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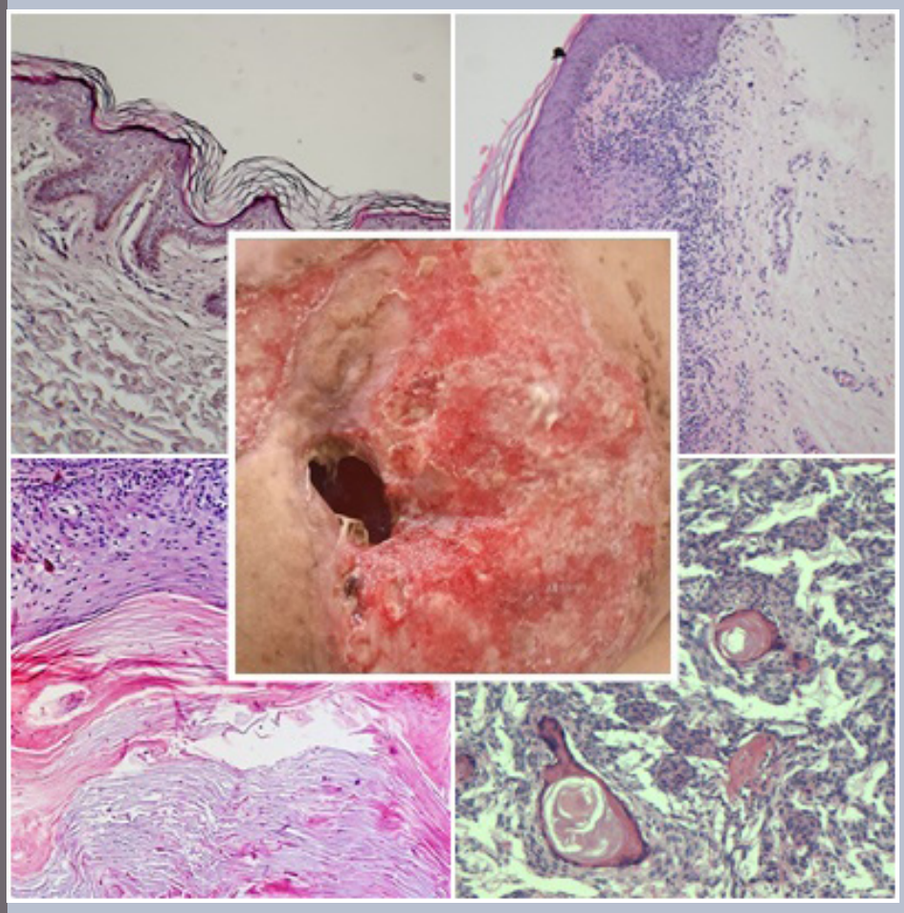

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Original Article

Effectiveness of the active ingredients (Capixyl, Procapil, and rosemary extract) of the Trust® tonic for the treatment of androgenetic alopecia in comparison to minoxidil

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ABSTRACT

Background: Androgenic alopecia (AGA) is a common hair loss disorder seen in both males and females and continues by presenting thinning and miniaturization because of androgens, genetics, extracellular matrix (ECM) protein destruction, and micro-inflammation. The most common treatments for AGA used in males are minoxidil and finasteride. These drugs have an effective role in the recovery and retardation of hair loss; however, there are different side effects and limitations to their efficacy. **Materials and Methods**: In this research, we compared the effectiveness of the Trust tonic's active complex, Capixyl, Procapil, and rosemary extract (CPR), and 2% minoxidil solution in reducing hair loss and stimulating hair growth. The study was conducted on two groups of male subjects with an average of 45 years for twenty-four weeks using 1 ml of each solution everyday in the morning and evening. **Results**: The results of this study revealed that the subjects treated with the Trust active complex, obtain significantly higher self-assessment (64% in the Trust tonic group and 36% in the minoxidil group) and the staff assessment scores of hair growth improvement in 60% and 30%, respectively, for the Trust tonic group and minoxidil group. Furthermore, the scores obtained by the photographic method also revealed a 57% and 8% improvement in hair growth in the patients who used the Trust complex and minoxidil, respectively. **Conclusions**: The active complex of the Trust tonic solution could be an effective alternative for minoxidil in the treatment of AGA.

Key words: androgenic alopecia; Trust tonic; minoxidil; hair growth

INTRODUCTION

Hair loss is the transformation of terminal hair into vellus hair (thin, short, light-colored hair that usually goes where it naturally lacks hair) [1-3]. These conditions occur gradually and to varying degrees in both males and females. The most generic form of hair loss has a genetic origin and is related to androgens (steroid hormones responsible for secondary traits) [4-7]. Thus, androgenic baldness, or common hair loss, is a natural phenomenon related to aging and occurs in both sexes [2,8]. Studies have revealed that mammalian hair follicles have three growth phases: the anagen (growth), catagen (transfer), and telogen (rest) [9,10]. The duration of each phase varies depending on the person's anatomy, nutritional and hormonal status, and age. More than forty years ago, Hamilton found that androgens were the most crucial factor in male-pattern hair loss [11]. Testosterone is an androgen produced by the gonads and adrenals and plays a vital role in controlling human hair growth. The pattern of hair loss is more complex for females than for males. Therefore, the term *male-pattern baldness* is employed for patterns of baldness that begin at the crown of the head and move forward or begin at the forehead and move backward until a pattern of baldness is created. Post-menopausal females show

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this pattern of male baldness [12]. The main cause of hair loss, despite various stimulants, is the shortening of the anagen to the telogen phase of hair growth. As the balding process progresses, the ratio of anagen to telogen hair decreases [13]. There are common and effective treatments for all types of hair loss. The use of these compounds may prevent hair loss or reduce the rate of hair loss. The common treatments for hair loss include herbal supplements reducing or preventing hair loss orally, topically, and surgically [14]. For instance, the combination of biochanin A, acetyl tetrapeptide-3, and ginseng extract versus 3% minoxidil was employed in the latest research for the potential treatment of AGA by decreasing side effects and increasing patient adherence to this complex [15]. These herbal extracts in a combination with peptides created an increase in hair matrix proteins such as collagen and laminin, strengthening hair anchoring, hair growth, and hair follicle size [16]. The common treatments for age-related hair loss include minoxidil, finasteride, and others. Minoxidil is an over-the-counter drug that helps hair regrowth and slows down hair loss, yet it has side effects such as inflammation and itching of the scalp and the growth of unwanted hairs on the scalp, face, and areas adjacent to the treated area. Finasteride is also a prescription drug prescribed as oral pills. Similarly, this compound promotes new hair growth and slows down hair loss six months after administration. Nowadays, however, due to the side effects related to these two drugs, other effective actives have been employed to treat AGA. For this purpose, we evaluated the efficacy of the three active compounds (Capixyl, Procapil, and rosemary extract, called the CPR) employed simultaneously in the formulation of Trust tonic solution as a beneficial complex for the treatment of androgenic alopecia in comparison to 2% minoxidil.

MATERIALS AND METHODS

Materials used to formulate the active treatment solutions comprise all the active ingredients and the basic ingredients of a formulation. The Trust's tonic solution formulated by the Mahloran Cosmetics company prepared with the active ingredients of Capixyl, obtained by the Lucas Meyer Cosmetics company (Canada), in 1% w/w, Procapil, obtained by the Sederma company (France), in 1%, and rosemary extract, prepared by the Giah Essence Phytopharma company, in 0.5%. Other basic ingredients, as well as water, are added to reach 100% of w/w. Furthermore, the minoxidil compound in the concentration of 2% was purchased from a local drug store in IRAN. All devices used in this study included a pH meter (Benchtop Meter, PH500, CLEAN, China), a digital scale (PS 600.R2, RADWAG, Poland), a beaker, a mixer (MS 280D, MTOPS, Korea), and a heater-stirrer (MS300HS, MTOPS, Korea).

In this study, two groups of twenty healthy males with an average age of 45 years were selected. All participants had stage II–V androgenic alopecia based on the Norwood–Hamilton classification (Table 1) [17, 18]. Patients with dermatological disorders such as lung disease or cardiovascular, liver, or kidney disorders and patients on steroids, antihypertensives, cyclosporine, beta-blockers, or antidepressants [19] were excluded from the research. All clinical investigations were conducted according to the principles of the Declaration of Helsinki. All subjects were trained to use the test compounds and instructed in the topical use of these compounds on hairless areas. All subjects were asked to cut their hair to the same length and form, use the same shampoo, and standardize all variables during the treatment period. The subjects were requested to use the Trust tonic active ingredients (Capixyl, Procapil, and rosemary extract) in one group and minoxidil as the comparative active in the other group. These compounds were applied to the hair everyday in the morning and evening with the fingertips in 1 mL of volume each time for a period of twenty-four weeks. The subjects in both groups were unaware of the materials employed in the formulation of the treatment compounds, and the numbered solutions provided them with no clues.

Efficacy Measurements

After preparing the subjects and solutions, they were asked to answer the questions (Table 2). This questionnaire regarded the self-assessment of hair

Table 1: Norwood–Hamilton classification of hair loss [17,18]

Type I:	There is no recession in the frontotemporal region of hair or with a little recession.
Type II:	There is a symmetrical triangular recession area in frontoparietal regions with a hair loss and hair sparse in the middle of the frontal area of the head.
Type III:	A deep, lateral asymmetrical hair thinning, and sparseness is evident in frontotemporal regions.
Type IV:	A deep symmetrical frontotemporal recession extends posteriorly with thinning of the hairs in the vertex area typically represents by baldness.
Type V:	An extensive recession of hairs in frontotemporal and frontal regions of the head with the sparseness of the crown hairs.
Type VI:	Increase of hair loss in the hairband region with the frontotemporal sparse region.
Type VII:	The severe form which starts from the upper part of the ears and extends backward. Only the horseshoe-shaped area of hair at the posterior side of the head remains

density, hair growth and length, the hair loss rate, and satisfaction after every four weeks. Finally, each subject informed the researchers about their satisfaction with a rating scale varying from -3 to +3.

In addition, the researcher staff assessed the efficacy of the formulation and amount of hair growth and density in the hairless area with seven-point scaling criteria, with +3 meaning improvement to -3 meaning worsening (Table 3).

Also, a global photographic evaluation with a seven-point scale was employed to compare the top and front area of the head skin before and after 24 weeks of administering the Trust tonic and minoxidil topically. For this purpose, some pictures were taken from the front and top of the hair of all subjects including the group treated with the Trust tonic and the group treated with minoxidil before and after the treatment. Then, the growth rate and the efficacy of the Trust tonic were compared with minoxidil and the results were reported.

Ethics Statement

This manuscript describes recent work and is not under consideration for publication by any other journal. All authors approved the manuscript and this submission.

RESULTS

The primary aim of this study was to assess the effectiveness of the Trust tonic's active ingredients (Capixyl, Procapil, and rosemary extract) in decreasing or eliminating hair loss as well as improving or increasing hair growth and its quality. Thus, a study was conducted on two groups of males with an average age of 45 with the Trust tonic's active ingredients and minoxidil in each group, respectively. During the study, the effectiveness of these compounds on hair condition and its changes were assessed with a seven-point, photographic evaluation, a seven-point, self- and staff-assessment scale. According to the data collected in this study, the active complex of the Trust tonic and minoxidil both demonstrated a positive trend in hair growth and condition, yet the efficacy of the Trust tonic was significantly greater than that of minoxidil. These results are shown in the parts following below.

Table 2: Subject's self-assessment form

Questions of Self-Assessment Form
1. Did your scalp's bald area get smaller? The answers could be strongly agreed, agree, no opinion, disagree, or strongly disagree.
2. How is your appearance of hair after the treatment? The answers could be Much better, better, same, worse, a lot worse
3. Since the start of the research, what is your new hair growth rating in the case of hair size, length, and hair density? The answers could be Perfectly increased, a little increased, no change, slightly decreased, decreased
4. Does your hair loss slowdowns? The answers could be highly effective, effective, partly effective, not effective
5. What is the current satisfaction level with your hair? The answers could be very satisfactory, moderately satisfactory, slightly satisfactory, slightly unsatisfied, moderately unsatisfied, very dissatisfied

Table 3: Standardized rating scale for the assessment of our subjects

Assessment Rating Score
Improved: +3
Moderately improved: +2
Slightly improved: +1
No change: 0
Slightly decreased: -1
Moderately decreased: -2
Decreased: -3

Staff-Evaluation

Among the forty individuals who had participated in this research, all completed the study. Based on staff evaluation and rating scores, the assessment revealed better recovery and improvement as a greatly improved label in the group treated with the Trust active complex (10%) than in the group treated with minoxidil (5%), and as a moderately improved label in the group treated with the Trust tonic active ingredients (50%) when compared to minoxidil (25%) (Fig. 1).

Self-Evaluation

The evaluation of the self-scoring form and all of the subjects' responses indicated that the subjects in the group treated with the Trust tonic and the subjects in the group treated with 2% minoxidil answered the first question in Table 2 as *strongly agree* and *agree*, which was statistically significant ($p < 0.05$) (Table 4).

Also, the subjects treated with the Trust tonic displayed a greater improvement in the appearance of the head

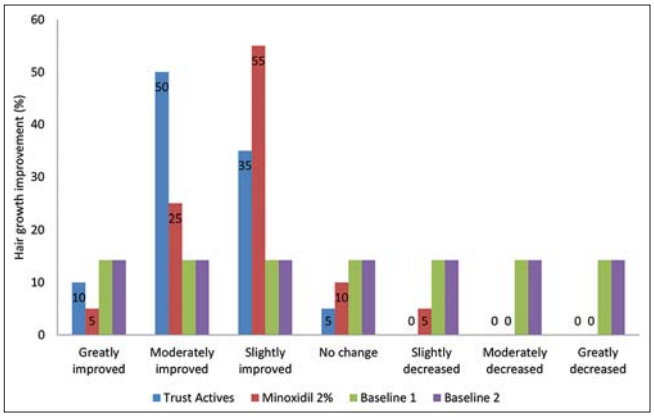

Figure 1: Staff-evaluation scores ($p < 0.05$).

skin in the bald areas. They stated that the topical use of the Trust tonic had impressive effects on parameters such as hair growth, hair length, and hair density, and they were satisfied with the results of hair loss retardation (Tables 5 – 7).

Photographic Scoring

In all subjects with AGA, the evaluation of hair growth and of the appearance of the bald areas was done with a photographic method in both groups. The global photographic assay revealed a significantly greater improvement in hair growth in the patients treated with the Trust tonic in comparison to the group treated with minoxidil (Fig. 2).

DISCUSSION

As described before, hair loss is a common concern seen in 50% of males under their fifties [20], and is known as androgenic alopecia (AGA). The conversion of testosterone to dihydrotestosterone by the 5α-reductase enzyme is the main trigger of AGA. In this situation, the hair follicle miniaturizes and falls out. Depending on the severity of hair loss and hormonal disorders, different types of AGA are seen in the frontotemporal regions and crown of the head [21]. Much research has been done to stop or retard hair loss in patients suffering from AGA. For this reason, minoxidil and oral finasteride are the two common drugs approved by the FDA to regulate the biological responses and hinder hair loss. Although these drugs have been accepted to be applied as treatments for AGA, they produce several topical and systemic side effects [22]. For instance, the growth of unwanted hairs, burning, inflammation, and irritation or allergic contact dermatitis of the head skin in the applied area, and a faster heart rate are the main topical and systemic complications of minoxidil, respectively [23]. Thus, other active compounds as safer and more effective alternatives for these two compounds have been investigated. Capixyl is an innovative complex of biomimetic peptide (acetyl tetrapeptide-3) combined with the red clover extract (*Trifolium pratense*) employed as one of the main active ingredients in the formulation of the Trust tonic. One of the main effects of Capixyl is an increase in hair density and width [24]. This extract is enriched with the isoflavone biochanin A, which is a powerful inhibitor of 5α-reductase type I and II enzymes [25,26]. Also, based on other research studies, biochanin A strongly suppresses these two isoforms of the 5α-reductase enzyme found in the scalp, especially the type II isoform that contributes to AGA [27]. In the case of peptides, recent studies have shown that the size of hair follicles is determined by the number of cells in the dermal papilla and the volume of extracellular matrix proteins (ECM). These proteins express collagen type I, III, and VII and laminins, which have a particular role in maintaining the hair follicle and the dermal

Table 4: Self-evaluation score of hair appearance after treatment with the Trust tonic and minoxidil in both groups

Appearance of Hair Scoring					
Treatment	**Better**	**Somewhat Better**	**Same**	**Worse**	**A lot worse**
Trust tonic	11	7	1	0	0
Minoxidil	5	9	5	1	0
Total	16	16	6	1	0

Table 5: Subjects' self-evaluation scores in declining the bald area and hair loss retardation

Baldness Scoring in Treated Area (Improvement)					
Treatment	**Strongly agrees**	**Agree**	**No opinion**	**Disagree**	**Strongly disagree**
Trust tonic	6	12	2	0	0
Minoxidil	0	9	6	5	0
Total	6	27	8	5	0

Table 6: Evaluation score of the groups treated with the Trust tonic and minoxidil after 24 weeks.

Hair Growth Rate, Size, and Density Scoring					
Treatment	**Perfectly increased**	**Moderately increase**	**No change**	**Slightly decreased**	**Decreased**
Trust tonic	6	10	3	1	0
Minoxidil	2	7	10	1	0
Total	8	17	13	2	0

Table 7: Hair loss decreasing evaluation by the patients in the two groups after treatment with the Trust tonic and minoxidil.

Hair Loss Scoring				
Treatment	**Highly effective**	**Effective**	**Partly effective**	**Not effective**
Trust tonic	4	11	4	1
Minoxidil	2	9	8	1
Total	6	20	12	2

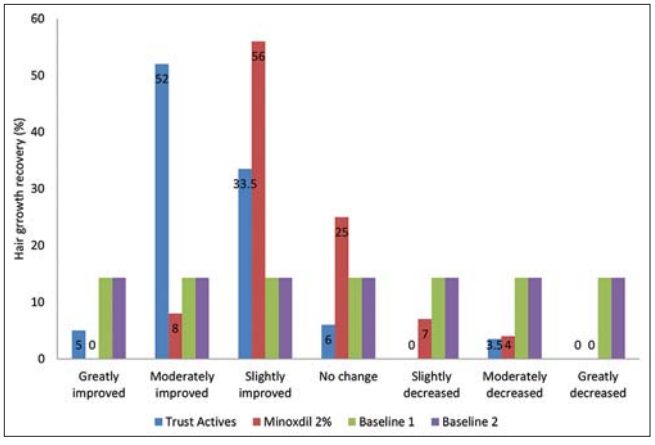

Figure 2: Photographic scoring of hair growth improvement ($p < 0.05$).

papilla's cell proliferation and differentiation [28, 29]. Hence, these biomimetic peptides employed in this study in combination with the red clover extract based on former research, are shown to produce a significant effect on the synthesis of ECM proteins and further improve the hair morphology and growth via the strengthening the hair follicle anchorage [24]. Same as Capixyl, Procapil is another important active ingredient applied in the formulation of the Trust tonic to improve hair growth and retarding hair loss in cases with complaints of AGA on various levels. Procapil is a vitaminized complex of apigenin and oleanolic acid. Apigenin derived from the citrus peel has a vasodilation effect, increasing scalp microcirculation and hindering follicle aging and premature hair loss. Oleanolic acid extracted from the olive tree leaves is a potent inhibitor of 5α-reductase I and II enzymes and plays a key role in follicle atrophy by preventing dihydrotestosterone production. The third part of this effective anti-hair loss ingredient is a vitaminized peptide that encompasses glycine–histidine–lysine peptides essential for the metabolic activity of hair follicles [19].

Rosemary extract from the *Rosmarinus officinalis* herb is employed as one of the active complexes in the Trust tonic and is another innovative active compound that acts as an antibacterial, antifungal, anti-inflammatory, and antioxidant compound [30]. Rosemary was used as an enhancer of microcapillary perfusion in 100 patients with AGA in a concentration of 3.7 mg/mL in a recent comparative study on two groups with 2% minoxidil. The results revealed that the hair count increased in both groups, yet the common adverse effect of itching related to minoxidil was reported in the group treated with minoxidil and not in those taking rosemary extract. Thus, as a natural and safe ingredient, rosemary extract could be used as an alternative option for minoxidil in patients with AGA [31,32].

In this study, we evaluated the effectiveness of the Trust tonic's active ingredients in a concentration of 2.5% as an alternative to 2% minoxidil, which is known as an accepted drug for the treatment of AGA. The researchers' scores on the evaluation of hair growth revealed that the maximum hair growth was seen in the patients treated with the Trust tonic (60%: *greatly* and *moderately improved*; $p < 0.05$) in comparison to the patients treated with minoxidil (30%: *greatly* and *moderately improved*; $p < 0.05$) after the 24 weeks of treatment. Hence, hair growth improvement in the group on the Trust tonic was five times greater than in the group on minoxidil, which was significant statistically. In the self-assessment tests, results in both groups using the Trust tonic and minoxidil showed the efficacy and satisfaction of the patients in the group using the Trust tonic than the group using minoxidil. Based on the patients' scores, the appearance of hair after the Trust tonic and minoxidil scored much better and somewhat better in the average of 68.75% and 31.25%, respectively. Furthermore, the results of self-evaluation of scalp baldness revealed a decrease of 56.25% and 43.75% in the subjects on the Trust tonic and minoxidil, respectively. Also, hair growth and the size and density of the hair in the patients treated with the Trust tonic represented an averagely perfect and moderate increase of 64%, which was significantly higher in the patients treated with minoxidil (36%). The effectiveness of the Trust tonic in decreasing hair loss showed a score of 57.69% (*effective* and *highly effective*) on average, which was more significant in the group on minoxidil (42.30%).

The photographic evaluation of the head scalp revealed a significant improvement (*great*, *moderate*, and *slightly improved*) in the group treated with the Trust tonic compared to the group treated with minoxidil (90.5% in the Trust tonic group and 64% in the minoxidil group; $p < 0.05$) (Fig. 2). Therefore, the Trust active complex showed a 1.4 times higher recovery rate in the patient's hair count and appearance and could be a fair substitute for minoxidil in patients suffering from AGA.

CONCLUSION

Natural compounds such as herbal extracts, antioxidants, and vitamins may prevent androgenic alopecia by radical scavenging activity, hindering inflammation, and increasing the volume of extracellular matrix proteins (ECM) in the hair follicle area. Thus, this research focused on novel complexes in the treatment of androgenic alopecia and receding hair loss. Using these effective compounds in combination could be an effective alternative for minoxidil in the treatment of patients with AGA.

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

Teledermatology and COVID-19 in a resource-limited country such as Nepal

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ABSTRACT

Background: Teledermatology has become a popular alternative tool for providing dermatology services during the COVID-19 pandemic worldwide. Despite being a rising health care modality, it helped to deliver uninterrupted services. The study aimed to determine the implementation, utilization, and acceptance of teledermatology services during the pandemic. **Objectives:** The aim was to assess the satisfaction of patients utilizing teledermatology services and to obtain their clinical and epidemiological data. **Methods:** This was a retrospective, observational, single-center study on patients using teledermatology services. Demographic data was analyzed and a questionnaire survey was conducted through phone calls regarding their experience of the service. **Results:** The mean age of the patients was 33.48 ± 17.89 years. Out of 122 teleconsultations, 89 patients could be contacted again for feedback, among which 81 (91%) found the service easy to use, 75 (84.3%) were able to express their problems similarly to visits in person, 49 (55.05%) regarded teleconsultation as the same as an in-person visit, 80 (89.9%) were satisfied, and 85 (95.5%) agreed to use the service in the future. Superficial fungal infection was the most common diagnosis (24.6%). Newly registered patients were more satisfied in comparison to follow-up patients (96.36% of new cases vs. 79.41% of follow-up cases, $p = 0.01$). **Conclusion:** Teledermatology was well accepted by the patients in the current scenario. Telehealth services have a promising role in the future in fulfilling public health demands.

