited speakers, who have to presume that the audience possesses a basic knowledge of the subject and expects to listen to novel or exciting content. One may present a brief introduction and swiftly proceed to emphasize the latest innovations and the scope for further research, which will consistently hold the audience's attention [14].

CONCLUSION

With educational technology and smart classes becoming increasingly popular, education becomes more interactive, engaging a large number of students in taking advantage of the digital mode. Clinical presentations, if prepared and presented proficiently, may significantly augment teaching, learning, and assessment in an engaging and comprehensive manner, thereby promoting the multi-faceted professional growth and development of the clinician.

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Obituary

Prof. Dr. Antonio Guzmán Fawcett (1954-2020)

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Figure 1: Prof. Dr. Antonio Guzmán Fawcett (1954-2020).

Prof. Dr. Antonio Guzmán Fawcett was a member of the scientific board of the journal Our Dermatology Online (Fig. 1).

He was born in Santa Marta, Colombia, in 1954 and died after a long illness in Asunción, Paraguay, on October 8, 2020. He was a doctor from the University of Cartagena in 1981 and trained as a dermatologist at the Dr. Ladislao Dermatological Center in Easter, in Mexico City (1983-1985), under the tutelage of Dr. Fernando Latapí and very closely with Roberto Arenas. He marry Dr. Elisa Isabel Cubilla, originally from Paraguay, on April 27, 1985. From February 1985 to March 1986, he studied dermatological surgery and stomatology at the Hospital das Clinics, of the Faculty of Medicine of the University of São Paulo, under the tutelage of Professor Sebastião Sampaio. He was a co-founding member and general coordinator of the Stomatology Chapter of the Ibero-Latin American College of Dermatology (2016-2018). His dermatological areas of interest were very varied, from his articles and book chapters we can point out the following: "Local anesthesia in dermatological surgery", "Cutaneous lupus erythematosus in children", "Surgery of the oral cavity, surgical therapeutics, oral pathology in Pediatrics" and "Oral signs of tropical, fungal and parasitic diseases".

He got master's degree in geriatrics in Spain about diseases of the oral and genital mucosa.

After their stay in Brazil, Antonio and Elisa decided to settle in Asunción and started a family with their two sons, Julián Fernando and José Antonio. He held different positions: Director of PRAMED CILAD (Medical Care and Educational Program); General Coordinator of the Stomatology Chapter of the Ibero-Latin American College of Dermatology 2016 -2018; Full Member and Ex-President of the Paraguayan Society of Dermatology; Honorary Member of the Mexican Academy of Dermatology; Honorary Member of the Bolivian Society of Dermatology; Honorary Member of the Venezuelan Society of Dermatology; Corresponding Member of the Colombian Association of Dermatology.

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He wrote a large number of poems, some of them collected in the work Piel, prose and Latin American poetry (Piquero Martin J, Guzman Fawcett A, Rondon Lugo A and Poletti Vázquez, 2005), presented at the XVI Congress of the cilad in Cartagena.

ODA A UNA PSORIASIS

Tengo esperanzas, oh tegumento mío,
el dermatólogo me prescribió un jabón,
además de ungüento de vaselina tibio,
y me que exponga a ratos al inclemente sol.
Por eso te decía: hay esperanza,
con las prescripciones que ayer yo le escuché.

"De parir queratina, tu piel no se cansa,
y eso evitaremos con la indicación que haré",
Eterno descanso al Dr. Guzman.

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2. https://piel-l.org/blog/35973

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Obituary

Prof. Christopher Magala Ndugwa (1940-2022)

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Figure 1: Prof. Christopher Magala Ndugwa (October 21, 1939 - January 21, 2022).

Prof. Christopher Magala Ndugwa was a member of the scientific board of the journal Our Dermatology Online (Fig. 1).

Prof. Christopher Magala Ndugwa, a Sickle Cell specialist and Board member of the Uganda Sickle Cell Rescue Foundation (USCRF).

Prof. Ndugwa has been a renowned Pediatrician, a pioneer of the Mulago Sickle Cell clinic and former head of Mulago Pediatrics department.

He was also the Chairman of the Polio Eradication Campaign in Uganda and has been running a sickle cells clinic at Nakivubo which is considered a role- model clinic for sickle cell Anemia in the East African region.

Until his untimely death, Prof Ndugwa is believed to have been Uganda's most experienced sickle cell expert. He has been guiding the strategic direction of USCRF so as to enable impactful service delivery.

Long servinge Makerere University Professor of Paediatrics and Child Health.

Born in 1940, was an icon of Sickle Cell Treatment and prevention, a Grand Father of Paediatrics and former Head of Department of Paediatrics and Child health at Makerere University College of Health Sciences.

Thanks to him was learned the common causes of anemia in children.

His other passion was in the care of his patients with Sickle Cell Disease.

He left a legacy of well-trained hematology and oncology specialists like Dr. Phillip Kasirye, Dr. Deo Munube, Dr. Ruth Namazzi, Dr. Joyce Kambugu, Dr. Peter Wasswa, Dr. Joseph Lubega.

Rest in peace

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