Key words: Teledermatology; COVID-19; Resource-limited countries; Nepal

INTRODUCTION

Telemedicine is the use of telecommunication technologies to deliver health care over long distances [1,2]. The history of telemedicine may be traced centuries back, yet in the twentieth century, the first report of the transmission of electrocardiographic data by telephone wires was published [3]. In the 1920s, teleconsultations were provided to sea crew via radio transmissions, following which, in the 1960s, commercial types of equipment for telemedicine were employed by military and space technology departments [4,5]. Since then, telehealth services have steadily increased globally and numerous countries have established proper telehealth programs.

The word *telemedicine* was introduced in 1970 [5]. According to the WHO, telemedicine is defined as "the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for the diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and continuing education of health care providers, all in the interest of advancing the health of individuals and their communities" [6]. Teledermatology refers to a branch of telemedicine that provides dermatological care from a distance with electronic telecommunication tools [7]. It has been used in the diagnosis and treatment of skin diseases, in monitoring skin conditions, and for educational and research purposes [8].

Teledermatology services have become popular in recent years and have been integrated into various public health sectors in a number of countries [9].

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Although face-to-face consultations remain the gold standard for diagnosis, teleconsultations have been accepted as a viable tool that reduces the unnecessary time taken, increases cost-effectiveness, and reduces the number of in-person consultations by triaging [10].

Teledermatology is delivered as synchronous or real-time, asynchronous or store-and-forward, and hybrid modalities. Synchronous teledermatology is delivered through live video conferencing between the dermatologist and patient. In the asynchronous or store-and-forward technique, clinical images taken by the clinician or patient are digitally stored and forwarded to the attending dermatologist, while the mixed or hybrid teledermatology modalities combine live video conferencing and the store and forward technique [11]. Novel modalities such as mobile teledermatology and teledermoscopy employ social smartphone applications along with dermoscopic attachment to deliver images [1,12]. In addition, there are some new app-based dermatology services available that provide direct dermatology services [13].

The individual's access to quality health care remains a challenge in a country such as Nepal. Geographic complexity, shortage of healthcare manpower, unavailability of healthcare facilities, higher costs, and urban–rural disparity of medical professionals are some of the other challenges in the health sector of low-to-middle-income countries. The implementation of teledermatology has helped to overcome these barriers and improve healthcare services [14].

Lockdowns and social distancing due to COVID-19 have hampered dermatological services. Recently, due to the ongoing worldwide pandemic of COVID-19, teledermatology has emerged as an alternative to overcome the crisis of disrupted dermatological services [15]. Dermatologists have been increasingly using teledermatology services to reduce face-to-face contact, limit the spread of coronavirus infection, and overcome the current barriers to providing dermatology services to patients. Due to frequent lockdowns, it is not only in the rural areas yet also in the urban areas that teledermatology has been providing healthcare services around the world [16].

As our center is a pioneering institute providing telehealth services for both rural and urban areas of Nepal, we conducted this study to explore the use of teledermatology services and how they are received by patients in a low-income country such as Nepal [17].

MATERIALS AND METHODS

An observational, single-center study was conducted at a skin health center in Nepal. A retrospective data review of teledermatology services from May 2020 to July 2021 was conducted. Patients included in the study were those who had received teledermatology services from our center in the country. The teledermatology model service was based on real-time videoconferencing and a hybrid model. The initial registration of the patients was performed through phone calls to the registration department by the phone number provided on the official website of the institute. The patients were instructed to be ready with previous prescriptions, medicines, or any reports. Then, real-time videoconferencing was done via Skype on an Android smartphone or a computer with a 4G Internet connection. The teledermatology service was provided by the doctor as specified by the patients. A detailed history was obtained from the patients and examination was done on live videoconferencing. Informed consent was taken from the patients to obtain photos and videos. Patients below eighteen years of age were consulted in the presence of their guardian. Images, recordings, and investigations were sent by the patients with the application. A provisional diagnosis was reached and treatment was provided. Follow-up was advised to the patients as required. An in-person visit to the center was advised to the patients requiring a skin biopsy or any emergencies. Details about the patient's history, examination, diagnosis, treatment, and follow-up were recorded in a patient's datasheet.

The patient's details, including age, sex, address, new case/follow-up case, chief complaints, duration of the disease, provisional/definitive diagnosis, and management, were noted from the patient's datasheet. An approximate distance from the patient's address to the location of the institute and the total time required for travel were measured with Google Maps and noted. The patients were contacted and asked to share their experience of using teledermatology services. The patient's questionnaire was taken from the telehealth usability questionnaire (TUQ) with modifications [18,19]. Five questionnaires representing ease-of-use, interaction quality, reliability, satisfaction, and future use were selected and asked to the patients (Table 1). Responses from the patients in the form of yes-or-no answers were noted.

Statistical analysis was performed using SPSS Statistics, version 20. Qualitative data was described as

frequencies and proportions. $p < 0.05$ was considered significant. The Pearson's chi-square test was used to compare categorical variables. Missing data was excluded from the study.

Ethics Statement

Ethical clearance was obtained from the institute's review committee.

RESULTS

A total of 134 patients were provided with teledermatology services during the study period. Out of 134 teleconsultations, 122 were done in the country, while 12 were done outside of it. There was a peak in the number of patients using teledermatology services during lockdowns (May to August 2020 and May to July 2021) in the country (Fig. 1).

Patient Demographics

The mean age of the patients using teledermatology services was 33.48 ± 17.89 years (from 6 months to 87 years). Among the 122 patients, 49 (40.2%) were males and 73 (59.8%) were females. The majority of the patients (64.8%; $n = 79$) were from outside the city where the institute was located, and 35.2% of the patients ($n = 43$) were from the city. The average distance from the institute to the patient's residence was 144.84 ± 157.20 km (2–721 km). The mean travel time was estimated at 385.31 ± 889.52 minutes (10–8600 minutes). Out of the 122 patients, 74 (60.7%) were new cases, while 48 (39.3%) were follow-up patients (Table 2).

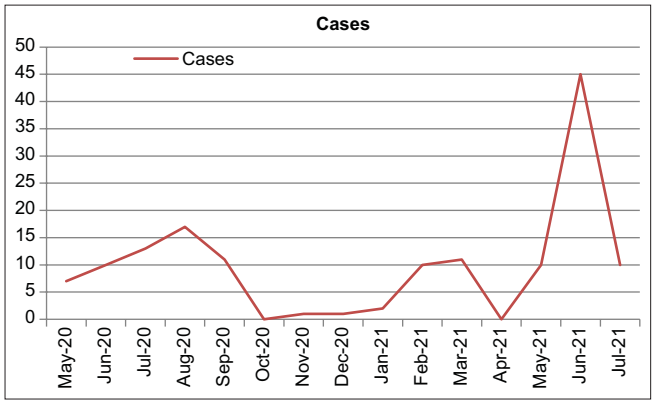

Figure 1: Trend of teledermatology consultation.

Table 1: Survey questionnaire for the patients

1. Was it convenient for you to use the system? Yes/no. (ease of use)
2. Were you able to express yourself as effectively as during an in-person visit? Yes/no. (interaction quality)
3. Was the visit provided by the teledermatology service similar to an in-person visit? Yes/no. (reliability)
4. Were you satisfied with the teledermatology service? Yes/no. (satisfaction)
5. Will you use the teledermatology service in the future? Yes/no. (use in future)

Disease Characteristics

The average duration of illness was 7.53 ± 19.51 months, ranging from 4 days to 144 months. A definitive diagnosis was reached in 112 cases (91.8%), while in ten cases, in which a skin biopsy was required for confirmation, only a probable diagnosis was given. Fungal infection was the most common diagnosis ($n = 30$; 24.6%), followed by pigmentary disorders ($n = 26$; 21.3%), urticarial disorders ($n = 19$; 15.6%), eczematous or dermatitic disorders ($n = 17$; 13.9%), acne vulgaris ($n = 10$; 8.2%), hair and nail disorders ($n = 7$; 5.7%), acne vulgaris and pigmentary disorders ($n = 4$; 3.3%), papulosquamous disorders ($n = 3$; 2.5%), other diseases ($n = 3$; 2.5%), bacterial and viral infection ($n = 1$; 0.8%), immunobullous disorder ($n = 1$; 0.8%), sexually transmitted disease ($n = 1$; 0.8%) (Table 3).

Patient's Experience

Eighty-nine patients could be contacted again and asked to share their experience regarding the teledermatology service. Among the 89 patients, 81 (91%) regarded the service as simple to use, while 8 (9%) as inconvenient. Regarding the ability to express themselves, seventy-five patients ($n = 75$; 84.3%) were able to express their problems similarly to direct visits, while fourteen patients ($n = 14$; 15.7%) were unable to do so. Forty-nine patients ($n = 49$; 55.05%) thought teleconsultation was the same as in-person visits, and forty patients ($n = 40$; 44.95%) did not find it similar. The majority of the patients ($n = 80$;

Table 2: Demographic data of the patients

Total number of patients (*n*)	122
new cases	74 (60.7%)
follow-up cases	48 (39.3%)
Mean age	33.48 ± 17.89 yrs.
Sex	
male	49 (40.2%)
female	73 (59.8%)
Mean disease duration	7.53 ± 19.51 months (4 days to 144 months)
Average distance (from the institute to the patient's residence)	144.84 ± 157.20 km
Average travel time	385.31 ± 889.52 minutes
Definitive diagnosis	112 (91.8%)
Probable diagnosis	10 (8.2%)

89.9%) were satisfied, while only nine (n = 9; 10.1%) were unsatisfied with the service. Finally, 85 patients (95.5%) agreed to use teledermatology services in the future, while four (4.5%) did not agree (Table 4).

Overall satisfaction was independent of age (p = 0.81), sex (p = 0.64), definitive/probable diagnosis (p = 0.81), the patient's residence (p = 0.48), and the disease diagnosed (p = 5.42). Yet, the difference in satisfaction between newly registered cases (53/55; 96.36%) and follow-up cases (27/34; 79.41%) was statistically significant (p = 0.01) (Table 5).

DISCUSSION

In a developing, low-income country such as Nepal, the health system is unable to meet the demand of the rural and marginalized population due to limited resources and facilities. The higher cost and time required to access health services have worsened the situation even more [14]. A large number of dermatologists are concentrated in urban areas in comparison to rural areas, creating a disparity [20]. Teledermatology may bridge the gap between the demand and supply of dermatological healthcare facilities by allowing specialists to evaluate, diagnose, manage, and provide follow-ups to underserved populations [17]. Patient care in remote areas reduces the expenses related to distance traveled and referrals; hence, teledermatology overall improves the healthcare system of the country. Several studies have highlighted the importance of telemedicine in resource-limited settings to overcome barriers and improve health services [21,22]. However, geographic difficulties, weather conditions, poor communication systems, lack of healthcare facilities in rural areas, and the economic burden of accessing health facilities are the issues that have limited the expansion of teledermatology services in the country [14].

Teledermatology has emerged as a viable healthcare service amid the pandemic [23]. It has proven to become an effective way of providing essential health services along with a reduced risk of transmission of infection in the community [24]. Apart from this, teledermatology has also demonstrated its advantage of being cost-effective and time-saving during the pandemic in comparison to direct consultations in

Table 3: Prevalence of the skin diseases

Diseases	Number of Patients	Percentage
Acne vulgaris	10	8.2%
Pigmentary disorders	26	21.3%
Acne vulgaris and pigmentary disorders	4	3.3%
Eczematous/dermatitic disorders	17	13.9%
Fungal infections	30	24.6%
Papulosquamous disorders	3	2.5%
Bacterial and viral infections	1	0.8%
Urticarial disorders	19	15.6%
Hair and nail disorders	7	5.7%
Sexually transmitted diseases	1	0.8%
Immunobullous disorders	1	0.8%
Other diseases	3	2.5%
Total	n = 122	100%

Table 4: Responses to the survey

Parameter	Responses (n = 89)	Percentage
Convenience/ease of use		
yes	81	91%
no	8	9%
Able to express oneself		
yes	75	84.3%
no	14	15.7%
Same as an in-person visit		
yes	49	55.05%
no	40	44.95%
Satisfied		
yes	80	89.9%
no	9	10.1%
Will use in the future		
yes	85	95.5%
no	4	4.5%

Table 5: The patients' satisfaction

Variable	Overall Satisfaction (n=89)		p Value
	yes	no	
Age	—	—	0.81
Sex			
Male	33	3	0.64
Female	47	6	
Registration			
New	53	2	**0.01***
Follow-up	27	7	
Diagnosis			
Definitive	73	8	0.81
Probable	7	1	
Patient's residence			
Inside the city (institute's location)	27	2	0.48
Outside the city (institute's location)	53	7	
Disease diagnosis			
Acne vulgaris	7	1	5.42
Pigmentary disorders	16	3	
Acne vulgaris and pigmentary disorders	3	0	
Eczematous/dermatitic disorders	10	3	
Superficial fungal infections	19	1	
Papulosquamous disorders	1	0	
Bacterial and viral infections	1	0	
Urticarial disorders	15	1	
Hair and nail disorders	4	0	
Sexually transmitted diseases	1	0	
Immunobullous disorders	1	0	
Other diseases	2	0	

* P value significant.

different studies [25,26]. There has been an increased demand for teledermatology services not only in rural areas, yet also in urban [27]. Also, there has been higher patient satisfaction with teledermatology services during COVID-19. In a study by Ruggiero et al., 92.3% of acne patients were satisfied with the dermatologist after a teleconsultation [28]. However, the inability to receive clinical procedures, the uncertainty of reimbursement to the treating physician, missing diagnoses, poor visual resolutions for reaching a diagnosis, a lack of infrastructure, and mental distress among the dermatologists are some of the challenges faced during the pandemic [29].

This retrospective review was conducted to determine the implementations, advantages, drawbacks, and future possibilities of teledermatology services in our center. In this study, we observed a peak in the use of teledermatology services in August 2020 with seventeen cases per month and, then, in June 2021 with forty-five cases per month, which was the time of a strict, nationwide lockdown. This indicates an increased demand for teledermatology services at times of difficulty in accessing health services. However, in comparison to direct consultations at the outpatient department, the number of cases seen was lower.

The sex distribution among those seeking teledermatology services was similar in our study. Most of the patients were outside the city in which our center was located, which highlights the improved access to health services to underserved populations at the time of the pandemic. The distance of care provided was as far as approx. 721 km, which included the rural areas of the country. In studies by Coustasse et al. and Maddukuri et al., similar uses of teleservices in rural areas were found [30,31].

A definitive diagnosis was reached in 91.8% of the cases in our study. In a study by Oliveira et al., teledermatology services showed a high level of diagnostic agreement and accuracy [32]. However, diagnostic accuracy could not be assessed in our study due to the inability of the patient to visit the center to confirm the diagnosis during COVID-19.

Regarding the patients' experiences with teledermatology services, a majority found the service easy to use and were able to express their problems properly. Similarly, most of the patients were satisfied with the service and agreed to use it again in the future. These findings were similar to results observed in previous studies [19,33,34].

In contrast to a review by Hadeler et al., the number of individuals who preferred teleconsultations and face-to-face consultations was almost equal [34]. Newly registered cases were more satisfied in comparison to follow-up cases with a statistical significance, probably due to prior in-person visits by a large number of follow-up patients. Patients with superficial fungal infection had the highest level of satisfaction, which was around 95%, similarly to results achieved by Handa et al. [33].

Decreased travel costs and time, shorter waiting lists, and the avoidance of unnecessary face-to-face contact are some of the reasons for the acceptance of teledermatology by the general population. Teledermatology has been well accepted not only by patients but also by dermatologists [35]. Unfortunately, we were not able to assess the acceptance of teledermatology by dermatologists in our study.

Teledermatology has its challenges and limitations in a country such as Nepal. An expensive setup and equipment, a lack of a legal framework, medical practitioners lacking skills on telemedicine, and poor integration of telemedicine in the healthcare system are some of the shortcomings. One non-government organization, Community Health Education Services by Telehealth (CHEST), has provided telemedicine services to remote areas of Nepal without access to healthcare, even during the pandemic [17]. Recently, telemedicine guidelines were also provided by the Nepal Medical Council under the Nepal Medical Council Act of 1964 to strengthen teleservices in the country [36].

Although most patients are satisfied, there are many who still prefer in-person consultation over teleconsultation. Also, numerous skin diseases require diagnosis and management under the direct care of a treating doctor, which is a drawback for the dermatologist. Thus, we should understand that both face-to-face consultation and telemedicine have their benefits and limitations. Teledermatology, however, has emerged to provide skin healthcare during the difficult times of the COVID-19 pandemic, the importance of which cannot be underestimated.

CONCLUSION

This study provided insight into patient acceptance of teledermatology in Nepal. Although teledermatology is

a rising subspeciality in Nepal, it has established itself as a powerful tool for providing health services with a high degree of acceptance among people. Still, a poor Internet connection in parts of the country, inability to access Internet services due to socioeconomic reasons, and illiteracy are some of the hurdles in the implementation of teledermatology services in Nepal. The limitations of the study were the small number of patients, the single-center location of the study, and the retrospective design. Further studies are required to understand the role of teledermatology, its implementation and integration in health services, and its establishment as a viable alternative health service during times of crisis.

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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

Atopic dermatitis in Senegalese children with skin phototype VI: Prevalence, clinical features, and risk factors of severity

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ABSTRACT

Background: Atopic dermatitis (AD) is the most common inflammatory skin disease of childhood. Yet, in sub-Saharan Africa, data on AD in children is scarce. Herein, we aimed to determine the prevalence, clinical features, and risk factors of severity of AD in Senegalese children with skin phototype VI. **Materials and Methods:** This was a cross-sectional study including children with AD and skin phototype VI younger than fifteen years old seen in two dermatology centers in Senegal over a period of six months. The diagnosis of AD was based on the United Kingdom Working Party (UKWP) criteria. The severity of AD was evaluated with SCORing of Atopic Dermatitis (SCORAD). **Results:** Among the 630 children consulted during the study period, 104 had AD, yielding a hospital prevalence of 16.5%. The mean age of children with AD was 36 months with a sex ratio of 1. A personal and family history of atopic disease was reported in 86.5% and 84.6% of the patients, respectively. Xerosis was the most common clinical feature, observed in 80.8% of. Post-inflammatory hyperpigmentation and keratosis pilaris were observed in 44.2% and 37.5%, respectively. Severe AD was noted in 12.5%. Risk factors associated with the severity of AD were exposure to incense smoke, an age of onset before 24 months, food allergies, and *impetiginisatio*. Daily use of shea butter was a protective factor. **Conclusion:** Our study showed a high hospital prevalence of AD in Senegalese children with skin phototype VI. The result observed with shea butter as a protective factor against severe AD is highly important, although it needs to be confirmed by randomized studies.

Key words: Atopic dermatitis; Children; Phototype VI; Senegal

INTRODUCTION

Atopic dermatitis (AD) is a common, highly pruritic chronic inflammatory skin disorder in children, which is often associated with other atopic diseases, such as asthma and allergic rhinitis [1].

The prevalence of AD varies significantly across the world [2]. Historically, the prevalence of AD in Africa has generally been lower than in the West, yet recent trends have shown an increasing prevalence in developing countries [3,4].

AD, especially in children, remains a particularly underestimated disease in sub-Saharan Africa, with a considerable lack of data in the general population and at the hospital level. Yet, it has become a real worldwide health problem due to its increasing prevalence, its negative impact on quality of life, and the high cost of its management [5]. In addition, in individuals with skin phototype VI, AD has numerous clinical specificities mainly linked to skin pigmentation [6]. Skin typing refers to the classification of the skin according to its sensitivity to sun exposure. The Fitzpatrick classification is the most widely employed

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method of skin typing. According to this classification, skin phototype VI corresponds to black skin that never burns and always tans darkly [7].

Herein, we aimed to determine the prevalence, clinical features, and risk factors of severity of AD in Senegalese children with skin phototype VI.

MATERIALS AND METHODS

This cross-sectional, descriptive, and analytical study was conducted over a period of six months—from January 1 to July 1, 2019—in two dermatology centers in Senegal (Institute of Social Hygiene Hospital of Dakar and Regional Hospital Centre of Saint-Louis). The study population was children aged fifteen years or younger consulting for AD during the study period. For this study, the UKWP criteria for the diagnosis of AD were employed to identify the cases. A diagnosis of AD was reached in the presence of a pruritic rash and three or more of the following features:

- a history of rash in the skin creases (fold of the elbow, behind the knees, front of the ankles, and around the neck);
- a personal or family history of asthma and hay fever;
- history of generalized dry skin (xerosis);
- onset before the age of two years;
- visible flexural dermatitis.

Data was collected with a pre-established questionnaire. The clinical examination of the children was performed in the compulsory presence of the parent/guardian. The first step was an interrogation with the collection of sociodemographic data, the child's personal and family history, cosmetic habits, and anamnestic data. The child's physical examination was then conducted to identify the elementary lesions and their topography.

The SCORAD index was employed to assess the disease severity of AD. It consisted of a combination of three items: the extent of skin involvement, the intensity of dermatitis, and the subjective symptoms. To measure the extent of AD, the Wallace rule of nines was applied to the front/back drawing of the patient's inflammatory lesions. The extent was graded from 0 to 100. The intensity part of SCORAD consisted of six items: erythema, edema/papulation, excoriations, lichenification, oozing/crusts, and dryness. Each item was graded on a scale from 0 to 3. The subjective items included daily pruritus and sleeplessness. The SCORAD formula was as follows: A/5 + 7B/2 + C. Here, *A* was defined as the extent (0–100), *B* as the intensity (0–18), and *C* as the subjective symptoms (0–20). The maximal SCORAD score was 103. AD was classified as mild with SCORAD < 25, moderate with 25–50, and severe with > 50.

Data was entered into Microsoft Excel and analyzed with SPSS Statistics, version 26.0. The Pearson's chi-square test and the Fischer's exact test were employed to find an association between the dependent variable (presence of severe AD) and the covariables, with the significance threshold at $p < 0.05$. In the case of a significant association, we assessed the strength of this association with the odds ratio with 95% confidence limits.

The participants and/or their parents/guardians were provided with detailed information on the study and assured that confidentiality would be ensured. Informed consent from the parent and/or guardian was required before inclusion.

RESULTS

A total of 630 children with skin diseases were seen during the study period. Among these, 104 had AD according to the UKWP diagnostic criteria, giving a hospital prevalence of 16.5%. Their mean age was 56 months and the sex ratio was 1. Among the children with AD, 29 (27.9%) were infants and 75 (72.2%) were children older than two years.

A personal history of the atopic disease was reported in 90 (86.5%) patients. These were allergic rhinitis in 66 (63.5%), asthma in 36 (34.6%), allergic conjunctivitis in 28 (26.9%), and a food allergy in 13 (12.5%) cases. AD was the first step in the "atopic march" in 61 (58.7%) patients. A family history of atopy in the first degree was reported in 88 (84.6%) patients.

Thirty-six (34.6%) patients developed AD within the first six months of life, 64 (61.5%) before the age of two years, and 93 (89.4%) before the age of five years.

The mean duration of AD was 26.5 days, with extremes ranging from five to ninety days. Pruritus was present in all patients and sleeplessness in 47 (45.2%).

The main clinical feature was xerosis, observed in 84 (80.8%) patients. The erythematous-squamous

aspect, corresponding to chronic eczema, was observed in 82 (78.8%). Some minor signs of AD such as post-inflammatory hyperpigmentation and keratosis pilaris were also common, observed in 46 (44.2%) and 39 (37.5%) patients, respectively. *Impetiginisatio* of the lesions was observed in 26 (25%) patients. Table 1 shows the distribution of the different clinical features of AD observed in our patients depending on age.

The most frequent locations of the eczematic lesions were the trunk in 72 (69.2%) cases, the face in 49 (47.4%), the folds of the elbow in 50 (48.1%), the neck in 46 (44.2%), and the knee in 44 (42.3%). Table 2 shows the distribution of the different topographies in our patients depending on age.

The mean SCORAD score was 31.3. AD was mild in 35.6% (n = 37), moderate in 51.9% (n = 54), and severe in 12.5% (n = 13). The risk factors associated with the severity of AD were regular exposure to incense smoke (p = 0.009; OR = 6.4 [1.9–17.4]), a food allergy (p < 0.001; OR = 10.3 [2.7–39.1]), an age of onset before twenty-four months (p = 0.01; OR = 9 [1.2–13.7]) and *impetiginisatio* (p = 0.01; OR= 4.4 [1.3–4.7]). Daily application of shea butter to the entire body was a protective factor (p = 0.005; OR = 0.1 [0.01–0.7]) (Table 3).

Table 1: Distribution of the different clinical features of AD in our patients depending on age.

Clinical Feature	Infants	Age≥2 yrs.	Total
	n (%)	*n* (%)	*n* (%)
Xerosis	18 (62.1)	66 (88)	84 (80.8)
Erythematous-squamous aspect	21 (72.4)	61 (81.3)	82 (78.8)
Post-inflammatory hyperpigmentation	7 (24.1)	39 (52)	46 (44.2)
Keratosis pilaris	8 (27.6)	31 (41.3)	39 (37.5)
Excoriation/ulceration	6 (20.7)	21 (28)	27 (25.9)
Lichenification	2 (7)	23 (30.7)	25 (24)
Retro/infra-auricular fissures	1 (3.4)	18 (24)	19 (18.3)
Dennie–Morgan lines	2 (6.9)	9 (12)	11 (10.6)
Acute eczema lesions	3 (10.3)	7 (9.3)	10 (9.6)
Prurigo	none	9 (12)	9 (8.7)
Palmoplantar keratoderma	1 (3.4)	6 (8)	7 (6.7)
Pityriasis alba	none	5 (6.7)	5 (4.8)
Nummular dermatitis	1 (3.4)	3 (4)	4 (3.8)
Erythroderma	1 (3.4)	1 (2.7)	2 (1.9)

Table 2: Distribution of the different topographies in our patients according to age

Location	Infants	Age≥2 yrs.	Total
	n (%)	*n* (%)	*n* (%)
Trunk	18 (62.1)	54 (72)	72 (69.2)
Face	18 (62.1)	31 (41.3)	49 (47.4)
Extensions of the limbs	14 (48.3)	26 (34.7)	40 (38.5)
Folds			
Elbows	10 (34.5)	40 (53.3)	50 (48.1)
Neck	16 (55.2)	30 (40)	46 (44.2)
Knees	9 (31)	35 (46.7)	44 (42.3)
Armpits	4 (13.8)	13 (17.3)	17 (16.3)
Groin	3 (10.3)	3 (4)	6 (5.8)
Scalp	13 (44.8)	20 (26.7)	33 (31.7)
Buttocks	5 (17.2)	11 (14.7)	16 (15.4)
External genitals	6 (20.7)	6 (8)	12 (11.5)
Periorbital rims	none	9 (12)	9 (8.7)
Ears	none	6 (8)	6 (5.8)

DISCUSSION

The hospital prevalence of AD in children with skin phototype VI is variously assessed in sub-African series. The prevalence of 16.5%, found in our study, differs from that reported by Técléssou et al. in Togo with 31.3% and from that reported by Ahogo et al. in Ivory Coast with 9.2% [8,9]. The differences in prevalence also exist in a Chinese series, with the rates ranging from 9% to 24% [10]. These differences in the prevalence of AD are mainly due to difficulties in interpreting the criteria employed in the diagnosis of AD, especially those proposed by the UKWP. The differences in methodology are also sometimes noted, as in the study by Técléssou, in which recruitment was exclusively in vaccination centers [8]. In any case, the prevalence of AD remains high in African hospital studies, making AD an emerging disease in sub-Saharan Africa.

Air pollution also plays a key role in the prevalence and severity of AD [11]. Our study found a higher risk of severe AD in children regularly exposed to incense smoke. There are some studies on the effect of incense smoke on AD. In China, ZHANG et al. found a significant association between exposure to incense and increased prevalence of AD in children aged one to eight years [12]. To our knowledge, no studies have correlated the severity of AD with exposure to incense smoke. However, chemical analysis of incense smoke reveals a complex mixture of particulate and gaseous pollutants that may aggravate AD. Incense burning, which is an incomplete combustion process, is known to emit fine and ultrafine particles ($PM_{2.5}$ and $PM_{0.1}$) in large quantities, carbon monoxide (CO), nitrogen oxides (NO_x), toxic polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs), such as benzene and isoprene [13,14]. The effects of fine and ultrafine particles on the severity of AD were investigated in a longitudinal study by Song

Table 3: Risk factors associated with severe atopic dermatitis (univariate analysis).

Characteristics	Severe Atopic Dermatitis		*p* Value	OR [95% CI]
	Present n (%)	Absent n (%)		
Sex				
male	7 (13.5)	45 (86.5)	0.38	
female	6 (11.5)	46 (88.5)		
Age group				
infant	3 (10.3)	26 (89.7)	0.48	
children over 2 yrs.	10 (13.3)	65 (86.7)		
Exclusive breastfeeding	6 (9.8)	55 (90.2)	0.14	
Weaning age before the 18 month	2 (10.5)	17 (89.5)	0.47	
Food introduction before 6 months	4 (23.5)	13 (76.5)	0.17	
Incense exposure	11 (20.8)	42 (79.2)	0.009	6.4 [1.9–17.4]
Use of scented toiletries	8 (19)	34 (81)	0.06	
Daily use of shea butter	1 (2.3)	43 (97.7)	0.005	0.1 [0.01–0.7]
Asthma	7 (19.4)	29 (80.6)	0.07	
Allergic rhinitis	9 (13.6)	57 (86.4)	0.44	
Allergic conjunctivitis	3 (10.7)	25 (89.3)	0.51	
Food allergy	6 (46.2)	7 (53.8)	< 0.001	10.3 [2.7–39.1]
Age of onset before 24 months	12 (18.8)	52 (81.2)	0.01	9 [1.2–13.7]
Impetiginisatio	7 (26.9)	19 (73.1)	0.01	4.4 [1.3–4.7]

et al., which included 41 schoolchildren aged eight to twelve years. The study found that the itching score was significantly associated with the concentrations of ambient fine and ultrafine particles [15]. Concerning the effect of gaseous pollutants, a nationwide survey of middle school students in Taiwan involving 317,926 children demonstrated that severe flexural eczema was positively associated with exposure to CO and NO_x [16]. A double-blind, cross-over study by Huss-Marp et al. demonstrated that VOCs increased transepidermal water loss (TEWL) in patients with AD 48 hours after exposure, which aggravates xerosis [17]. Given all these findings, the aggravation of AD after exposure to incense smoke is easy to understand.

Regarding cosmetic habits, shea butter was found to be a protective factor against severe AD in our study. The protective effect of shea butter is explained by its anti-inflammatory and moisturizing properties. The anti-inflammatory properties of shea butter are attributed to the several derivatives of cinnamic acid contained therein [18]. Shea butter also contains vitamins A and E and has semi-solid characteristics and buttery consistency, which makes it an effective emollient and moisturizer for the skin [19]. Thus, shea butter could be an excellent alternative to classic emollients, which are often inaccessible to the majority of patients.

In our study, AD was frequently associated with a personal or family history of atopy. The frequent association between AD and a personal or family history of atopy is well documented in the literature [20,21]. Regarding the relationship between atopic diseases and the severity of AD, only a food allergy was statistically associated with severe AD in our study. This association was reported by several authors. In Turkey, Celiksoy et al. showed that sensitization to food allergens such as cow's milk and hen's eggs was significantly associated with the severity of AD in young children [22].

Xerosis was the most frequent clinical feature in our patients, observed in 80.8% of the cases. In a study by Bayonne-Kombo et al. from Congo, xerosis was also the most frequent feature, in 89.33% of the cases [23]. A meta-analysis by Yew et al. revealed that xerosis was the most frequent aspect of AD in all regions of the world, except southeast Asia [24]. The meta-analysis reported an average frequency of 65% for xerosis in three African regions: Nigeria, Tunisia, and South Africa [24]. The frequency of xerosis in atopic patients is explained by increased TELW, abnormalities in essential fatty acid metabolism, a decrease in ceramides in the stratum corneum, and a decrease in the content of hygroscopic molecules and their precursors.

Some minor signs of AD, such as keratosis pilaris and retroauricular fissures, were relatively common in our series. Keratosis pilaris was observed in 37.5% of our patients. Its frequency was 38.8% in an Ivorian study by Ahogo [9]. Compared to other

phototypes, keratosis pilaris appears more frequently in phototype VI according to several reviews [25]. Individuals with phototype VI also have a higher risk of developing pigment disorders after inflammatory dermatosis [26]. In our study, 42.2% of the patients had post-inflammatory hyperpigmentation. Depending on its extent, it may have a considerable impact on the child's self-esteem and quality of life.

In our study, *impetiginisatio* was common and associated with the risk of severe AD. Patients with AD have an increased risk of bacterial skin infections [27]. Staphylococcus aureus colonizes the skin of most patients with AD and is the most common organism to cause infections [28]. The correlation between bacterial colonization and the severity of eczema was reported by several studies in the literature [29].

CONCLUSION

Our study revealed a high hospital prevalence of AD in Senegalese children with skin phototype VI. The frequency of xerosis, post-inflammatory hyperpigmentation, and keratosis pilaris remains the main clinical characteristics of AD in children with skin phototype VI. Our study was remarkable for the contribution of shea butter in reducing the severity of AD. This result is promising and should be confirmed by randomized studies on large numbers of patients. The parapharmaceutical emollients classically employed for this purpose are often inaccessible in our region because of their high cost.

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

D-dimer levels in patients with chronic urticaria: A case–control study on a Kashmiri population

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ABSTRACT

Background: Chronic urticaria (CU) is a common skin condition, affecting 0.5–1% of the population. Multiple studies have demonstrated that plasma D-dimer levels could be employed as a biomarker for disease activity and treatment response in patients with CU. **Aim:** The aim was to evaluate the correlation between D-dimer levels and the disease activity of CU. **Materials and Methods:** This study was a case–control study conducted on 120 patients suffering from CU and 50 healthy subjects. Plasma D-dimer levels were measured using ELISA. **Results:** Mean plasma D-dimer levels in the patients with CU (720.5 ng/mL) were significantly higher than those in the controls (405.6 ng/mL) ($p < 0.001$). A significant correlation was observed between plasma D-dimer levels and the UAS (urticaria activity score). **Conclusion:** The patients with CU had higher plasma D-dimer levels than the control group. A positive statistical correlation was observed between plasma D-dimer levels and the severity of CU.

Key words: Chronic urticaria; D-dimer; Autoimmunity

INTRODUCTION

Chronic urticaria (CU) is a pruritic skin condition characterized by wheals and/or angioedema lasting for at least six weeks or longer [1]. It is a common cause in patients presenting to primary care, emergency rooms, and dermatologists [2]. With a point prevalence of 0.5–1% in the population, it is one of the most common skin disorders encountered [3].

Chronic urticaria may severely affect the quality of life of the patient, due to the duration of symptoms, which may persist for years [4]. Nearly half of the patients have persistent symptoms even after three years of onset [5].

The release of histamine and other inflammatory mediators from mast cells causes an acute inflammatory response, including vasodilatation, increased fluid permeability, and the recruitment of various cells, which constitute the basic pathogenesis of the disease [1].

In CU, autoimmunity plays a major role. In a subset of patients, the coagulation cascade is also activated through the extrinsic pathway, which may increase plasma D-dimer levels [6,7].

Recent studies have demonstrated the correlation between plasma D-dimer levels and CU, suggesting the possibility of the use of plasma D-dimer levels as a biomarker for disease activity and response to treatment in patients with CU [8-11].

There is a paucity of data concerning plasma D-dimer levels in Kashmiri patients with CU. This study investigates the relationship between plasma D-dimer levels and disease activity in a Kashmiri population.

MATERIALS AND METHODS

This study was conducted after receiving clearance from the institutional ethical committee. A total of 120 patients with CU (more than two episodes a week

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for more than six weeks) who visited the outpatient department of dermatology of the Government Medical College in Srinagar, India, from November 2020 to July 2021, aged at least eighteen years, and clinically diagnosed with CU were included in the study. Patients with diseases or taking medications that could have altered the coagulation pathways were excluded from the study.

A total of fifty age- and sex-matched healthy subjects undergoing routine check-ups comprised the control group.

All cases and controls voluntarily agreed to participate in the study and signed a written consent form. Demographic data and personal, family, and medical histories were recorded.

Assessment of Disease Activity

All patients were interviewed by a dermatologist and the urticaria activity score (UAS) was determined. Disease activity was assessed on the basis of the EAACI/GA2LEN/EDF activity score [1], comprising the wheal score and pruritis score. Disease activity was scored from 0 to 6, where 0 was considered no disease, 1–2 mild disease, 3–4 moderate, and 5–6 severe.

Methods

Plasma D-dimer levels were measured using the ELISA (enzyme-linked immunosorbent assay) in accordance with the manufacturer's recommendations (Instrumentation Laboratory Company, Bedford, MA, 01730-2443 (U.S.)). Levels below 500 ng/mL were regarded as normal.

Statistical Analysis

The data was analyzed with the SPSS software. Descriptive statistics and percentages were used to describe the demographic data, clinical features, and plasma D-dimer levels. Non-parametric tests (e.g., chi-squared test) were employed to evaluate differences between the groups. Correlation was calculated using Spearman's rank test and logistic regression analysis. The statistical significance at $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics

Out of the 120 patients, 52 were males (43.3%) and 68 were females (56.7%), with a mean age of 33.5 ± 8.4 years. The average age of onset was 31.5 ± 8 years. The duration of disease in the majority of the patients was ≤ 1 year with a mean duration of 15 months. Out of the 120 patients, 29 (24%) had associated angioedema, whereas 15 (12.5%) had a family history of atopy (asthma, allergic rhinitis, etc.). A majority of the patients (56; 46.6%) had moderate disease severity, 41 (34%) had mild severity, and 14 (11.6%) had severe severity. Nine patients had the disease well under control.

Correlation between Plasma D-Dimer Levels and Disease Severity

The patients were divided into three groups: < 1 year, 1–5 years, and > 5 years. It was noted that D-dimer levels in patients who had a longer duration of the disease were significantly higher ($p < 0.05$).

The difference in the proportion of abnormal plasma D-dimer levels in the patients with CU and the control group was statistically significant (60.8% vs. 44%; $p = 0.04$) (chi-squared test: 4.05). Plasma D-dimer levels were significantly higher in the patients with CU than in the control group (720.5 ng/mL vs. 405.6 ng/mL; $p < 0.001$). Table 1 shows disease severity and plasma D-dimer levels among all groups.

DISCUSSION

It is imperative to find reliable biomarkers to assess disease severity when determining the correlation between disease severity and treatment response. A study by Raffael et al. [11] found that disease severity may also predict the duration of chronic spontaneous urticaria.

Studies have shown a link in the pathogenesis of CU with the activation of the coagulation cascade [7,12,13]. The activation of this cascade results in thrombin formation and the activation of mast cells. This leads to the release of histamine from mast cells and causes edema formation in urticaria [7]. D-dimer, which is an FDP (fibrin degradation product) is formed after the lysis of thrombus. It may remain elevated in the serum for around one week [14].

In our study, we observed higher D-dimer levels in the patients with CU than in the control group. Similar results were found in other studies conducted in other regions [8,10,14]. Thus, our study provides further evidence of a possible mechanism of coagulation cascade activation in patients with CU.

Our study demonstrated statistically higher plasma D-dimer levels and a higher proportion of abnormal

Table 1: Disease severity and plasma D-dimer levels among all groups

Disease activity group	No. of patients (%)	Mean plasma D-dimer levels (ng/mL)	Proportion of abnormal D-dimer levels in each group (*n* (%))
None	9 (7.5%)	530.6	4 (44.4%)
Mild	41 (34%)	619.6	23 (56.1%)
Moderate	56 (46.6%)	765.8	37 (66%)
Severe	14 (11.6%)	950	9 (64.2%)
Total	120	720.5	73 (60.8%)

plasma D-dimer levels in patients with CU. This was corroborated in a study by Asero et al. [15]. This finding is also supported by a literature review by Pavel et al. [16].

D-dimer levels and CRP show a strong correlation with CSU activity [16]. Our study also found a positive correlation between disease severity and serum D-dimer levels. Hence, D-dimer may play a vital role as a biomarker for CU severity. Besides, D-dimer levels in the plasma may also be employed to assess treatment response and potential antihistamine resistance to CU [17]. Therefore, D-dimer may be a predictor of response to treatment, more so in refractory cases or antihistamine-resistant CU.

Although several studies show a possible correlation between plasma D-dimer levels and CU, larger studies are needed due to the lack of strong evidence.

Limitations

The following limitations were noted in this study:
1. The correlation between D-dimer levels and treatment response was not assessed.
2. Other biomarkers were not assessed.

CONCLUSION

In our study, the patients with CU had higher plasma D-dimer levels than the control subjects, and the levels of D-dimer were higher in more severe cases. D-dimer levels may be considered a biomarker for disease activity/severity.

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

Level of adherence to acne treatment and associated factors in patients with acne in Yaoundé, Cameroon (sub-Saharan Africa)

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ABSTRACT

Background: Acne is a chronic inflammatory disease of the pilosebaceous follicle. The aim of this study was to assess the level of adherence to acne treatment and to identify factors associated with adherence to therapy in patients with acne. **Materials and Methods:** This was a descriptive, analytical, cross-sectional study conducted from January to April 2017 in three hospitals in Yaoundé. We included patients followed for acne for at least one month. The sampling was consecutive and exhaustive. Adherence to treatment was assessed according to the Morisky score. Data was analyzed with Microsoft Excel 2013 and the SPSS software, version 23. We employed the ANOVA test to find associations between the different variables. *p* values below 0.05 were considered statistically significant. **Results:** A total of 113 patients were selected, with a mean age of 26.0 ± 6.4 years. The mean Morisky score was 5.6 ± 1.9. Adherence to treatment was low, medium, and high in 58 (51%), 31 (28%), and 24 (21%) patients, respectively. The factors associated with low adherence were the presence of relapses, a psychological history, the number of previous treatments above two, and the duration of treatment above three months. **Conclusion:** Adherence to acne treatment was low in over half of the patients. In our context, the presence of relapse, a psychological history, the number of previous treatments above two, and the duration of treatment above three months were associated with low adherence to therapy.

Key words: Acne; treatment adherence; associated factors; Cameroon; sub-Saharan Africa

INTRODUCTION

Acne is a chronic inflammatory disease of the pilosebaceous follicle that progresses in flare-ups [1]. Acne is a common skin disease that usually begins at puberty, affecting up to 80% of adolescents, and may persist beyond adolescence or, to a lesser extent, appear in adulthood [2-4]. In 2009, it represented 7.7% of dermatoses in dermatology consultation at the Yaoundé General Hospital, thus constituting the third reason for consulting [5].

Despite the multitude of anti-acne drugs, the management of this common pathology remains difficult due to low adherence to anti-acne treatment. Adherence to any treatment is a transdisciplinary problem; in the literature, the level of adherence to a treatment varies from 50% to 60% regardless of the discipline [6]. For the specific case of acne treatment, adherence is low according to the literature. There are two types of obstacles to treatment adherence: primary (obstacles to initiating treatment) and secondary (obstacles to adherence and causes of the premature

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discontinuation of treatment) [6]. Therapeutic adherence is one of the keys to therapeutic efficacy. Lack of therapeutic adherence and, therefore, therapeutic failure, combined with the chronicity of acne and its inaesthetic character contribute to the alteration of the patient's quality of life (QoL). According to Moradi Tuchayi et al., it is important to identify obstacles to therapeutic adherence to anti-acne treatment, determine solutions, and prescribe the appropriate therapeutic protocol for each patient [6].

In sub-Saharan Africa, in general and more particularly in Cameroon, a developing country with its own socio-cultural and economic context, we also experience non-compliance to anti-acne treatment and a lack of adherence to treatment in some patients during our dermatological consultations. The aim of this study was to assess the level of adherence to anti-acne treatment and determine the factors associated with adherence in patients seen in the outpatient dermatology clinic in Yaoundé.

MATERIALS AND METHODS

Type, Site, and Duration of the Study

This was a four-month, descriptive, analytical, cross-sectional study conducted from January to April 2017 in three hospitals in Yaoundé. These hospitals were chosen by convenience based on the availability of a dermatologist: 'Biyem-Assi District Hospital (BADH), Elig-Essono District Medical Center (EE-DMC), and University Teaching Hospital of Yaoundé Center (UTHY).

Study Population and Criteria of Selection

We included patients with acne seen in the aforementioned hospitals: 1) presenting for a follow-up consultation after a medical prescription for an anti-acne medication initiated at least one month previously, 2) received a dermatology consultation after failure of the current anti-acne treatment or stopped for less than a month, 3) having given their informed consent to participate in the study.

Sampling

Sampling was consecutive and exhaustive during the study period. The minimum sample size was calculated by the Cochrane formula for descriptive studies, considering a prevalence of 7.7% for acne reported in hospitals in Cameroon by Bissek et al. [5] and a degree of precision of 0.05, hence the minimum number of 109 participants.

Procedures

Data collection

Data collection was performed with a technical sheet and proceeded in several stages: 1) the recruitment of participants was conducted during dermatological consultations; patients fulfilling the selection criteria were selected for the study; 2) clinical examination: the questionnaire searched for sociodemographic characteristics and determined the history of acne; a physical examination allowed for the description and classification of the clinical type and the assessment of severity with the Acne Lesions Rating Scale (ECLA) grid; 3) the assessment of the impact of acne on QoL with the Cardiff Acne Disability Index (CADI) questionnaire; 4) the assessment of therapeutic adherence with the Morisky score.

Data Collection Tools

Technical form

The technical form included socio-demographic characteristics (age, sex, profession, level of education), history of acne, clinical type, and the ECLA grid with its 3 factors F1, F2, and F3 [7].

Quality-of-Life Assessment Tool (CADI)

The CADI questionnaire is a QoL grid designed to assess QoL in adolescents and adults with acne. It is composed of five items [8].

Therapeutic adherence assessment tool: Abreviation of Morisky Medication Adherence Scale 8 is MMAS-8.

This is a validated, self-administered questionnaire that assesses adherence to treatment with a sensitivity greater than 90% [9]. It consists of eight questions, each with two answers to choose from: *yes* and *no*.

INTERPRETATION OF SCALES AND DATA ANALYSIS

Interpretation of Scales

Interpretation of the acne lesions rating scale

The total score was obtained by adding the scores of factors F1, F2, and F3, ranging from 0 to 36. An ECLA

score of 12 or below represented mild to moderate acne, while a score above 12 represented severe acne.

Interpretation of the CADI quality of life score

The score for each response ranged from 0 to 3 points for each question. The CADI score was calculated by adding the score for each question, varying from 0 to 15. The interpretation was as follows: 1) 0: no alteration in QoL; 2) 1–5: mild alteration in QoL; 3) 6–10: moderate alteration in QoL; 4) 11–15: severe alteration in QoL.

Interpretation of the assessment score for adherence to MMAS-8 treatment

Adhesion was assessed in accordance with MMAS-8 by adding the number of points for each question. Thus, adhesion was graded as follows: 1) *low* for a score below 6; 2) *medium* for a score between 6 and 7; 3) *high* for a score equal to 8.

Statistical Analysis

The data collected was analyzed with SPSS, version 23, and Microsoft Excel 2013. The results were presented in the form of tables and figures and expressed in terms of means ± standard deviations for the quantitative variables on one hand and, in terms of numbers and percentages, for the qualitative variables on the other. We employed the ANOVA test to find associations between qualitative and quantitative dependent variables (level of adherence assessed with the Morisky score). *p* values below 0.05 were considered statistically significant.

ETHICAL CONSIDERATIONS

We obtained ethical clearance from the Institutional Ethics and Research Committee of the Faculty of Medicine and Biomedical Sciences. Research authorizations were obtained from the competent authorities of the hospitals. We conducted our study in strict accordance with the fundamental principles of the Helsinki Declaration on research involving persons.

RESULTS

Description of Sociodemographic Characteristics

During the study period, a total of 1930 patients were seen in dermatology consultation. Among these, we recruited 113 predominantly female participants (83.2%), with a sex ratio of 0.2. The mean age was 26.0 ± 6.4 years, with extremes of 8 and 48 years.

Students were the most represented (57.5%) in our sample. We also noted a predominance of individuals with higher school education (70.8%).

Level of Adherence to Acne Treatment and Associated Factors

Adherence level

The mean treatment adherence score assessed by the Morisky score was 5.6 ± 1.9. In our sample, more than half of the patients had a low level of treatment adherence (58; 51.3%); (Fig. 1).

Factors Associated with Adherence to Acne Treatment

Adhesion level and sociodemographic characteristics

Adherence to treatment seemed not to be influenced by the different sociodemographic characteristics studied (sex, profession, level of education) (Table 1).

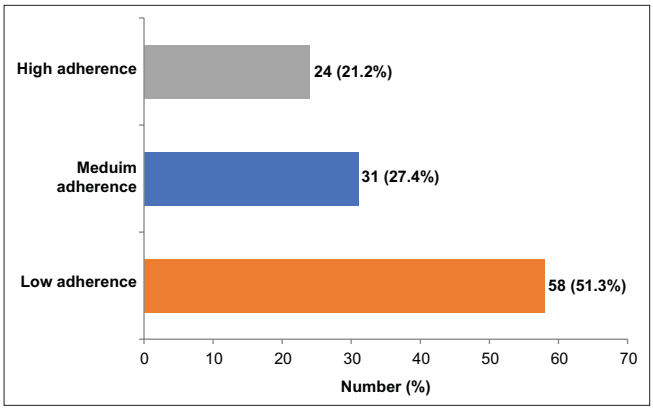

Figure 1: Level of adherence to acne treatment (*n* = 113).

Table 1: Sociodemographic characteristics (*n* = 133).

Variables	Morisky Score		*p* value
	Number	Mean	
Sex			
Male	19	5.9 ± 1.7	0.41
Female	94	5.5 ± 2.0	
Profession			
Unemployed	73	5.5 ± 2.0	0.85
Employed	40	5.6 ± 1.9	
Education			
Primary	7	5.8 ± 2.6	0.93
Secondary	26	5.5 ± 1.9	
University	80	5.6 ± 1.9	

Acne adhesion level and history

In our study, four variables explained the lack of adherence to treatment with a statistically significant association ($p < 0.05$). These were the notion of relapses ($p = 0.0001$), the duration of treatment ($p = 0.002$), the number of previous treatments ($p = 0.003$), and a history of psychological or psychiatric follow-up ($p = 0.012$) (Table 2). We deduced that the absence of relapses or a psychological history, the duration of treatment below three months, and the number of previous treatments equal to two or less would be associated with high adherence to treatment. In addition, the mean scores in patients on oral, topical, or combined therapy were 5.8 ± 1.8, 5.4 ± 1.9, and 5.6 ± 1.7, respectively. Patients, therefore, seemed to adhere better in the presence of oral treatment. However, this relationship was not statistically significant ($p < 0.05$) (Table 3).

Table 2: Association between the acne history and the level of adherence (n=133).

Variables	Morisky Score		p value
	Number	Mean	
Symptom onset (yrs.)			
< 10	5	3.7 ± 2.4	0.175
[10–24]	82	5.6 ± 1.9	
≥ 25	26	5.9 ± 1.8	
Therapeutic education			
Yes	56	5.5 ± 2.1	0.729
No	57	5.6 ± 1.8	
Relapse			
Yes	68	5.0 ± 1.8	0.0001*
No	45	6.3 ± 1.9	
Psychiatric and psychologic history			
Yes	4	3.2 ± 2.9	0.012*
No	109	5.6 ± 1,9	
Comorbidities			
Yes	10	4.9 ± 1.9	0.266
No	103	5.6 ± 1.9	
Number of previous treatments			
[1–2]	82	5.9 ± 1.9	0.003*
[3–4]	23	4.5 ± 2.0	
≥ 5	8	4.8 ± 1.6	
Duration of treatment (months)			
1–3	54	6.2 ± 1.9	0.002*
4–6	12	5.4 ± 2.1	
7–12	17	4.7 ± 1.8	

Table 3: Level of adherence and treatment (n=133).

Variables	Items	Morisky Score		p value
		Number	Mean	
Treatment	Local	98	5.4 ± 1.9	0.05
	Oral	69	5.8 ± 1.8	
	Combined	54	5.6 ± 1.7	
Adverse effects of local treatment	No	71	5.5 ± 2.1	0.72
	Yes	27	5.3 ± 1.5	
Frequency of daily application	Once	66	5.7 ± 1.8	0.06
	Twice	3	7.7 ± 1.6	
Adverse effect of oral treatment	No	55	5.4 ± 1.9	0.08
	Yes	14	6.4 ± 2.0	
Changement under treatment	Amelioration	90	5.4 ± 1.9	0.19
	None or aggravation	23	6.0 ± 2.1	

Table 4: Association between severity (ECLA score), quality of life (CADI score), and the level of adherence (Morisky score).

Variables	Items	MMAS-8 Score		p value
		Number	Mean ± ET	
ECLA score	Mild to moderate acne	84	5.5 ± 2.0	0.856
	Severe acne	29	5.6 ± 1.9	
CADI score	None	1	5.0 ± 0.0	0.576
	Mild	45	5.3 ± 1.9	
	Moderate	54	5.8 ± 2.0	
	Severe	13	5.6 ± 1.9	

Level of Adherence to Acne Treatment, Clinical Severity of Acne, and Quality of Life

We failed to find a statistically significant association between the severity of acne assessed with the ECLA score on one hand and the quality of life assessed with the CADI score and the level of adherence on the other ($p > 0.05$) (Table 4).

DISCUSSION

The aim of this work was to assess the level of adherence to anti-acne treatment and to research factors influencing this adherence in the sub-Saharan context, particularly, in Cameroon. Our participants were predominantly young (mean age: 26.0 ± 6.4 years; range: 8–48 years). According to the Morisky score (validated subjective assessment tool measuring adherence to anti-acne treatment), only 21.2% of our patients had a high adherence level to their treatment. Factors that influenced high adherence to treatment were the absence of relapses under treatment, the absence of a psychological history, the duration of treatment below three months, and the number of previous treatments equal to two or less.

Adherence to treatment influences its therapeutic effectiveness. This therapeutic adherence remains a real challenge for clinicians as the overall adherence to treatment, all specialties combined, falls at between 50% and 60% [6]. Tan et al. in their series in the U.S. found especially low therapeutic adherence to anti-acne treatment (11.8%) [10].

This corroborated our results, since only 21.2% of our participants had a high level of adherence to treatment. However, even if therapeutic adherence to acne treatment is never ideal, a meta-analysis by Snyder et al. underlines a great disparity in the level of therapeutic adherence. According to them, adherence varied from 7% to 96% for topical treatments and from 35.2% to 60% for systemic treatments [11]. These significant differences between the studies were linked to methodological differences, in particular, the use of different evaluation grids, thus enhancing the problem of reproducibility. Reproducibility is, indeed, difficult as most of the grids employed are not only different, yet are, above all, subjective. They are based on the patient's memory, such as the patient's ability to remember the names of the drugs they have been using [11]. Objective methods, such as counting tablets during consultations, are less often employed. In the meta-analysis by Snyder et al., 3 of the 14 studies employed objective methods [11]. The Morisky scale that we used in this work was certainly a subjective, yet validated method [9]; moreover, it seemed to us to be more appropriate. Indeed, while the counting of remaining tablets (oral treatment of acne) was easy to perform during routine consultations, the objective evaluation of the use of creams seemed more difficult to us. This difficulty stems, among other things, from the fact that, even if the precision scale is available, the amount of cream administered daily by each patient differs due to the variable application site from one patient to another.

The subsequent standardization of tools for assessing adherence in the specific case of acne would allow to better share experience between researchers and clinicians and a more comprehensive and efficient approach to solving the issue of adherence.

Furthermore, the mean adherence score in patients taking oral versus topical treatment was 5.8 ± 1.8 versus 5.4 ± 1.9, meaning better adherence to oral treatment when compared to topical treatment. Nevertheless, this difference may be explained by beliefs in the African context in general and in the Cameroonian in particular. Indeed, in the Cameroonian sociocultural context, there are popular beliefs according to which systemic drugs are more effective and act better from "inside" because of their "direct" passage through the body. In addition, several studies have noted superiority in adherence to oral treatment when compared to topical treatment [10,12].

Better adherence to oral treatment may also be justified by the rapid and undeniable effectiveness of oral isotretinoin, particularly in severe forms of acne. The rapid clinical efficacy of the molecule could encourage the patient to be more observant. This suggestion was supported by Tan et al., who specifically reported the effectiveness of isotretinoin treatment adherence when compared to antibiotics and topical treatment [12]. It should be noted, however, that some authors are not unanimous on the superiority of adherence to oral treatment when compared to topical treatment, as a recent work by Salamzadeh et al. has concluded that there is no significant difference in adherence between patients taking oral versus topical therapy [13]; this superiority, when found, is believed to be linked to isotretinoin. It would be appropriate to point out in favor of low adherence to systemic treatment, the conditions for taking certain anti-acne antibiotics, which could reduce compliance, in particular, taking them during a meal (to limit digestive side effects) and taking them in the evening (to limit phototoxicity, which is relatively common in the tropical zone).

Factors significantly associated with adherence to treatment were no relapse, no psychological history, the number of previous treatments less than two and the duration of treatment below three months ($p < 0.05$). The duration of treatment above three months and the presence of relapses could cause discouragement in patients, explaining the negative impact on treatment adherence. Regarding the negative impact of a psychological history on adherence to therapy, Moradi et al. in their meta-analysis identified and classified them among the secondary obstacles to treatment adherence [6].

Patients with psychiatric or psychological co-morbidities may lack understanding of the disease and treatment and frequently forget to take their medication. Identifying psychiatric co-morbidities in acne patients and proposing a therapeutic education plan adapted to their co-morbidity may provide a solution for this group of patients. Sex, onset of the lesions, side effects, and frequency of administration did not significantly influence adherence to treatment in our patients. Similar trends were found by Salamzadeh et al. in Iran, where patient adherence was not influenced by sex [13]. Conversely, an American study even found therapeutic adherence significantly associated with males [10]. Nevertheless, in 2008,

Jones Caballero et al. reported better adherence in females in Spain ($p < 0.05$) [14].

One would always expect to observe higher therapeutic adherence to anti-acne treatment in females when compared to males as females are generally more concerned about their appearance, yet this disparity could, today, reflect an increasingly frequent search for aesthetics in males as well. Some studies raise the age beyond 18 to 20 years as a factor of high therapeutic adherence. Growing beyond adolescence, patients may take medical prescriptions more seriously, especially with regard to respecting the rhythm of application of topical anti-acne and/or taking oral medications [10,14].

Moreover, with the popularization of mobile phones, computers, and the Internet, it seems important to note the American work by Park et al. [12] and the Italian work by Donnarumma et al. [15] and Fabbrocini et al. [16], who proved the effectiveness of daily or even twice-daily SMS reminders and the use of web-based acne training and monitoring tools. In addition to improving therapeutic adherence to acne treatment, these tools improved patient satisfaction. Experimental studies with similar tools in the Cameroonian context could be performed and contribute to the improvement of therapeutic adherence if effectiveness is also proven in our context.

Limitations of the Study

Certain aspects of this work might have constituted limits: 1) data collection tools, namely the acne lesion rating scale (ECLA) and the CADI grid, which assessed QoL, validated the Caucasian population and not the Negroid population; 2) the evaluation of adherence to treatment using indirect and, therefore, subjective methods could have made our results insensitive; 3) the lack of standardized tools for measuring adherence made it difficult to compare results and share experience between researchers and clinicians. However, this study could constitute a preliminary for further work on a larger scale or even experimental studies.

CONCLUSION

This study enabled us to observe a low level of adherence to anti-acne treatment in more than half of the patients in the Cameroonian context. The factors to be controlled in order to improve therapeutic adherence are relapses, psychiatric and psychological comorbidities, treatment longer than three months, and the multiplicity of previous cures. In the digital age, exploring the contribution of SMS and web tools to therapeutic adherence during subsequent studies in our context would be relevant.

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

Red gums as primary manifestations of skin diseases

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ABSTRACT

Background: Red gums, as a manifestation of chronic mucocutaneous diseases, is an infrequent oral complaint and are commonly due to plaque-induced gingival diseases in which a microbial biofilm and bad oral hygiene may precipitate gingivitis. **Patients and Methods:** This is descriptive, case-series study was conducted during the period from October 2019 to October 2020. Ten patients were presented primarily with red gums without an apparent identifiable cause. A full clinical history and examination were done. Laboratory investigations and biopsy were performed selectively. **Results:** Ten patients during the period of one year were included in this work. Two (20%) males and eight (80%) females were complaining of red gums. Their age on presentation ranged from 7 to 55 years, with a mean of 39.6 ± 12.4 years. Oral burning and discomfort with a bad odor were recorded in all patients, and this was moderate to severe, thus interfering with the process of consuming food. Also, gum bleeding after brushing or when minimally traumatized was a complaint in all patients. This study revealed that pemphigus vulgaris was the main diagnosis behind red gums in seven (70%) patients, followed by lichen planus in two (20%) patients, and viral reactionary gingival hyperplasia in one (10%) pediatric patient. Minimal skin involvement was observed in seven (70%) patients, with some patients unaware of its presence and it being discovered accidentally. **Conclusion:** Red gums are a common manifestation of chronic orodental conditions, yet could be part of systemic diseases and oral manifestations of primary cutaneous diseases. The current study highlighted that pemphigus vulgaris and lichen planus may initially and/or primarily present themselves as red gums, possibly delaying the proper diagnosis for months or even years. Hence, dermatologists and oral physicians should be aware of this clinical finding.

Keywords: Red gums; Pemphigus vulgaris; Lichen planus; Desquamative gingivitis

INTRODUCTION

Gingiva is a common location for both non-neoplastic and neoplastic lesions [1]. Gums presenting as shiny red, painful, and friable gingiva, which is clinically termed as desquamative gingivitis, may develop as a manifestation of various underlying conditions and may be divided into plaque-induced desquamative gingivitis and non-plaque-induced desquamative gingivitis. Plaque-induced desquamative gingivitis is a commonly recognized problem in daily dental practice [2]. Dental plaque-induced desquamative gingivitis is the most common form of gingival disease, in which the gingival inflammation results from microbial plaque accumulation. Local oral factors such as xerostomia and systemic conditions such as hyperglycemia, leukemia, and nutrient deficiencies may influence the severity of the inflammation. Red to deep purple and swollen gingiva with gingival bleeding is also a common sign in patients with leukemia. A deficiency of plasma ascorbic acid seen in scurvy is the only nutritional deficiency with documented effects on the periodontium, in which red, shiny, and swollen gums with bleeding on minor trauma, hyperkeratotic papules with corkscrew hairs in association with perifollicular hemorrhage, and petechiae and ecchymoses were the major mucocutaneous manifestations of scurvy [3,4].

Non-plaque-induced desquamative gingivitis is less frequent, yet often of great importance for patients [5],

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with middle-aged to elderly females being commonly affected. Mucocutaneous conditions, particularly lichen planus (LP), pemphigus vulgaris (PV), and mucous membrane pemphigoid (MMP), were responsible for the majority of these cases [2]. In LP, which is a chronic disease of an ill-defined etiology with an autoimmune reaction affecting the skin and the mucous membrane, isolated gingival involvement commonly presents itself as erythematous lesions affecting the gingiva, resulting in desquamative gingivitis; this was described in around 10% of patients [6]. PV is a rare, potentially fatal autoimmune disease in which oral lesions are the preliminary symptom in up to 70% of patients, with gingival lesions having been reported in a limited number of patients affected by PV, and is usually described as desquamative gingivitis manifested as red gingival erosions [7]. In MMP, the oral cavity, particularly the gingiva, is the most commonly involved site, in which gingival lesions are manifested by marked redness, erosions, and ulcerations [8].

In one review, oral LP was the major disease responsible for desquamative gingivitis in 75% of patients, followed by MMP (9%) and PV (4%), in a study performed by Lo Russo et al. on 125 patients with desquamative gingivitis [9], which is similar to a study by Leao et al., in which oral LP (71%), followed by MMP (14%) and PV (13%), was primarily responsible for desquamative gingivitis [10]. In another study, performed by Vaillant et al., MMP was the main cause of desquamative gingivitis in 39% of patients, followed by OLP and PV in 36% and 15% of patients, respectively [11].

Overall, MMP, oral LP, and PV are the main causes of desquamative gingivitis, with the first two accounting for about 80% of cases, whereas PV and other uncommon or rare disorders are responsible for the remaining proportion [9].

Other causes of red gums include chronic ulcerative stomatitis, Crohn's disease, allergic reactions to chemicals or mouth wash [2], and specific infections, including herpes simplex virus types 1 and candidiasis [5].

Therefore, the aim of this study was to recognize the dermatologic causes behind red gingival lesions and to report the gums as the primary and/or the only site of involvement in potentially significant dermatologic diseases.

PATIENT AND METHODS

Ten patients complaining of red gums were involved in this descriptive, observational, case-series study. The study followed the principles of the Declaration of Helsinki and informed consent was obtained from each patient after explaining the nature of the study. Close-up photographs were taken at the same place with a constant distance and illumination. A comprehensive history regarding the age of onset, the duration and progression of the disease, the associated cutaneous symptoms, and systemic diseases was taken from each patient. A trauma history, an oral hygiene history, and a family history of any autoimmune diseases were also reviewed in each patient.

The oral cavity of each patient was closely examined with an appropriate light source. The gingival and buccal mucosa, tongue, and palate were carefully examined against discoloration, swelling, vesiculation, or ulceration. The skin, nails, hair, eyes, and genital mucosa were also included in the clinical examination in an attempt to detect any associated cutaneous lesions. The lymph nodes were also examined. Diagnosis primarily relied on the clinical presentation, examination with laboratory investigations, and biopsy, and these were performed selectively.

Statistical Analysis

SPSS, version 23, was employed for data entry and analysis. The data was statistically described in terms of means, frequencies (number of cases), standard deviations (SD), male-to-female ratios, and percentages (%).

RESULTS

Ten patients, two (20%) males and eight (80%) females complaining of red gums with oral burning and discomfort, were included in the present study. The age of the patients on presentation ranged from 7 to 55 years, with a mean of 39.6 ± 12.4 years. The characteristics of the lesions and their severity in the studied patients were illustrated in Table 1. In all patients, oral discomfort was moderate to severe, interfering with the process of consuming food. Gum bleeding after brushing or when minimally traumatized was a complaint in all patients. In addition, a bad mouth odor was reported by many patients. Isolated gingival involvement was a complaint in only one (10%) patient, while primary gingival involvement in association with minimal erythema or

erosions elsewhere in the mouth was observed in the remaining nine (90%) patients. Also, minor skin lesions of PV and LP were detected, yet were often neglected by the patients unless they were specifically asked about their existence or they were discovered accidentally on examination. Biopsy was performed in selected cases, revealing either intraepidermal blisters with numerous inflammatory cells consistent with the diagnosis of pemphigus or dense, band-like, lymphocytic infiltrate in the papillary dermis with acanthosis of the epidermis in the cases of LP. Accordingly, based on the clinical and histopathological findings in the studied patients, PV was the chief diagnosis behind red gums (Fig. 1), affecting seven (70%) patients, five (71.4%) females and two (28.6%) males, with a mean age of 43.3 ± 6 years. Gingival and other minor oral mucosal involvement were seen in all pemphigus patients, while mild extraoral skin involvement was observed in five patients. LP was the second most prevalent disorder, affecting two (20%) female patients, with a mean age of 43 ± 8 years, in whom the main problem was gingival involvement with minimal oral mucosal lesions in one case and skin lesions in both patients (Fig. 2).

In one (10%) young female patient with a history of a sore throat persistent for five days, presenting with an isolated red gingival lesion with no other oral or extraoral lesions, a complete blood count (CBC) was performed to exclude the possibility of leukemia. While CBC was normal, a diagnosis of viral gingivostomatitis (viral reactionary gingival hyperplasia) was established.

In nine patients, the diagnosis was delayed for months or years and the patients had attempted different treatment approaches by the dentist, yet with no beneficial results, while, in a young female, the diagnosis was made early on the first visit.

DISCUSSION

The mouth plays a paramount role in speech, mastication, digestion, and immunologic defense. The oral mucosa is a common site for primary inflammatory or neoplastic disorders. However, it may show the early manifestations of systemic disease and, in many cases, oral findings may precede systemic diseases by months or even years [12].

Because desquamative gingivitis is not a diagnosis and is only a clinical term commonly used to describe a shiny red, painful, and friable gingiva, and may be a misleading term, in the present work, we advise the use of the simple descriptive term *red gums*, as many dermatologists are more familiar with this description of the lesions. In addition, gum problems presented in the current study were just red, hyperplastic

Table 1: Characteristics of the lesions and their severity in the studied patients.

Lesion Characteristics	Number of Patients	Percentage of Total
Only gingival involvement	1	10
Gingiva and other minor oral mucosal lesions	9	90
Diffuse involvement of the gums	10	100
Burning and discomfort	10	100
Bleeding on brushing or minor trauma	10	100
Minor cutaneous lesions	7	70

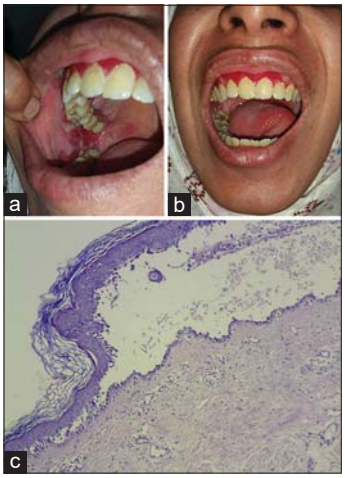

Figure 1: (a-b) 39-year-old female with pemphigus vulgaris showing red gums with minimal mucosal ulceration; (c) histopathology for the same patient showing an intraepidermal blister with numerous inflammatory cells (H&E, 10×).

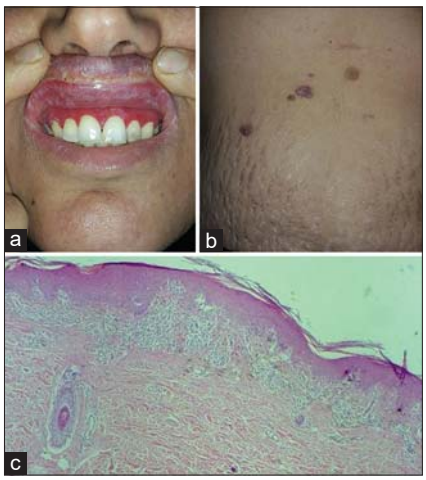

Figure 2: (a) 37-year-old female with lichen planus showing red gums and scaly lips; (b) cutaneous lichen planus lesions on the abdomen and (c) showing histopathology of lichen planus of the skin. (H&E, 10×).

discolorations of the gingival mucosa rather than inflammation, desquamation, or ulceration.

Red gums may develop as a manifestation of various underlying dermatological disorders [2]. In the literature, LP [13] and MMP [11] were the most prevalent etiologies behind red gums.

In the present work, diffuse gingival involvement was the predominant complaint observed in all patients with pemphigus, and LP manifesting itself as red gums was a finding consistent with a previous report [13].

This study clearly revealed that the two disorders were the main causes responsible for the development of red gums, including PV (70%) and LP (20%), which were documented in a period of one year.

Pemphigus vulgaris is a rare, potentially fatal autoimmune disease in which the oral mucosa is the first site involved in up to 70% of patients [7]. While in the Iraqi population, PV is not an uncommon endemic skin problem [14], this is the reason why, in the present study, pemphigus vulgaris was the major cause of red gums in seven (70%) patients. This finding is inconsistent with other studies, in which LP and MMP were the most prevalent diseases [11,13]. The mean age of the presenting patient was 43.3 ± 6 years and females were mainly affected. This finding agrees with a previous report [15].

Also, the present study showed that LP was the second disease responsible for red gums, affecting two (20%) female patients, although LP is a common problem in the Iraqi population [16,17]. This finding is inconsistent with previously mentioned studies [11,13]. The mean age of the presenting patient was 43 ± 8 years, and females were largely affected, which is in correspondence to another study [18].

Children may be affected by numerous gingival diseases, which may be due to local oral factors or reflect serious systemic diseases such as leukemia. Viral, fungal, and bacterial infections may result in non-plaque-induced gingival diseases in children. Viral infection of the gingiva may affect all age groups, presenting with a diffuse, erythematous, shiny gingiva and adjacent oral mucosa [19].

In the present work, one (10%) young female patient presented with an isolated red gingival lesion with no other oral or extraoral lesions. While CBC was normal, a diagnosis of viral gingivostomatitis manifested itself as viral reactionary gingival hyperplasia, a condition that may be commonly encountered in children, and this finding is in line with previous reports [19].

The present work did not report MMP, which is in contradiction to previous reports [11,13]. This may be explained by the rarity of cases of MMP in comparison with PV and LP in the Iraqi population [14,16].

Also, lupus erythematosus as a cause of gingivitis was not observed in this study, which is inconsistent with a previous study, in which gingivitis and red gingival macules were a common finding in patients with systemic lupus erythematosus [20].

The present work is one of the most important reports highlighting the significance of red gums (desquamative gingivitis) as the only or the earliest manifestation of skin diseases such as PV and LP.

It has been considered that the oral cavity is a diagnostic mirror and may be deemed as a window of the body, reflecting numerous important systemic diseases in their early stages [21]. The current work demonstrated that the mouth may be considered a mirror for dermatological disorders, as numerous skin diseases such as PV and LP may manifest themselves in the mouth as red gums prior to skin involvement.

CONCLUSION

The present work is an important documented report, revealing that PV and LP may manifest themselves as red gums earlier in the course of the disease, which makes the diagnosis especially difficult, possibly leading to unnecessary investigations and unsuccessful therapies. Hence, dermatologists and oral physicians should be aware of this clinical observation.

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 clinicoepidemiological study on topical steroid misuse in a tertiary-care hospital in North India and the role of dermoscopy as a non-invasive diagnostic modality

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ABSTRACT

Background: Topical corticosteroids (TCs) are one of the most frequently prescribed medications by dermatologists, yet may lead to an array of side effects due to prolonged and improper use. Because of the easy availability of topical corticosteroids as over-the-counter medications in India, these drugs are misused and abused. **Objective:** The objective was to determine the extent and the side effect profile of topical corticosteroid misuse/abuse in patients attending the OPD, to determine the demographic data and the reason and source of procuring TCs, and to characterize the dermoscopic findings of TSDF. **Materials and Methods:** This was a prospective, cross-sectional, clinical study conducted over a period of two years in which a predesigned, questionnaire-based proforma was employed. Patients above the age of fifteen reporting to the OPD giving a history of the application of a steroid cream continuously or intermittently for the minimum duration of four weeks were included in the study. A total of two hundred patients who met the clinical criteria were subjected to dermoscopic examination with a handheld dermoscope (DermLite DL4; 3Gen, U.S.; 10×). **Results:** A total of 2400 patients (fifteen-year-old or older) were enrolled in the study, in which 65% of the patients were females while 35% were males. Mostly, the patients procured these medicines from the pharmacist or paramedic, followed by general practitioners. The most common indications for which topical preparations were used included acne, followed by photodermatoses and ephelides. Most of the patients used combination creams, followed by potent steroids such as clobetasol propionate and betamethasone valerate. The most common side effects were erythema (74%), followed by photosensitivity (49%), hypertrichosis (47%), telangiectasia (42%), acneiform eruption (33%), contact dermatitis (21%), wrinkles (23.50%), etc. The main findings noticed on dermoscopy were irregularly dilated, branching, tortuous vessels almost interconnecting with each other in 79.78%, followed by hypertrichosis in 56.34%, white structureless areas representing atrophy in 42.33%, red dots in 7.22%, and a reddish background in 92.20%. **Conclusion:** The rampant use of TCs by patients for a prolonged period of time leads to a variety of side effects. Due to the topographical location, the climate of the valley, and the lighter skin type of the local population, the indications for which TCs were employed in our study group and the side effect profile were unique from the rest of the country. Dermoscopy may play a vital role in improving the diagnostic accuracy of TSDF and help us to differentiate it from close mimics.

Key words: Topical corticosteroids; Abuse/misuse; Side effect profile; Indications; Dermoscopy

INTRODUCTION

Topical corticosteroids (TCs) were introduced in dermatology in the 1950s. Owing to their potent anti-inflammatory and anti-proliferative effects [1], they became one of the most frequently prescribed medications by dermatologists. Soon after the advent of topical corticosteroids, their side effects began

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to surface. Prolonged and improper use of TCs may lead to an array of side effects, including skin atrophy, telangiectasias, striae, rosacea, acneiform eruption, ecchymosis, and steroid addiction [2-5].

Topical steroid damaged/dependent facies (TSDF) is a term denoting the phenomenon in which the misuse of and dependence on steroids applied to the face lead to a number of side effects such as erythema, telangiectasia, rosacea, atrophy, and acne. It is semipermanent or permanent damage to the skin of the face precipitated by the irrational, indiscriminate, unsupervised, or prolonged use of TCs, resulting in a plethora of cutaneous signs and symptoms and psychological dependence on the drug [6]. Similar side effects may be seen on any other part of the body as well when TCs are used over a prolonged period of time and may lead to atrophy, erythema, telangiectasias, and ecchymosis. Due to the easy availability of topical corticosteroids as over-the-counter medications in India, these drugs are misused and abused, which is responsible for the increasing number of patients presenting to the dermatology outpatient department (OPD) with signs and symptoms suggestive of steroid damage [7].

Objective

The objective was to determine the extent and the side effect profile of topical corticosteroid misuse and abuse in patients attending the OPD on any part of the body, to determine the demographic data, reason, and source of procuring TCs, and to characterize the dermoscopic findings of TSDF.

MATERIALS AND METHODS

This was a prospective, cross-sectional, questionnaire-based, clinical study conducted over a period of two years from May 2017 to May 2019. A predesigned, questionnaire-based proforma was employed for the study. Institutional ethical clearance was sought before undertaking the study. Patients above fifteen years of age reporting to the OPD giving a history of the application of a steroid cream continuously or intermittently to any part of the body for the minimum duration of four weeks were included in the study. The brand names of the preparations available on the market were requested. All patients younger than fifteen years, with PCOS, Cushing, or thyroid disorders, and those unwilling to answer the questionnaire were excluded from the study. Patients on systemic steroids, oral contraceptives, and hormone replacement therapy were also excluded from the study. Dermoscopic evaluation of the patients was performed in a later part of the study with a handheld dermoscope (DermLite DL4; 3Gen, U.S.; 10×) as the dermoscope was not available throughout the study period. Both polarized and non-polarized modes were used to study the characteristic features of TSDF. Images were recorded directly with the digital camera of the dermoscope with an attachment for a smartphone.

RESULTS

A total of 2400 patients (fifteen-year-old or older) were enrolled in the study and subjected to further questioning and examination. The majority of the patients were females (65%), as compared to males (35%). Most of the patients were in the 21–30 age group (35%) (Table 1). We noticed that the rural population consisted of 60% of the study group, while 40% were the urban population. The occupation-wise distribution included 28% of students, 26% of housewives, 24% of laborers, 12% of office workers, and 10% of businessmen and professionals. As for literacy level, 28% were undergraduate, 20% were graduate, 14% were postgraduate, and 38% were illiterate. Seventy-eight (78%) of the participants had heard about one or more of these topical preparations. Among them, 64% revealed the use of these preparations by a close family member or friend. None was aware of their side effects. Thirty-two (32%) were not ready to accept the fact that side effects were due to the use of TCs on the face and were not ready to stop their use despite our counseling. Most of the patients (83%) had been using TCs on the face, 9% had been using it on other parts of the body, and 8% had been using TCs on the face as well as on other parts of the body.

Most of the patients had procured these medicines from pharmacists or paramedics, followed by general practitioners and others (Table 2). Only in the case of 4%, these preparations were prescribed by the dermatologist. Twenty-seven percent of the patients had employed these preparations for acne, 19% for

Table 1: Age distribution of the study population

Age Distribution	Number of Patients (%)
< 20 years	504 (21%)
21–30	840 (35%)
31–40	648 (27%)
41–50	216 (9%)
> 50 years	192 (8%)

photodermatoses, 17% for ephelides, 14% for fungal infections, 12% for melasma, 7% for facial xerosis, and 4% for other indications (Table 3). The duration of application was not advised in 81% of the patients, yet 19% of the patients were advised not to prolong the use of these preparations without medical advice. In most cases, such information was given by the dermatologist.

The frequency of application was once a day in 76% of the cases, twice a day in 19.4%, and more than twice a day in 4.6%. Sixty-eight percent of the patients applied topical steroids to the entire face while 32% to the affected areas only. The duration of use was one to three months in 29%, three to six months in 33%, six months to one year in 20%, and more than one year in 18%. On questioning about the effects of treatment, 83% of the patients believed to have a transient improvement, while 17% saw no improvement after the use of TCs. Among these 17%, the primary disorder for which the drug was used worsened in 6%, while it remained as it was in 11%. On the stoppage of the drug, there was worsening of the symptoms in 89% of the patients and no effect in 11%. Asked about the reasons for continued drug use, the patient stated reasons such as maintaining improvement (79%) and the avoidance of withdrawal side effects (16%), while the remaining 5% gave various other reasons.

40.3% of the patients used clobetasol propionate while 29.4% used combination creams with clobetasol or gentamicin. 18.9% used betamethasone valerate, and 11% used mometasone cream, 1.3% used fluticasone cream. One side effect was seen in 15% of the patients and two side effects in 68%. Only 17% had three or more side effects. The most common side effect was erythema in 74% of the cases, followed by photosensitivity in 49%, hypertrichosis In 47%, telangiectasia in 42% (Figs. 1a and 1b), acneiform eruption in 33% (Figs. 1c and 1d), contact dermatitis in 21% (Fig. 2), pigmentary changes in 11% (Fig. 3a), papulopustular rosacea in 5% (Fig. 3b), atrophy in 5% (Fig. 3c), steroid-induced folliculitis in 4%, tinea incognito in 3%, and perioral dermatitis in 2.1% (Fig. 3d) (Table 4).

A total of two hundred patients were subjected to dermoscopic evaluation in our study. The main findings noticed on dermoscopy were irregularly dilated, branching, tortuous vessels almost interconnecting with each other in 79.78% of the cases, followed by hypertrichosis in 56.34%, structureless areas representing atrophy in 42.33%, red dots in 7.22%, and a reddish background in 92.20% (Figs. 4a – 4f). Other features observed were a fine, brown, reticular pattern on the background of a faint, light brown, structureless area in the cases of melasma (14%) and grayish-brown macules with interspersed, confetti-like, hypopigmented, macular areas in the cases those using combination creams for melasma, corresponding to exogenous ochronosis (3.5%).

Table 2: Source of procurement of topical corticosteroids (TCs)

Source of Procurement of TCs	Number of Patients
Pharmacists/paramedics	1032 (43%)
General practitioners	648 (27%)
Friends/relatives	456 (19%)
Advertisement	168 (7%)
Dermatologists	96 (4%)

Table 3: Disorder for which the patient had been using topical corticosteroids

Disorder Treated with TCs	Percentage of Patients
Acne	27%
Photodermatoses	19%
Ephelides	17%
Fungal infections	14%
Melasma	12%
Facial xerosis	7%
Other indications.	4%

DISCUSSION

TC misuse is a growing concern for dermatologists in India as it is slowly evolving into an epidemic-like condition. The rampant availability and use of TCs is alarming especially in a developing country such as India, as these medications are freely available on the market at very low prices. Also, for a significant number of patients, the first point of contact is the local pharmacist rather than the practicing doctor, selling these medications without proper prescription due to relaxed government guidelines [8]. Similar reports have been published in other countries [9-14].

Table 4: Adverse effects of topical corticosteroids in our study

Adverse Effects	Percentage of Patients
Erythema and telangiectasia	74%
Photosensitivity	49%
Hypertrichosis	47%
Acneiform eruptions	33%
Contact dermatitis	21%
Hypertrichosis	17%
Pigmentary changes	11%
Papulopustular rosacea	5%
Atrophy	5%
Steroid induced folliculitis	4%
Tinea incognito	3%
Perioral dermatitis	2.1%

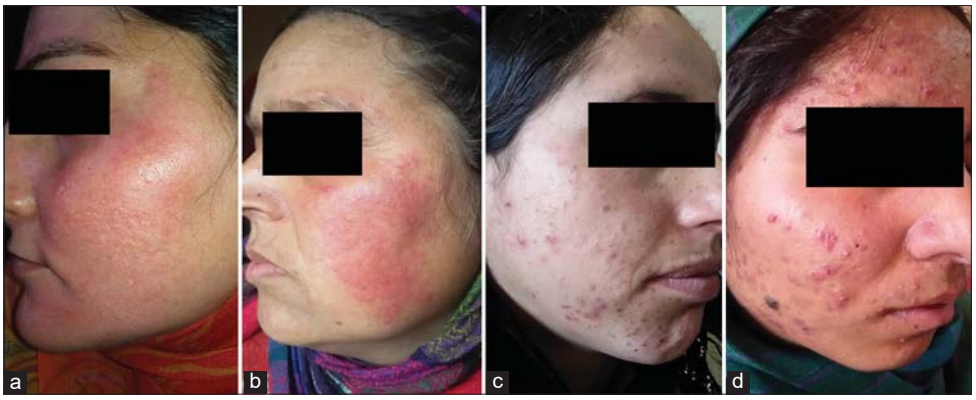

Figure 1: (a-b) Patients with erythema and telangiectasias of the face after the application of topical corticosteroids associated with photosensitivity. (c-d) Patients with acneiform eruption following the misuse of TCs.

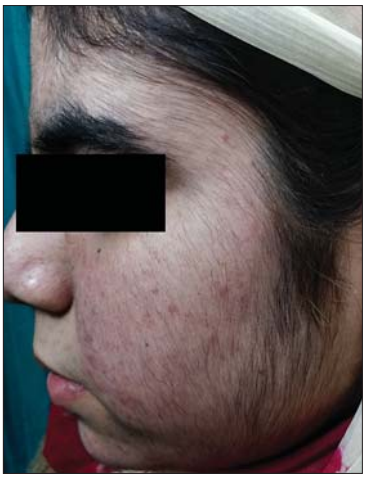

Figure 2: Patients with hypertrichosis after the use of topical steroids for a long time.

In our study, the total number of patients enrolled over the period of two years was 2400. We found that a higher number of patients were misusing TCs in our study when compared to studies done in India by Mahar et al. [15] and Jha et al. [16], in which 256 and 410 patients misusing TCs were enrolled over a period of six months and one year, respectively. The majority of the patients in our study were females, with a male-to-female ratio of 1:1.8, which may be attributed to females being more concerned about dermatological issues. This finding is in accordance with other studies from India [15-17]. Also, a majority of the patients were from rural areas, with an urban-to-rural ratio of 1:1.5, which was possibly because of the lesser availability of practicing dermatologists in the rural areas of our country. These patients have easy access to local pharmacies in which TCs are easily available and sold by the shop owner without prescription [8]. Also, due to the low price of these medications, the underprivileged people of rural areas purchase them instantly without seeking further medical advice [7].

In our study, we noticed that the majority of the patients were illiterate. Also, there was a decrease in the number of patients misusing TCs with an increasing level of literacy. However, we even noticed patients with higher qualifications misusing TC. The patients in our study group were from different occupational groups, including housewives, students, laborers, office workers, businessmen, and professionals.

Most of the patients obtained the drug from the local pharmacist or paramedic. This trend is an indication of the level of malpractice in our society in which even the most potent TCs are easily available at very low prices on the market and are sold by the pharmacist without effort due to relaxed government guidelines. Similar findings have been observed in other studies from India as well [16,17]. Also, there is a need to increase awareness among general practitioners who prescribe TCs, especially in combination with antibiotics and antifungals for common skin diseases presenting to them, as 27% of our patients had received TCs from the general practitioner. Another factor responsible for this trend in our society is the dearth of dermatologists in rural areas in our valley where the first point of contact for the patient is a pharmacist, followed by a general practitioner. Advertisements regarding the use of TCs should to be banned completely in our country. Also, the dermatologist needs to counsel all patients being prescribed TCs for relevant indications that the prolonged use of TCs may damage the skin and these medications are not safe for use by other family members. A prescription from the dermatologist should include the duration of application of the TC, as incomplete information may promote the misuse of such medicines.

In our study, we found that most of the patients had been using TCs for acne vulgaris, followed by

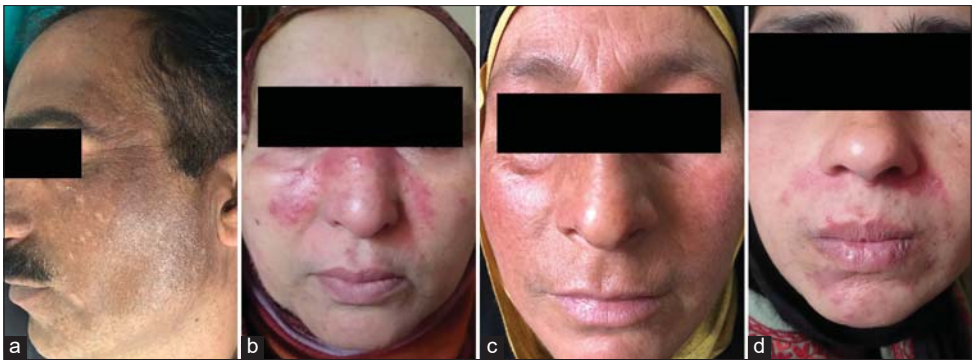

Figure 3: (a) Patient with exogenous ochronosis after the use of combination creams containing steroids. (b) Patient with papulopustular rosacea of the face following TC misuse. (c) Patient with topical steroid damaged facies with marked atrophy and erythema. (d) Patient with perioral dermatitis after the misuse of TCs for months for the prevention of facial dryness.

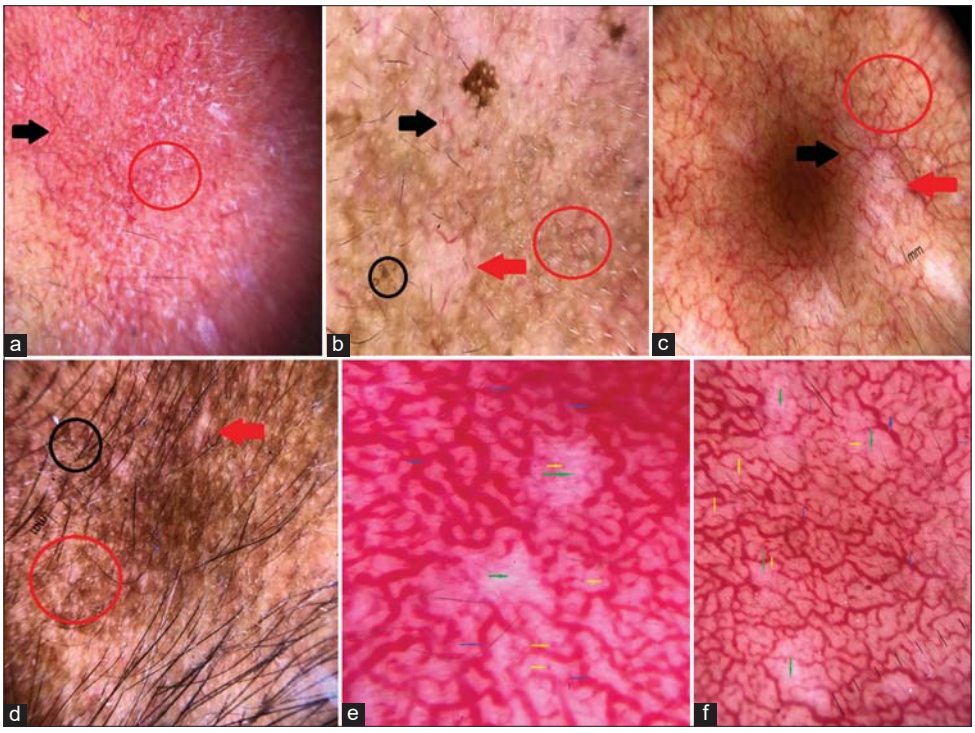

Figure 4: (a-d) Dermoscopic features in our patients, including white, structureless areas (red arrows), prominent, irregularly dilated, branching, tortuous vessels (black arrows), hypertrichosis (red circles), and a brownish background with dots and globules (black circle). (DermLite DL4, polarized, 10×). (e-f) Dermoscopic features in our patients, including white, structureless areas (green arrows), prominent, irregularly dilated, branching, tortuous vessels (blue arrows), hypertrichosis (red circles), red dots (yellow arrows), and a reddish background (DermLite DL4, polarized, 10×).

photodermatoses. Since Kashmir is situated at a high altitude, there is increased UV exposure in patients involved in outdoor agricultural activities. These patients use TCs to receive relief from common conditions such as polymorphic light eruptions and sunburns. However, as these patients use higher potency TCs such as clobetasol propionate and betamethasone valerate for prolonged periods of time, the benefits of TCs are masked by their side effects. Seventeen percent of the patients used TCs for ephelides as fair skin in the valley and increased UV exposure in the local population render people more prone to ephelides. Another condition that we noticed in our study for which TCs had been used was facial xerosis (7%). Due to cold weather conditions in the valley, people are more prone to dry skin, which is aggravated by frequent washing of the face and forearms for prayers by the majority Muslim population in the area. The indications for steroid misuse found in our study were different when compared to other studies from India and other countries. In studies by Sinha et al. [8], Rathi et al. [18], Sharma et al. [19], and Hammed AF [20],

TCs were used most commonly as a fairness or cosmetic agent. In a study by Mahar et al. [5], TCs were used most frequently for dermatophytosis. However, we noticed that, in our population, the use of TCs as a fairness agent was not seen frequently, as the local population has fair skin and a lighter skin phototype (Type 3). Also, in none of the studies published so far have TCs been misused for photodermatoses and facial xerosis. These conditions are common in the Kashmiri population due to the high altitude, increased UV exposure, poor sun protection, minimal use of sunscreens, and dry weather conditions of the valley. Most of the patients had used TCs once a day, followed by twice a day. However, several patients applied it numerous times a day to the drying effect of the cold weather in which TC application was associated with the relief of the dryness.

The main symptom noted in our study group was erythema and telangiectasias in 74% of the patients, followed by photosensitivity in 49% and acneiform eruption in 33%. Our findings were different from a study done in India [15] in which tinea incognito was the most common side effect seen, followed by acneiform eruption. Other studies from India [16,19] have found acneiform eruption topping the list of side effects. We also noted acneiform eruption in quite a number of patients. However, due to the fairer complexion of the majority of the population in the valley, the most common side effect noted was erythema with telangiectasias, which was early to occur and most noticeable, followed by photosensitivity.

Dermoscopic evaluation was done in two hundred patients at the end of the study. The main dermoscopic features seen in our study were consistent with other studies, which included prominent telangiectasias, ivory-white-to-strawberry-colored patches, and lesional hypertrichosis [21]. The white structureless areas correspond to areas of dermal atrophy [22]. Also, features of melasma and exogenous ochronosis on dermoscopy were observed in 14% and 3.5% of the patients, respectively, who were using combination creams for melasma. These findings were consistent with the dermoscopic features seen in these patients as reported in other studies [23]. However, in a recent study done in India, dermoscopy of TSDF revealed brown globules (96.2%), followed by red, diffuse areas (92.4%), and vessels (87.1%) as the most common findings, which could represent the melasma for which the patient applied TCs [24].

CONCLUSION

Topical corticosteroids are a highly important class of drugs for the dermatologist. However, the rampant use of TCs by patients for a prolonged period of time leads to a variety of side effects. Due to the topographical location and climate of the valley, the indications for which TCs were used in our study group varied from other studies done in India. Also, due to the lighter skin type in our population, the side effect profile was also unique from the rest of the country. Thorough knowledge of the pattern of side effects with the need to increase awareness among practitioners and prevent the sale of TCs as over-the-counter medications will help to bring down the side effects associated with the misuse and abuse of TCs. Dermoscopy may play a vital role in improving the diagnostic accuracy of TSDF and help us to differentiate it from close mimics.

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

Mucosal involvement in bullous pemphigoid in Northeast Morocco

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ABSTRACT

Background: Bullous pemphigoid is a common autoimmune bullous disease that mainly affects the elderly. Mucosal involvement in bullous pemphigoid remains rare and is in the order of 10% to 30%. Our objective was to evaluate the prevalence of mucosal involvement in our patients with bullous pemphigoid and to study its epidemiological, clinical, and therapeutic particularities. **Material and Methods:** We conducted a prospective epidemiological study, collecting patients with bullous pemphigoid, over a period of eleven years. We divided our study population into two groups, with and without mucosal damage, and compared different parameters between these two groups. **Results:** We collected 85 patients diagnosed with bullous pemphigoid. The mean age at diagnosis was 70.54 years. A neurological history was reported in nine (10.7%) of our patients, Drug intake was noted in 14.3%. Associations with autoimmune diseases were found in 25 patients. The typical form of PB was found in 74% of our patients with extensive skin involvement of more than 30% of the body surface in 44.7% of the patients. Twenty-nine patients (34.1%) presented mucosal lesions. The oral mucosa was the most frequently affected surface. Among the patients with mucosal involvement, twenty-five (86.2%) had isolated mucosal surface involvement. In patients with oral involvement, the most frequent mucosal lesions were erosions of the soft palate and the inner face of the cheeks. The comparative analysis between the two groups revealed that patients with mucosal involvement were younger, with an average age of 69.5 years vs. 71.12 years, $p = 0.54$. We also noted that patients with mucosal involvement more frequently presented with heard skin disease ($p = 0.01$). Regarding therapeutic management, we noted a more frequent need for the addition of systemic treatment to topical corticosteroids as compared to other patients ($p = 0.01$). **Conclusion:** The involvement of the oral mucosa remains rare and is correlated with more severe and extensive involvement of the disease with the ineffectiveness of first-line treatment. Further studies are needed at the national level to better assess these characteristics in the Moroccan population.

Key words: Bullous pemphigoid; Mucosa; Severity

INTRODUCTION

Bullous pemphigoid is a common autoimmune bullous disease that mainly affects the elderly. It is characterized by the presence of autoantibodies directed against basement membrane proteins [1]. Clinically, the typical form associates naked pruritus with eczematous and urticarial lesions that precede the appearance of tense bullae, usually large, bilateral, and symmetrical. In more atypical forms, eczematous lesions, prurigo type lesions, vesicles, cocoon lesions, and scratching excoriations are found [2,3]. Mucosal involvement in bullous pemphigoid remains rare and is in the order of 10% to 30% in the form of bullae or erosions, it mainly affects the oral mucosa and generally is the involvement of a single mucosa [4]. The objective of our study was to evaluate the prevalence of mucosal involvement in our patients with bullous pemphigoid and to study their epidemiological, clinical, and therapeutic particularities.

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MATERIALS AND METHODS

Study Design

We conducted a prospective, epidemiological study, bringing together patients with bullous pemphigoid hospitalized or followed in consultation at the dermatology department of the Hassan II CHU in Fez, Morocco, over a period of eleven years.

The diagnosis of PB was retained by confrontation with clinical data: a bubble stretched on an erythematous or healthy skin, histological; a subepidermal bubble with eosinophilic infiltrate and immunohistochemistry; direct immunofluorescence IFD showing deposits of IGG and complement the slow of the dermo–hypodermic junction. Indirect immunofluorescence has been performed only in several patients, showing the presence of anti-PB180 and anti-PB230 antibodies.

Faced with an atypical presentation of bullous pemphigoid, NACL cleavage was performed. All patients with subepidermal labeling in favor of acquired epidermolysis bullosa in the cleavage were subsequently excluded.

All patients were interviewed and examined. Patient information and clinical, biological, and therapeutic data were entered into a computer system, allowing easy data collection. Photographs were taken during hospitalization or at the first consultation, then during follow-up after patient consent.

The severity of the disease was evaluated depending on the skin surface. The diagnosis of a severe form was retained if the skin surface involved was higher than 30%.

We divided our study population into two groups—with and without mucosal involvement—and compared different parameters between these two groups.

Statistical Analysis

Descriptive, univariate analysis with SPSS Statistics, version 21, was performed. In descriptive analysis, the quantitative variables were expressed by means ± standard deviations and the qualitative variables by percentages. The chi-squared test was employed to compare the percentages in order to determine the factors associated with mucosal involvement in patients with BP. A p value less than 0.05 was considered statistically significant.

RESULTS

Descriptive Study

Characteristics of the general population

Over this period, we collected 85 patients diagnosed with bullous pemphigoid, among which 37 (43.5%) were males and 48 (56.5%) were females. The mean age at diagnosis was 70.54 years, ranging from 24 to 113. Fifty-six patients (65.9%) reported the presence of a personal history, including diabetes (n = 17; 21.3%), dyslipidemia (n = 8; 10.0%), hypertension (n = 21; 25.9%), and heart disease (n = 4; 4.9%). Regarding neurological ATCDs, these were reported in nine (10.7%) of our patients. We noted a stroke in eight (9.9%) patients and Parkinson's disease in five (7.7%) patients. Drug intake was noted in twelve (14.3%) of our patients. Associations with autoimmune diseases were found in twenty-five patients (29.8%), including diabetes in seventeen patients, dyslipidemia in three patients, one case of vitiligo, Biermer's disease, psoriasis, and also lupus. Clinically, the typical form was found in 74% of our patients, with extensive skin involvement of more than 30% of the body surface in 38 patients (44.7%). Mucosal involvement was reported in 29 patients (34.1%); IC 95% (25.4%; 42.8%). Biologically, 62.4% of the patients had hypereosinophilia. All our patients were administered a protocol for PB: clobetasol propionate with a recourse to another systemic treatment (oral corticosteroid, DDS, cyclins, rituximab, etc.) in 38.8% of the cases.

Mucosal involvement

Twenty-nine patients (34.1%) presented mucosal lesions. Descriptive analysis of this group of patients (Table 1) showed that the oral mucosa was the most frequently affected surface (n = 27; 93.1%). Seven patients (24.1%) had genital involvement, two (6.9%) had nasal involvement, and one (3.4%) had anal and eye involvement. Among the patients with mucosal involvement, 25 (86.2%) had isolated mucosal surface involvement, while seven (24.2%) patients had two types of mucosal surface involvement concomitantly. In patients with oral involvement, the most frequent mucosal lesions were erosions of the soft palate (n = 17; 62.9%) (Fig. 1), followed by erosions of the inner faces of the cheeks (n = 16; 59.3) (Fig. 2), the tongue (n = 4; 14.8%), the gums (n = 2; 7.4%), and the labial mucosa (n = 2; 7,4%) (Fig. 3).

Genital involvement was observed in six patients, four of whom were females with erosions of the lips. Two

Table 1: Distribution of mucosal involvement in the study population.

Characteristic	Patients with Mucosal Involvement (*n*=29)	Patients without Mucosal Involvement (*n*=56)	*p* value
Mean age	69.5 yrs.	71.12 yrs.	0.54
Sex			
Male	13 (44.8%)	24 (42.8%)	0.34
Female	16 (55.2%)	32 (57.2%)	
Associations			
Neurological pathology	5 (17.2%)	4 (7.14%)	0.28
Autoimmune pathology	6 (20%)	19 (33.9%)	0.30
Medication intake	3 (10.3%)	9 (16.07%)	0.69
Distribution of bullous lesions			
Limbs	27 (93.1%)	40 (71.4%)	0.67
Trunk	27 (93.1%)	46 (82.1%)	0.29
Head and neck	14 (48.2%)	20 (35.7%)	0.37
Extent (> 30%)	18 (62.1%)	20 (35.7%)	0.01*
Peripheral eosinophilia	20 (68.9%)	33 (58.9%)	0.54
Need for systemic treatment	17 (58.6%)	16 (28.5%)	0.01*

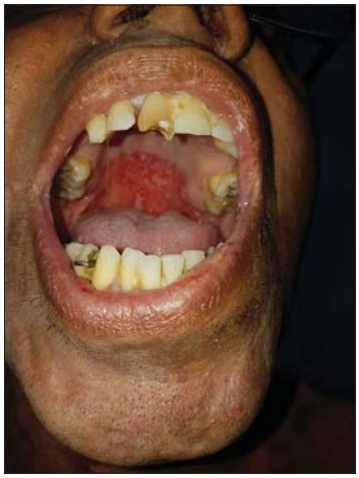

Figure 1: Erosions on the palate

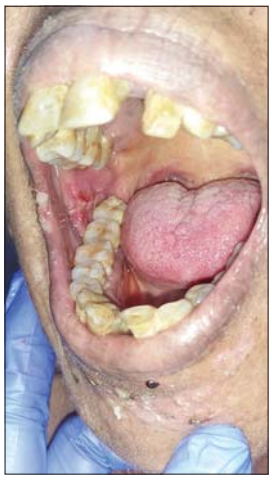

Figure 2: Multiple erosions on the inner side of the cheeks.

male patients presented with erosions on the glans penis. We noted nasal involvement in two patients with endonasal erosions and anal involvement in only one patient. Ocular involvement was detected in only one patient with conjunctival hyperemia without ophthalmic sequelae.

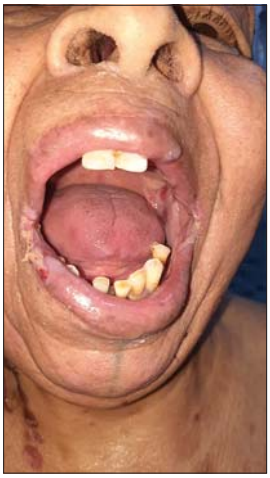

Figure 3: Bulla and erosions on the labial mucosa.

Analytical Study

We studied the epidemiological, clinical, biological, and therapeutic differences between patients with BP with mucosal involvement (n = 29) as compared to other patients with BP without mucous damage (n = 56) (Table 2). Patients with mucosal involvement were younger, presenting with an average age of 69.5 years vs. 71.12 years, without a statistically significant association ($p = 0.54$). We noted no significant difference regarding sex. Regarding the association of neurological pathologies and autoimmune disease, respectively, they were reported in 4 (7.14%) and 19 (33.9%) in the group without mucosal involvement, in 5 (17.2%) and 6 (20%) in the group with mucosal involvement without a statistically significant association ($p = 0.28$) and ($p = 0.30$). Concerning the anatomical distribution

Table 2: Demographics, clinical characteristics, and treatment of patients with bullous pemphigoid with mucosal involvement vs. other patients without mucosal involvement.

Mucosal Involvement	*n* (%)
Mucosal lesions	
yes	29 (34.1%)
no	56 (65.9%)
Distribution	
Oral mucosa	27 (93.1%)
soft palate	17 (62.9%)
inner face of the cheeks	16 (59.3%)
tongue	4 (14.8%)
gum	2 (7.4%)
labial mucosa	2 (7.4%)
Genital mucosa	7 (24.1%)
Nasal mucosa	2 (6.9%)
Ocular mucosa	1 (3.4%)
Anal mucosa	1 (3.4%)

of the bullous lesions, we observed no statistically significant difference between the two groups in relation to the involvement of the trunk, limbs, face, and folds. On the other hand, we noted that patients with mucosal involvement presented more frequently with heard skin disease (SC > 30%): n = 18 (62.1%) vs. n = 20 (35.7%), respectively ($p = 0.01$). We also noted peripheral eosinophilia in 20 (68.9%) patients with mucosal involvement vs. in 33 (58.9%) in the group without mucosal damage without a statistically significant relationship ($p = 0.54$). Regarding therapeutic management, we noted a more frequent need for the addition of systemic treatment to topical corticosteroids when compared to other patients (n = 17, 58,6%, vs. n = 16, 28,5%) ($p = 0.01$). The main associated systemic treatments were oral and bolus corticosteroid therapy, cyclins, Disulone, and rituximab with good evolution.

DISCUSSION

Mucosal involvement during bullous pemphigoid is generally rare. Its absence is one of the clinical criteria for the positive diagnosis of bullous pemphigoid. Several studies have been interested in estimating the prevalence of mucosal involvement in patients with PB as well as studying the characteristics of these patients. The prevalence of mucosal involvement in PB varies between 10% to 30% depending on the series [4,5]. Higher prevalence rates of 18.6% and 14.5% were observed in northern France [6] and Switzerland [7], respectively. A low prevalence of 5.7% was reported in Singapore [8]. In our study, we noted mucosal damage in 28 out of the 85 patients (34.1%).

Regarding the mucosal locations most affected in bullous pemphigoid, some studies as well as ours report that the involvement of the oral mucosa is the most frequent. In an Israeli study, the involvement of the oral mucosa was present in 45 out of 56 patients (80.4%). This mucosal involvement was mainly limited to non-keratinized mucous surfaces. The involvement of the oral mucosa and soft palate was observed in 25 (55.6%) and 24 (53.3%) patients with oral involvement, respectively, while the involvement of keratinized mucous structures, such as the gums and the back of the tongue, was less common. They also observed a prevalence of laryngeal involvement estimated at 4.8% following the performance of systematic laryngoscopy in all patients with mucosal involvement, even in the absence of laryngeal symptoms [5]. This was a new finding, only reported in anecdotal case reports and not found in other studies [9]. In our study, the oral mucosa was the most frequently affected surface (n = 27; 93.61%) with more frequent involvement of the palate and the inner face of the cheeks and less frequent in the tongue, gums, and lips. The other mucous membranes in bullous pemphigoid, including genital, ocular, and nasal, are less common [10].

Regarding the age of patients and its relationship with the presence of mucosal involvement, the results of studies are contradictory. Some studies have shown a significant relationship between a younger age and mucosal involvement. Others have not. In a 2019 Israeli study, patients with mucosal involvement were significantly younger at presentation (71.8 (14.4) years vs. 79.3 (8.10) years, respectively; $p < 0.001$) [5]. As in a study by Clapé et al. as in ours, we did not report this finding. This may be explained by a small sample size [6]. We found no significant association between sex and mucosal damage, and this was the case in most studies [11]. Clinically, we found that the presence of mucosal involvement was correlated with more extensive involvement, more than 30% of the skin surface, 62.1% versus 35.7%, $p = 0.01$. This is consistent with a recent French study, showing that patients with mucosal involvement had both more active and more extensive disease [6]. We found no relationship between the presence of mucosal involvement and the location of bullous lesions in the skin, unlike Kridin et al., who found that patients with mucosal involvement more frequently had skin lesions in the head and neck ($n = 29$; 51.8%). Biologically, we found no significant associations between peripheral eosinophilia and mucosal involvement, and this agrees with the conclusion of a recent study, which found no significant correlation between the severity

of mucosal damage and peripheral eosinophilia [12]. On the other hand, another study revealed a higher prevalence of mucosal damage in patients with BP with normal eosinophils when compared to those with peripheral eosinophilia ($p = 0.002$), which led them to question a likely protective role of peripheral eosinophilia in bullous pemphigoid with mucosal involvement [13]. In the present study, we found no correlation between mucosal involvement and the presence of neurological, autoimmune, or drug-induced disease. Recently, Chijiwa et al. reported more severe mucosal involvement in patients with BP when taking dipeptidyl peptidase-4 [14]. In addition, 36 patients with BP associated with dipeptidyl peptidase-4 were recently found to have mucosal lesions more frequently [15]. Regarding autoantibodies to bullous pemphigoid, the presence of mucosal involvement was correlated with the presence of IgG against the NH2- and COOH-terminals of BP180, the absence of anti-BP230 antibodies, and high deposits of IgA and C3 at the dermal–epidermal junction [16]. This was also reported in a study by Clapé et al., who objected that the absence of anti-BP230 autoantibodies was the only factor independently associated with mucosal involvement. In our study, we did not analyze this parameter.

Finally, in our study, we used systemic treatment in addition to topical treatment in patients with mucosal involvement (58.6% vs. 28.5%; $p = 0.01$). This result is similar to an Israeli study in which patients with mucosal involvement were treated with higher doses of systemic corticosteroids and adjuvants as compared to other patients with BP [5]. Another study showed that mucosal lesions respond more slowly to conventional treatment, thus prolonging the duration of treatment [17].

Through our study and the literature, we were able to focus on several characteristics of patients with bullous pemphigoid with mucosal involvement. In particular, patients with mucosal involvement tend to be younger with statistically varying degrees of significance depending on the study. Mucosal involvement is correlated with more extensive and severe disease with more probable involvement of the face and neck, the absence of anti-BP230 antibodies, and the presence of IGG against the NH2- and COOH-terminals of BP180. A low level of peripheral eosinophilia may also be correlated with the presence of mucosal involvement. Generally, in these patients, drug intake is, in particular, the oral antidiabetic, and these will resort to a systemic treatment for the control of the disease. This could lead us to think about attempting a systemic treatment in the case of PB with mucosal involvement for an earlier control of the disease. Further studies are needed at the national level to increase the study sample size and better assess these characteristics in the Moroccan population.

CONCLUSION

The involvement of the oral mucosa in patients with PB is frequent, with a prevalence ranging from 10% to 30% according to various studies. In our study, the prevalence was estimated at 34.1%. It is associated with more severe and extensive involvement of the disease, with the ineffectiveness of first-line treatment.

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.

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Our Dermatology Online

Original Article

Dermatoses among snow skiers in North India

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ABSTRACT

Background: Snow skiers are directly exposed to a variety of extreme environmental conditions, which may lead to numerous physiological and pathological changes in the skin, and potentially increased chances of various specific and non-specific skin diseases. Although there are studies on skin diseases caused by exposure to cold and high altitudes, yet those on snow skiers are scarce as the study population is small. **Objective:** This study was undertaken to observe various dermatoses existing exclusively in snow skiers. **Methods:** It was a descriptive, cross-sectional, community-based study conducted at the world-famous ski resort Gulmarg Kashmir in North India. The initial questionnaire-based assessment and the subsequent examination of those exhibiting skin involvement were undertaken by visiting places of accommodation for snow skiers as well as on-spot visits to skiing slopes. **Result:** The most common dermatological manifestations in our study were dryness (xerosis) and its related aftereffects such as pruritus and chapping of the lips, followed by UV-related skin damage such as whole-face tanning, various types of infections and infestations, and endogenous eczema, including seborrheic and xerotic eczema. Direct cold-related injuries such as perniosis and various forms of urticaria were also common presentations. **Conclusion:** Snow skiers are especially susceptible to a variety of dermatoses because of exposure to cold conditions and direct contact with the snow. Proper protective measures against cold and snow and awareness about preventive strategies may decrease the chances of snow skiers developing various dermatoses, thereby reducing morbidity and work and economic loss.

Key words: Snow Skiers; High Altitudes; Cold; Dermatoses; Gulmarg

INTRODUCTION

Snow skiers are subject to a variety of environmental conditions during skiing activities. Direct contact of the skin with ice and snow and exposure to low temperatures, low humidity, high altitudes, and cold air, wind, and water lead to transepidermal water loss with subsequent dry and scaly skin [1,2].

Extreme temperature shifts due to cold outside and hot and/or dry conditions inside due to the use of various heating equipment, as well as hot water baths, initiate and aggravate the dry skin conditions. High UV exposure due to direct sunlight and that reflected from snow (the so-called *albedo effect*), lead to UV damage causing erythema, tanning, polymorphic light eruptions, and the aggravation of pre-existing photodermatoses [3-7].

Increased sweating during workouts and compromised skin hygiene because of the decreased frequency of bathing and changing one's clothing due to various social and circumstantial inhibitions and overcrowding also lead to skin changes.

As a result of the multitude of exposures, numerous physiological and sometimes pathological changes occur in the skin. As a result, skiers are prone to experience a variety of new skin diseases and exhibit the aggravation of those already existing, which may be specifically related to snow skiing activities along with other non-specific as seen in the general population.

Sun damage (erythema, tanning, light eruptions), xerosis, frostbites, and the trench foot are known skin involvements in snow skiers [8-12]. Cold urticaria is common as well [13-15].

Various infestations such as pediculosis, scabies, and bacterial, viral, and fungal infections are also common. Other dermatoses, such as insect bite reactions,

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dermatitis neglecta, and terra forme dermatitis, were also reported [16].

Worldwide, a number of studies have been conducted on dermatological diseases in those residing at high altitudes and in cold areas [17,18]. Yet, studies exclusively on snow skiers are scarce. This encouraged us to conduct this study on snow skiers to search for skin diseases specifically related to snow skiing activities and document any other skin diseases.

MATERIALS AND METHODS

This descriptive, prospective, observational, cross-sectional, community-based cohort study was conducted at Gulmarg in the Kashmir province of India, a world-famous winter sports resort. Our cohort consisted of snow skiers visiting and camping at the ski resort.

Included were snow skiers aged fourteen years or above camping at the ski resort for the sole purpose of snow skiing. Excluded were smokers, those with comorbidities such as thyroid, kidney, or liver diseases, and those with known hypersensitivity reactions to drugs.

New dermatoses developing after the arrival at the ski resort or those exacerbating were included in the study, such as xerosis, UV-related skin disorders, cold-related injuries, insect bite reactions, infestations, and others, whereas those not specific to high altitudes, such as acne vulgaris, vitiligo, keloids, congenital diseases, were not considered unless specifically exacerbated by exposure to cold and snow.

The snow skiers were screened at hotels, huts, tents, and other places of accommodation and on the spot on snow skiing slopes by a team of dermatologists, who camped at the ski resort for two weeks every year for two consecutive years in 2020 and 2021 one week each in January and February. Subjects once enrolled for a dermatological condition were excluded for the same dermatoses on subsequent visits or in the subsequent year.

All snow skiers coming in contact with the same study team were asked about the appearance of symptoms and signs of new skin conditions or the aggravation of existing diseases after the arrival at the ski resort. After taking proper informed written consent from those with the presence of any skin-related concern, a detailed history was taken and dermatological examination was performed and documented in a prepared format at the places of accommodation or another convenient place by the same team, keeping subject privacy in consideration. Those in need of necessary investigations were asked to report to our practicing hospital for the same.

Three hundred subjects were studied over the study period of two years, confining to this number for the convenience of statistical analysis.

Approval from the institutional ethics committee of our institute was obtained. Voluntary participation, subject confidentiality, and human subject protection were ensured. The study subjects were made aware of preventive strategies in order to avoid snow-, cold-, and high-altitude-related dermatoses and other medical conditions, and at times provided with some of the medications free of cost from the samples available with the study team.

The data was collected in an Excel sheet and the calculations were performed with Excel formulas.

RESULTS

The study was conducted on three hundred study subjects, which were all snow skiers. Their age ranged from twelve to sixty years, with an average age of 22.39 years. There were 225 males and 75 females, with a male-to-female ratio of 3:1. Most of the study subjects, 174 (males: 99, females: 75) were in the age range less than or equal to twenty years, followed by 90 (all males) in the age group from 21 to 40 years and 36 (all males) in the age group 41 to 60 years (Table 1).

Some of the skiers were beginners and some regular skiers. The duration of the stay at Gulmarg for the present course of snow skiing varied from eleven days to fifty days.

For the purpose of heating and warmth, 183 subjects employed wood bukharis (chimneys made from iron, in which wood or coal is burnt to provide heat), 45 employed kangris (traditional Kashmiri fire pots), 45

Table 1: Age and sex characteristics of the study group.

	n = 300		
Age Group	**Males**	**Females**	**Total**
≤ 20 yrs.	99	75	174
21–40 yrs.	90	0	90
41–60 yrs.	36	0	36
Total	225	75	300

employed both kangri and a heat convector, and 27 employed central heating facilities.

Among the three hundred study subjects with dermatological complaints, some showed more than one type of presentation.

The most common dermatological manifestation was related to dryness (xerosis) and its related aftereffects, such as pruritus and chapping of the lips. This was seen in 254 manifestations, out of which eighty had significant chapping of the lips, 78 had visible dryness and scaling of the face, 60 had pruritus, and 36 had visible xerosis of the body.

UV-related skin damage was found in 134 manifestations, with 128 developing whole-face tanning and six with polymorphic light eruption (PMLE).

Infections and infestations were found in 78 cases, out of which scabies was found in 26, folliculitis/furunculosis in 22, superficial fungal infection, including pityriasis versicolor, tinea cruris, and corporis, in 16, labial/facial herpes simplex in 10, and chicken pox in 4.

Endogenous eczema as a manifestation was seen in 78 cases, including 58 cases of seborrheic dermatitis of the scalp and face and twenty cases of xerotic eczema.

Direct cold-related injuries were found in 56 cases, with 48 having perniosis and eight having frostbites.

Various forms of urticaria were found in 44 study subjects, with 24 having insect bite reactions or papular urticaria, fourteen having cholinergic urticaria, and six having cold urticaria.

Thirty-eight skiers presented with other manifestations, which we grouped as miscellaneous dermatoses: non-specific erythema of the face in 28, a non-specific burning sensation of the body in eight, and neglected dermatitis in two (Table 2).

DISCUSSION

Gulmarg is located at a distance of around 53 kilometers from Srinagar, the summer capital of Jammu and Kashmir in North India. Snow skiing is conducted by various governmental and non-governmental institutions for all interested. Rides on snow scooters and sleds are also an important part of the activities that Gulmarg abounds with during the winter season.

Snow skiers begin their day in the early morning, facing the cold morning breeze, which predisposes to increased chances of facial erythema and dryness (xerosis) [19]. In our study, xerosis, chapping of the lips, and subsequent pruritus and xerotic eczema were the most common occurrences, found in 114, 80, 60, and 20 manifestations, respectively, which was in accordance with previous studies found in the literature [1,8]. Facial erythema was found in twenty-eight cases.

Forced hot and dry conditions indoors because of the use of various heating equipment and hot baths predispose to flushing/erythema and xerosis. These factors lead to transepidermal water loss and subsequent damaging effects on the skin.

Tanning is a usual occurrence among snow skiers due to exposure to UV radiation, both direct and reflected from the snow. Our study found this as well, with 128 subjects having developed visible and significant tanning of the entire face, similar to findings in the literature [8,9].

Exposure to cold air, compromised hygiene, and overcrowding predispose skiers to various infections and infestations. In our study, scabies, folliculitis/furunculosis, superficial fungal infections, and herpes virus infections were found in twenty-six, twenty-two, sixteen, and fourteen cases, respectively [20].

Overcrowding and a decreased frequency of bathing compared to normal routine practice also predispose to pruritus, infestations with lice, scabies, and discoloration. The same reason, along with infrequent floor cleaning and change of bedding, may be cited for the increased predisposition to insect bite reactions, found in twenty-four cases in our study, as also in the literature [21].

Direct exposure to cold air and snow also results in increased chances of cold-related injuries, such as perniosis and frostbites, as was also evident in our study, in which 56 cases developed these conditions. Similar results have also been reported in the literature [22,23].

Cold urticaria was found in six cases in our study, consistent with previous studies [24].

Workout-associated sweating and a raised body temperature increase the likelihood of superficial fungal infections and cholinergic urticaria, as found in sixteen and fourteen patients, respectively, in our study [25,26].

Table 2: Patterns of the various dermatoses observed in the study group.

Type of Dermatosis	Dermatosis	No. of Subjects (*n* = 300)	Total
Xerosis and pruritus	Chapping of the lips	80	254
	Dryness and scaling of the face	78	
	Pruritus	60	
	Xerosis of the body	36	
UV-related skin damage	Tanning	128	134
	Polymorphic light eruption (PMLE)	6	
Infections and infestations	Scabies	26	78
	Folliculitis/furunculosis	22	
	Superficial fungal infection (pityriasis versicolor, tinea cruris/corporis)	16	
	Herpes simples labialis/facial	10	
	Chicken pox	4	
Eczema	Seborrheic dermatitis (scalp, face)	58	78
	Xerotic eczema	20	
Cold-related injuries	Perniosis	48	56
	Frostbite	8	
Urticaria	Insect bite reactions/papular urticaria	24	44
	Cholinergic urticaria	14	
	Cold urticaria	6	
Miscellaneous	Non-specific erythema of the face	28	38
	Burning sensation of the body (non-specific)	8	
	Neglected dermatitis	2	

The use of coal and wood for bukharis (chimneys made from iron in which wood or coal is burnt to provide heat) and kangris (earthen pots with burnt coal) results in burns, external tattooing, and discoloration. Placing a kangri between thighs also predisposes to burns, erythema ab igne, and Bowen's disease. In our study, we found no such cases.

CONCLUSION

The common dermatoses among snow skiers directly exposed to environments of high altitudes, cold, and snow include xerosis with associated pruritus and eczema, tanning, infestations, insect bite reactions, and direct cold injuries such as perniosis. The awareness among snow skiers about the adoption of various preventive measures may decrease the chances of skiers developing most of the dermatoses. This may help in mitigating the suffering and decreasing morbidity and economic loss occurring as a result of these otherwise preventable dermatoses.

ACKNOWLEDGMENTS

We would like to thank all study participants for their cooperation and patience.

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

Bullous pemphigoid and the associated co-morbidities: A prospective study at a tertiary-care center

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ABSTRACT

Background: Bullous pemphigoid is an autoimmune blistering disorder of the skin. Recent studies have shown that there are various associated co-morbidities existing even before the diagnosis of the condition. **Objectives:** The aim was to study the association of co-morbidities in bullous pemphigoid at a tertiary-care center. **Methodology:** This was a hospital-based prospective study of forty cases of bullous pemphigoid conducted over a period of thirty months at a tertiary-care center. **Results:** The mean age of the participants was 73. There was a male preponderance, with a male-to-female ratio of 1.8:1. Bullous pemphigoid was significantly associated with hypertension in 80% (32) of the patients, followed by diabetes mellitus in 75% (30), cerebrovascular accidents in 35% (14), coronary artery disease in 27.5% (11), depression in 12.5% (5), hypothyroidism in 12.5 % (5), and chronic kidney disease in 5% (2). **Conclusion:** Screening for co-morbid health conditions is paramount in patients with bullous pemphigoid for an optimal outcome since treatment options have an impact on the control of comorbidities and vice versa. It should be a multidisciplinary approach for optimal management and the improvement of the quality of life, thus reducing the number of hospital visits and medications to reduce the economic burden and morbidity, hence improving the quality of life.

Key words: Bullous pemphigoid; Co-morbidities; BPAG1; Hypertension

INTRODUCTION

Bullous pemphigoid (BP) is the most common blistering disorder, predominant among the elderly yet, in rare instances, may affect young adults and children. BP is a disease characterized by the presence of circulating IgG autoantibodies directed against the basement membrane zone. The causative antigens of BP, antigens 1 and 2 (BPAG1 and BPAG2), are detectable by both direct and indirect immunofluorescence [1].

The pathogenesis of BP remains not established with concrete evidence. Some studies have shown that BP has a correlation with co-morbid conditions such as neurological and psychiatric diseases, diabetes mellitus, and malignancies [2-4]. Recently, it has also been observed that the incidence of BP has raised, which could be attributed to factors such as an aging population, an increase in drug-induced cases, and the ameliorated diagnosis of the non-bullous forms [5].

The use of drugs such as dipeptidyl peptidase-4 inhibitors for diabetes mellitus, certain diuretics, antipsychotics, and drugs administered in the treatment of malignancies are also responsible for drug-induced cases [6].

Not only the etiology yet also the presentation of the disease is also quite varied. In the non-bullous phase, patients usually complain of generalized pruritus,

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erythema, or urticaria-like lesions, whereas, in the bullous phase, they present with tense vesicles or bullae on erythematous or healthy skin appearing symmetrically on the lower trunk, the flexor aspect of the extremities, and the abdomen [7]. The diagnosis of bullous pemphigoid is confirmed by biopsy of the lesions, perilesional direct immunofluorescence, indirect immunofluorescence from the patient's sera, and immunoblotting [8].

Previously, treating a case of bullous pemphigoid was challenging, as the mortality rate was around 26% [9]. In treating cases of BP, the first line of treatment was systemic and topical corticosteroids. However, the use of systemic corticosteroids produces severe adverse effects, sometimes even leading to death in elderly patients.

Doxycycline, dapsone, methotrexate, azathioprine, mycophenolic acid, intravenous immunoglobulin, rituximab, and omalizumab may be used in patients who cannot tolerate corticosteroids or in refractory cases [10,11]. The study aimed to evaluate demographic and clinical features and the associated comorbidities in cases of BP.

MATERIALS AND METHODS

A hospital-based prospective study was conducted on forty naive cases of BP at a tertiary-care center in South India from July 2019 to December 2021 (thirty months) at the dermatology department. Patients willing to participate in the study and with a histopathological confirmation of BP were included in the study. All cases with other existing autoimmune diseases and neoplasms were excluded.

After taking consent from the patients, data was collected with a pre-designed, semi-structured questionnaire. Data regarding sociodemographic variables and co-existing conditions was collected. Cutaneous and systemic examinations were performed. Histopathological examination and necessary blood investigations related to co-morbidities were conducted. The data was entered and analyzed with Microsoft Excel.

Ethics Statement

An institutional ethical committee certificate was taken.

RESULTS

In this study, the age of the patients ranged between 55 to 80 years, with a mean age of 73 years. A majority were in the 71–80 age group (60%), followed by the 61–70 age group (30%) (Table 1). Out of the forty patients, 65% (26) were male and 35% (14) were female, giving a male-to-female ratio of 1.8:1. All patients had cutaneous blisters (Figs. 1a - 1c) at the time of diagnosis, and 32 (80%) also had urticarial plaques (Fig. 1c). In addition, 3 (7.5%) had the oral mucosa affected and 38 (90%) had pruritus. Peripheral blood eosinophilia was present in 18 (45%) cases.

The use of chronic medications (at least 1 drug in the last 6 months) was seen in 37 cases (92.5%), ARBs (angiotensin receptor blockers) in 28 (70%), diuretics in 18 (50%), oral hypoglycemic drugs, biguanides in 30 (75%) and sulfonylureas in 24 (60%), lipid-lowering drugs (statins) in 21 (52.5%), antiplatelets in 14 (35%), beta-blockers in 8 (20%), levothyroxine in 5 (12.5%), escitalopram in 5 (12.5%), CCB (calcium channel blockers) in 3 (7.5%), and NSAIDs in 3 (7.5%) (Table 2).

The major co-morbidities in BP were hypertension in 80% (32) of the cases, diabetes mellitus in 75%(30), cerebrovascular accidents in 35% (14), coronary artery disease in 27.5% (11), depression in 12.5% (5), hypothyroidism in 12.5% (5), and chronic kidney disease in 5% (2) (Table 3).

Table 1: Age distribution of our cases

Age Group	*n* (%)
< 60 yrs.	4 (10%)
61–70 yrs.	12 (30%)
71–80 yrs.	24 (60%)

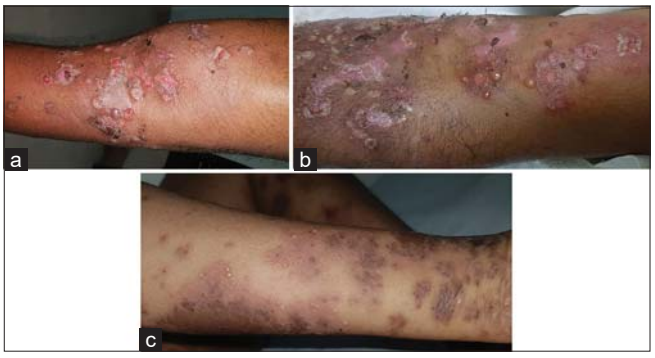

Figure 1: Multiple eroded areas and tense bullae on (a) the leg and (b) the hand. (c) Urticarial plaques with multiple blisters on the hand.

Table 2: Chronic medications (at least one drug in the last six months) in our cases

Chronic medication	*n* = 40 (%)
Angiotensin receptor blockers	28 (70%)
Thiazides	18 (45%)
Loop diuretics	2 (5%)
Biguanides	30 (75%)
Sulfonylureas	24 (60%)
Lipid-lowering drugs (statins)	21 (52.5%)
Antiplatelets	14 (35%)
Beta-blockers	8 (20%)
Levothyroxine	5 (12.5%)
Escitalopram	5 (12.5%)
CCB (calcium channel blockers)	3 (7.5%)
NSAIDs	3 (7.5%)

Table 3: Co-morbid diseases in our cases

Disease	*n* = 40 (%)
Hypertension (HTN)	32 (80%)
Diabetes mellitus	30 (75%)
CVA	14 (35%)
CAD	11 (27.5%)
Depression	5 (12.5%)
Hypothyroid	5 (12.5%)
Chronic kidney disease (CKD)	2 (5%)

DISCUSSION

The age of the patients ranged between 55 to 80 years, with a mean age of 73 years. Among the patients, 65% (26) were male and 35% (14) were female, giving a male-to-female ratio of 1.8:1.

In a study conducted by Teixeira et al. [12], the age of the patients ranged from 49 to 96 years. The mean age of the cases was 79.6 ± 8.3 years, and it was in near consonance with our study.

In a study conducted by Askin et al. [13], the age of the patients ranged from 15 to 103 years. The average age at the diagnosis of BP was 73.79 years, and the male-to-female ratio was 1.42:1, which was similar to our study.

However, in a study conducted by Kridin et al. [14], a strong female preponderance among cases of BP was observed, which was a discordant finding in comparison to our study. Most of the existing literature was in support of the finding that BP had a strong female preponderance just as in any other autoimmune disease, yet, in our study, males outnumbered females, which might have been because of a sex-selective and biased approach of the study area, as it was an area set back in a rural, developing part of India.

In our study, the major co-morbidities in bullous pemphigoid were hypertension in 80% (32) of the cases, followed by diabetes mellitus in 75% (30), cerebrovascular accidents in 35% (14), coronary artery disease in 27.5% (11), depression in 12.5% (5), hypothyroidism in 12.5% (5), and chronic kidney disease in 5% (2).

In the study conducted by Askin et al. [13], the most common co-morbidities observed in patients with BP were hypertension in 26 patients (45%), diabetes mellitus in 14 (24%), coronary artery diseases in 6 (1%), chronic kidney disease in 4 (0.7%), and osteoporosis in 4 (0.7%). Hypertension, diabetes mellitus, and coronary artery diseases were common in both sexes. On the other hand, Alzheimer's disease, osteoporosis, and hypothyroidism were observed more frequently in females; chronic kidney disease was observed more frequently in males.

In our study, the main co-morbidities associated with bullous pemphigoid were hypertension and diabetes, which was in concordance with other studies [15,16]. It has been proposed that an autoimmune response occurs after exposure to BP antigens by the glycation of proteins in the dermoepidermal junction.

In the study conducted by Teixeira et al. [12], a significant association with co-morbidities such as neurological diseases, dementia, a cerebral stroke, Parkinson's disease, and bed-ridden conditions was observed. This possible association with neurological abnormalities could be considered in line with the hypothesis of immunological cross-reactivity between the neuronal isoform of BPAG1 and its epithelial isoform. Neurological diseases could expose the neuronal isoform and trigger a subsequent immunological reaction causing the cutaneous lesions. Further studies are needed to better understand the underlying molecular pathways.

In a Finnish study conducted by Pankakoski et al. [17], a Finnish cohort of patients with BP was evaluated, with an average age of 77 years, also reporting that the most commonly observed co-morbidities were hypertension (44%), diabetes mellitus (34%), and ischemic heart diseases (26%). A significant association between bullous pemphigoid and a history of malignancies, diabetes mellitus, and chronic obstructive pulmonary disease was found. Furthermore, 46% of the patients had neurologic co-morbidities.

Numerous other studies also observed that cardiovascular conditions such as hypertension were common co-morbidities in cases with BP [18-20].

In our study, it was observed that the use of chronic medications (at least one drug in the last six months) was seen in 37 (92.5%) patients, ARBs (angiotensin receptor blockers) in 28 (70%), diuretics in 18 (50%), oral hypoglycemic drugs, biguanides in 30 (75%) and sulfonylureas in 24 (60%), lipid-lowering drugs (statins) in 21 (52.5%), antiplatelets in 14 (35%), beta-blockers in 8 (20%), levothyroxine in 5 (12.5%), CCB (calcium channel blockers) in 3 (7.5%), escitalopram in 3 (7.5%), fluoxetine in 2 (5%), and NSAIDs in 3 (7.5%).

In the study conducted by Teixeira et al. [12], a strong history of chronic drug use of more than two drugs for various medical conditions was also observed. The drug use profile was also in clear consonance with our findings.

CONCLUSION

Bullous pemphigoid is an autoimmune blistering disease of male predominance usually diagnosed during the sixth and seventh decade of life. Previous studies have shown that bullous pemphigoid is associated with cardiac diseases, diabetes mellitus, and neurologic and psychiatric diseases. Similarly to the literature, our study also showed an association between bullous pemphigoid and cardiac diseases and diabetes mellitus. Bullous pemphigoid was reported to be not associated with malignancies; similarly, our study did not find a significant prevalence of a history of malignant neoplasms in patients with BP, yet an association was found in chronic drug use. Thus, it is advised to elicit a clear history in cases of BP so that the associated gravity of the disease and the morbidity associated may be estimated beforehand, which will help in the further management of the cases.

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 epidemiology of cutaneous leishmaniasis in Al-Ramadi, Iraq

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ABSTRACT

Background: Cutaneous leishmaniasis is a disease caused by various species of the genus *Leishmania* via the bite of the different species of the vector infected female sandfly. It is an endemic disease in most Iraqi cities. This study was arranged to shed light on the epidemiological criteria of the disease in the city of Al-Ramadi. **Materials and Methods:** A descriptive study on cutaneous leishmaniasis in the city of Al-Ramadi was conducted over a three-year period from 2019 to 2021. The diagnosis of the disease was dependent mainly on the clinical features of the infection. Detailed information was obtained from all patients, who were grouped according to their age. Sites, numbers, and any previous scars were recorded during the clinical examination. **Results:** Five hundred and thirty-two patients affected by cutaneous leishmaniasis were examined in the dermatology clinic of Al-Ramadi Teaching Hospital in a period of three years from 2019 to 2021. The prevalence rate was 59/100,000. The highest number of patients affected during the year 2020 constituted around 39.5% of the cases. Mostly, infections appeared during the winter months (December, January, and February). Those younger than 2o years were mainly attacked by cutaneous leishmaniasis, constituting 63.3%. Males were more involved than females (57.5%). The hands, face, and feet were the most commonly involved sites, corresponding to around 20.57%, 20.11%, and 17.68% of the cases, respectively. **Conclusions:** Cutaneous leishmaniasis is an endemic disease in Al-Ramadi, representing a public health problem for both the individuals and the community. For individuals, scarring of the face represents the main cosmetic and psychological trauma.

Key words: cutaneous leishmaniasis; Sandfly; vector; Old World; Scarring

INTRODUCTION

Cutaneous leishmaniasis (CL) is a protozoal disease resulting from infection with the protozoan of the genus *Leishmania* (L.) via the bite of the infected female sandfly [1]. The disease is distributed globally and geographically in the Old World and New World [2]. There are around twenty species of the genus *Leishmania* that attack humans: in the Old World, *L. tropica*, *L. major*, *L. aethiopica*, *and L. donovani infuntum*, and in the New World, *L. brazelience complex* and *L. Mexicana complex* [3]. There are different species of the sandfly, *Phlebotomus* species (*P.*) in the Old World and the *Lutzomyia* species in the New World [4].

CL is considered a zoonotic disease: the human is incidentally affected, and wild and domestic animals represent the primary reservoir host [5]. In some cases, the human plays the role of the primary reservoir host, as in the disease caused by the strains of *L. tropica* [6]. Another rare mode of transmission is venereal, vertical, and via infected blood and needles [7].

The life cycle of the *Leishmania* consists of two forms, the promastigote (the flagellated form that presents

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in the gut of the sandflies) and the amastigote in the vertebrate animals [8]. When the vector inoculates the parasites into the human body, the appearance of the disease depends on the species, the inoculum of the parasite, and the host's immune status [3]. The clinical manifestations range from self-healing nodules to chronic and diffuse skin involvement with ugly, disfiguring scar formation [9].

In endemic regions, the diagnosis of CL is not difficult and mainly depends on the endemicity and clinical manifestations of the infection, in addition to tissue smear, histopathology, and culture [10-12].

In Iraq, two species of *Leishmania* are usually present: *L. tropica*, anthroponotic cutaneous leishmaniasis, and *L. major*, the zoonotic species [6,11]. Also, the number of sandflies is different according to the geographical region and time of the year (its peak being present during June and September) [13,14]. In Iraq, the most common species are *P. papatasi* and *P. sergenti* [15]. CL was reported in most Iraqi provinces, yet the epidemiological characteristics of the disease in the Al-Ramadi district remain poorly studied. Herein, we try to describe the epidemiological criteria of the disease in this locality.

MATERIALS AND METHODS

This was a descriptive study on CL conducted in the city of Al-Ramadi, the capital of the Al-Anbar province, which lies to the west of Iraq and has boundaries with three countries: Saudi Arabia, Syria, and Jorden. The city is divided by the Euphrates river into two parts, in addition to many-branched rivers that divide the city further, with agricultural farms distributed along both sides and the city and its surroundings with around 900,000 inhabitants. The study was performed from the beginning of January 2019 to the end of December 2021 in the dermatology outpatient clinic of Al-Ramadi Teaching Hospital. This hospital was the only present in the city, which was attended by patients affected by CL. The diagnosis of CL was depend on clinical features, in addition to the history of insect bites. In cases in which the diagnosis was uncertain, a tissue smear was taken from the suspected lesion for microscopical examination. If negative, the case was excluded from the study. The patients were inquired about their age, sex, time of infection, residence, occupation, previous infections, a family history, and any history of medical diseases and immunosuppressive drugs. The patients were grouped into three groups according to their age: group 1 (< 20 years), group 2 (21–40 years), and group 3 (> 41 years). On examination of the patients, the sites and number of lesions were determined and any scars from previous infections were noted. The study was performed after obtaining approval from the ethical committee. Written informed consent was taken from all patients.

Statistical Analysis

The differences among variables in the period of three years were assessed by the chi-squared test and the data was analyzed by SPSS. A p value below 0.05 was considered significant.

RESULTS

Five hundred and thirty-two patients and a total of 1069 skin lesions were seen in the dermatology clinic of Al-Ramadi Teaching Hospital over a three-year period from 2019 to 2021 (Table 1). The prevalence rate of the disease in Al-Ramadi was 59/100,000. The highest number of patients affected was in the year 2020 (39.5%), followed by 2021 (34%) and 2019 (26.5%) (Fig. 1). Also, most lesions of CL were seen during the year 2020, and the difference was significant ($p < 0.01$). Males were more commonly involved, constituting

Table 1: Various parameters used to analyze the patients' data from the three-year period of the study. **: ($p \leq 0.01$); NS: not significant.

Variable	2019	2020	2021	Total	X^2	p value
No. of cases	141	210	181	532	13.5	0.001**
No. of lesions	360	427	282	1069	29.5	0.0001**
Sex						
Male	81	120	105	306	0.036	0.98 NS
Female	60	90	76	226		
Site of lesions						
Face	65	107	43	215	31.2	0.005**
Neck	30	32	20	82		
Trunk	54	38	31	123		
Hands	59	86	75	220		
Feet	60	68	61	189		
Arms	30	30	17	77		
Forearms	31	32	18	81		
Legs	31	34	17	82		
Season						
Winter	89	147	101	337	17.4	0.008**
Spring	33	28	40	101		
Summer	4	12	20	36		
Autumn	15	23	20	58		
Age						
Group 1 (< 20 years)	72	142	115	329	14.2	0.006**
Group 2 (21–40 years)	43	41	50	134		
Group 3 (> 40 years)	26	27	16	69		

around 57.5% of the cases, while females comprised around 42.5% (Fig. 2). The exposed sites, the hands (20.57%), face (20.11%), and feet (17.68%), were the most often involved ($p < 0.01$) (Figs. 3 and 4). CL was most evident during the months of December, January, and February (winter season), constituting 63.3% of the cases, and was least so during June, Juley, and August (summer season), constituting 6.8% of the cases (Fig. 5). An early and young age were the primary culprits of the disease (Fig. 6), with ages ranging from two months to 85 years, those of an early age, less than twenty years old, were most affected (63.3%), followed by the age of 21–40 years, comprising 25.2% of the cases ($p < 0.01$). The presence of a previous scar of CL in association with novel lesions was reported in two cases (Fig. 7). A family history of the disease was present in 7.3% of the cases.

DISCUSSION

Leishmaniasis is recognized as one of the neglected tropical diseases [5,16]. It is endemic in around 98 countries, and around 0.7–1.2 million patients are affected yearly [17]. CL is endemic in Iraq, in addition to the high prevalence rate in the neighboring countries (Saudi Arabia, Iran, Turkey, and Syria) [12].

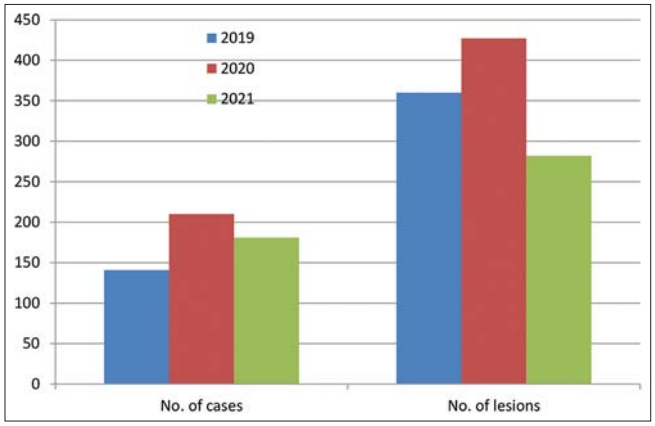

Figure 1: Patients diseased with cutaneous leishmaniasis during the three-year period.

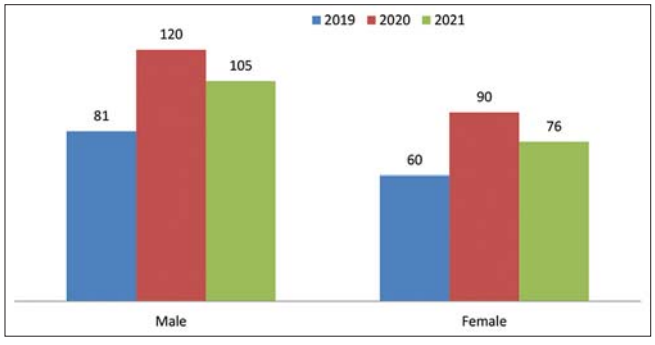

Figure 2: Sex distribution of the involved patients with cutaneous leishmaniasis during the three-years period.

CL cases are widespread in most Iraqi provinces, and the first patients affected were reported in the cities of Mosul and Baghdad [18]. Previously, medical education and health care in Iraq were the most developed in the area [19]. In 2003, Iraq was exposed to an invasion with different aspects of terrorist attacks. These led to the destruction of the health system in the country. As a consequence, the frequency of communicable diseases in Iraq increased, CL being one of these [19,20].

The prevalence rate in Al-Ramadi was 59/100,000 of the population, and this is considered high. In comparison to other parts of Iraq, in the Al-Diwaniya province, three hundred cases were reported in 2008, in the Al-Rhamania province, four hundred cases were recorded in 2009, and 45/10,000 in the Al-Haweja district [11,21]. In the Rabeea district, Mosul province, 1482 cases of CL were recorded over a twelve-month period in addition to an outbreak of CL in the northern provinces of Iraq observed in 2003 [6,12]. This may be related to the military operations in the West and some regions in the North of Iraq that lead to the augmentation of people poverty, forced displacement of people, and migration from endemic to the non-endemic regions, reduction in health services that people need in association with poor sanitary states, the presence of agriculture farms and rivers throughout the city resulting in an increased density of the sandflies distribution and their reservoir. The highest number of patients and lesions of CL was seen in the year 2020. This variation of the disease from one year to another, because CL is unstable epidemiologically, sometimes presents with huge and unpredictable fluctuations in

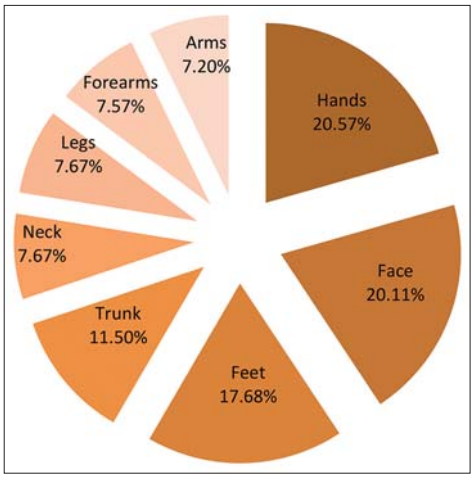

Figure 3: Distribution of cutaneous Leishmaniasis lesions according to body site involvement.

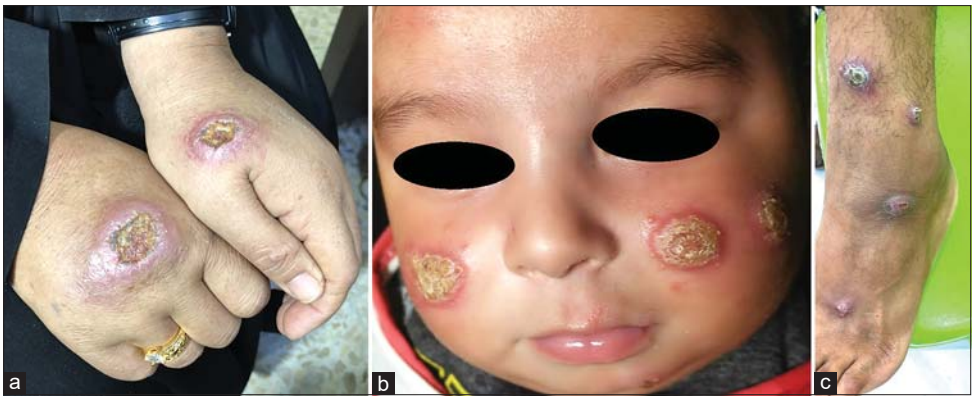

Figure 4: Cutaneous leishmaniasis of (a) the hands, (b) face, and (c) feet.

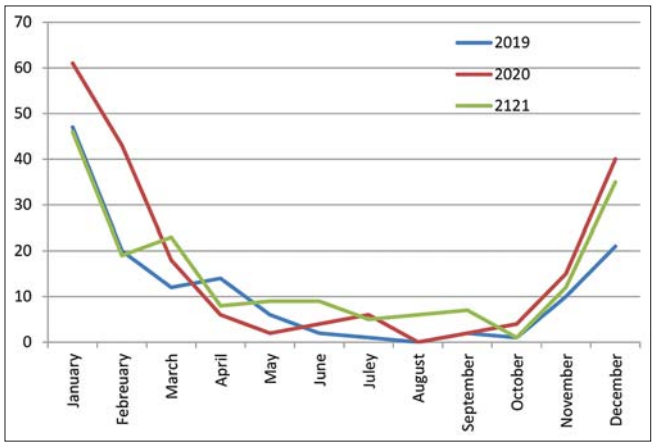

Figure 5: Patients involved with cutaneous leishmaniasis during the different months of the year.

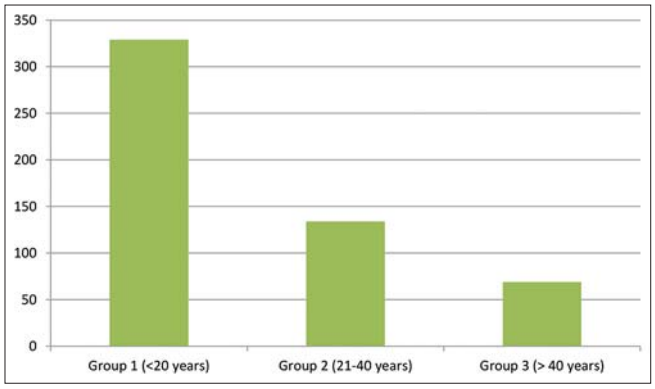

Figure 6: Number of patients affected with cutaneous leishmaniasis during the three-year period according to the age group.

numerous cases [11,22]. Although the number of cases in 2019 was less than in 2021, there were more lesions in that year, which is explained by the development of multiple lesions in most patients.

In CL, all ages and both sexes may be affected, yet we discovered that children and adolescents are

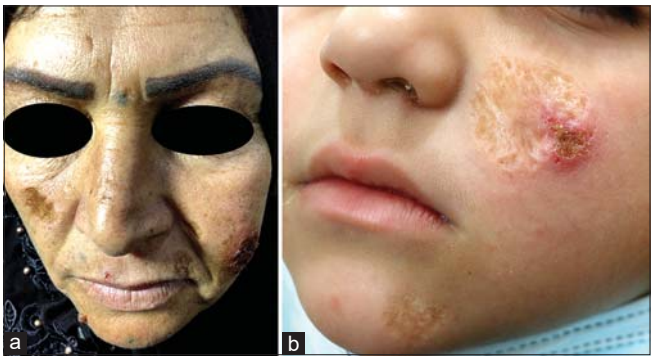

Figure 7: (a) Fifty-year-old female with two scars of previous cutaneous leishmaniasis on the right cheek and upper lip with a new lesion on the left cheek. (b) Fifteen-year-old child with two scars of previous cutaneous leishmaniasis of the left cheek and chin; a new lesion of leishmaniasis recidivans appearing at the border of the scar of the left cheek.

the most frequently affected. This was also seen in other studies [10] and by Al-Obaidi et al. and Klein et al. [23,24]. Younger individuals are more susceptible to being infected because they have not been exposed to bites of sandflies, thus they have not built an immune response against infections, in contrast to the elderly, who have been exposed to infections. Also, males were more often affected than females, which was also observed in other studies [23-25], yet another study found that females were more often affected [11]. In our locality, males are responsible mostly for outdoor work, thus are more prone to bites, especially performing farming and agricultural activities.

Cases of CL were recorded during cold weather, in the winter season, during December, January, and February, with the highest rate in January, then the rate decreasing slowly toward the hot season, with the lowest rate in August. Then, the rate of infections began to rise again toward the winter season. These

results were also mentioned by Al-Warid et al. and Al-Samarai et al., yet the peak was in February [11,15]. In Iraq, the most suitable periods for breeding sandflies are April to November, and their peak falls in September and October [14]. This may be related to the presence of the vector and animal reservoir at this time of the year. Hence, the appearance of the disease depends on the incubation period of the parasite, which ranged from 1 to 4 months and may be extended from two weeks to one year [26]. Also, the exposed parts of the body were the most affected and this is logically acceptable as the insect usually attacks the exposed parts of the body at night for sucking blood. This is determined by individual habits such as sleeping outdoors in hot weather or wearing certain clothing for sleeping. The same results were observed by Khan et al., Oetken et al., and Aytekin et al. [27-29].

CONCLUSION

Cutaneous leishmaniasis is endemic in the city of Al-Ramadi. Disfiguring scars on the face, particularly, are the main drawback of the infection. Thus, the study of the epidemiology of this parasitic infection is essential for the prevention of such complications.

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

In-hospital mortality in a dermatology department

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ABSTRACT

Background: Far from popular belief making dermatological conditions benign and harmless, we know that some dermatoses may be life-threatening. The aim of our study was to evaluate the overall mortality resulting from dermatological disorders in our department because of the rarity of similar studies. **Materials and Methods:** We conducted a retrospective, observational study on all patients who died in the Ibn Sina Hospital of Rabat between January 2017 and December 2021 (a period of five years), after they were initially admitted to the dermatology department. **Results:** Among 1731 patients hospitalized during this period, 45 died, corresponding to an average of 2.6%. The male-to-female ratio was 1.9 and the mean age at death was 63.2 years. The mean number of comorbidities per patient was 1.2, dominated by diabetes. The reasons for hospitalization were as follows: twenty-three cases of extensive bullous dermatoses (60.5% of the cases), four cases of severe toxidermia (10.5%), three cases of erythroderma (7.8%), one case of acro-lentiginous melanoma, one case of squamous cell carcinoma, and one case of pyoderma gangrenosum. In twenty patients (52.6%), the cause of death was directly related to the dermatosis. In sixteen, the cause of death was septic shock of cutaneous origin. Sixteen patients (42.1%) died of causes unrelated to dermatosis. **Conclusion:** This study showed that life-threatening dermatoses are not uncommon. Among these conditions, autoimmune bullous dermatoses and severe toxidermia, such as TEN and DRESS syndrome, were found to be the most lethal. An advanced age, a surface area of skin involvement, mucosal involvement, associated comorbidities, and the development of sepsis may be considered poor prognostic factors.

Key words: In-hospital mortality; Dermatology; Autoimmune bullous dermatoses; Toxidermia

INTRODUCTION

Far from popular belief making dermatological conditions benign and harmless, we know that some dermatoses may be life-threatening [1]. Hospital activity in dermatology is focused on specific skin diseases that have a substantial public health impact, in particular, autoimmune dermatosis, cancerology, immune-allergy, and infectiology. The in-hospital management of these patients is often beset with complications, which are sometimes serious and fatal. In Morocco, we lack data concerning the hospital mortality of dermatology patients, and, to our knowledge, no study concerning this subject has been published to date. Most international research available investigated the mortality of each dermatosis. The aim of our study was to evaluate the overall mortality resulting from dermatological disorders in our department because of the rarity of similar studies.

MATERIALS AND METHODS

We conducted a retrospective, observational study on all patients who died in the Ibn Sina Hospital of Rabat between January 2017 and December 2021 (a period of five years), after they were initially admitted to the dermatology department. We employed archived records. Data collected in the medical files included demographic characteristics (sex, age, urban or rural residence), the mode of admission to the hospital (emergency or scheduled hospitalization), associated comorbidities, the time from the onset of symptoms to the admission, the presumed cause of death, the

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and length of stay in the hospital before death. A total of thirty-eight records were analyzed for the purpose of this study.

RESULTS

Incidence and Prevalence

Between January 2017 and December 2021, 1731 patients were hospitalized in our dermatology department. Among these, there were forty-five deaths, with a ratio of 2.6% and an average of nine deaths a year (Fig. 1). Seven patients were excluded from the study because of missing data. Among the remaining thirty-eight patients, there were thirteen females (34.2%) and twenty-five females (65.7%), for a sex ratio (male-to-female) of 1.9. The average age of death was 63.2 years, with extremes ranging from 23 to 90 years (Table 1).

Comorbidities

The mean number of comorbidities per patient was 1.2, dominated by diabetes in eleven patients (28.9%), among which three were steroid-induced, and hypertension in ten cases (26.3%). Chronic renal failure was found in four patients, and two patients were followed for chronic heart disease. Neurological disorders were found in seven patients (18.4%), including stroke (three patients), dementia, Parkinson's disease, and intellectual disability. Their mean WHO/ECOG performance status was 3.

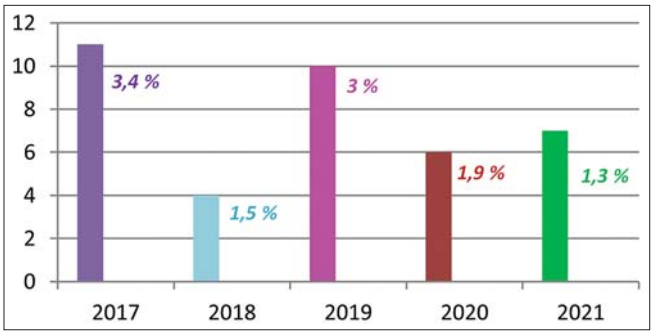

Figure 1: Number of yearly deaths and annual mortality rate.

Table 1: Age group distribution

Age Group (yrs.)	Number	Percent (%)
< 30	2	5.2
31–50	7	18.4
51–70	13	34.2
71–90	16	42.1
> 91	0	0

Causes of Hospitalization

Five patients followed in our department were hospitalized one last time for a relapse or aggravation of their dermatosis. There was a case of hypereosinophilic syndrome, diagnosed twelve years earlier, and two cases of cutaneous T-cell lymphoma, mycosis fungoides, and Sezary syndrome, followed for three and two years, respectively. A case of pemphigus in remission, followed for seven years, was hospitalized for the exploration of recent dysphagia, complicated by aspiration pneumonia, which was fatal. The last patient had been followed for *epidermolysis bullosa acquisita* for eleven years and was hospitalized with respiratory distress that revealed miliary tuberculosis, the cause of his death.

For all other patients (86.8%), it was the first hospital admission to the dermatology department. 36.8% of the deceased patients (n = 14) were admitted via the emergency department before being transferred to ours. The reasons for hospitalization were the following: twenty-three cases of extensive bullous dermatosis (60.5% of the cases), four cases of severe toxidermia (10.5%), three cases of erythroderma (7.8%), a case of acro-lentiginous melanoma, a case of squamous cell carcinoma, and a case of pyoderma gangrenosum.

In patients with bullous dermatosis, the mean skin surface area was 59.6%, with mucosal lesions in 73.9% of the patients (n = 17). The diagnosis of pemphigus was retained in seventeen patients (thirteen cases of pemphigus vulgaris, three cases of superficial pemphigus, and a case of paraneoplastic pemphigus). There were also six cases of bullous pemphigoid (BP).

Two cases of DRESS syndrome, one case of Stevens–Johnson syndrome, and one case of Lyell's syndrome were the cases of severe toxidermia. Allopurinol was incriminated in two cases. The three patients with erythroderma were diagnosed with Sézary syndrome in one case and generalized pustular psoriasis in two cases.

Duration of Hospitalization and Causes of Death

The average time from the onset of symptoms to hospital admission was four months, with a maximum of three years for the patient hospitalized for squamous cell carcinoma. It was noted that 63.2% of the patients had received inappropriate treatments for their dermatosis prior to admission, either prescribed or self-medicated. These treatments were mostly short-term systemic corticosteroid therapy. The average length

of stay in the hospital before death was 15.5 days (0–61 days) and 55.2% ($n = 21$) of the fatalities occurred within the first two weeks of hospitalization. In twenty-two patients, specific treatment was initiated, while, in sixteen, death occurred before.

In twenty patients (52.6%), the cause of death was directly related to the dermatosis. These included septic shock of cutaneous origin in sixteen cases (41.1%)—including nine cases of pemphigus—two cases of multiorgan failure secondary to DRESS and Sézary syndrome, bronchiolitis obliterans complicating paraneoplastic pemphigus, and macrophage activation syndrome in a patient followed for Sézary syndrome.

Among the sixteen patients with skin-onset sepsis, eleven had bullous dermatosis (Table 2). A total of sixteen samples (blood and skin) were positive for pathogens, which were all involved in nosocomial infections. The number of patients who died from a cause not linked to the dermatosis was sixteen (42.1%) (Table 3).

Treatment-related complications resulted in one death: decompensated acidoketosis complicating diabetes induced by long-term systemic glucocorticoid therapy initiated to treat superficial pemphigus. Finally, the cause of death was unknown in one patient.

Table 2: Dermatoses and germs responsible for septic shock

Dermatoses	Sample site	Germs
1. Pemphigus vulgaris	Blood	*Coagulase-négative Staphylococcus*
2. Bullous pemphigoid	Blood	*Staphylocoque aureus*
	Skin	*Staphylocoque aureus* *Pseudomonas aeruginosa*
3. Pemphigus vulgaris	Blood	*Staphylocoque aureus*
4. Pemphigus vulgaris	Blood	*Staphylocoque aureus* *Pseudomonas aeruginosa* *Klebsiella Pneumoniae*
5. Hypereosinophilic syndrome	Blood	*Coagulase-négative Staphylococcus*
	Skin	*Staphylocoque hominis* *Staphylocoque haemolyticus*
6. Pemphigus vulgaris	Blood	*Staphylocoque aureus*
7. Pemphigus vulgaris	Blood	*Staphylocoque aureus* *Pseudomonas aeruginosa*
8. Pemphigus vulgaris	Blood	*Staphylocoque aureus*
	Skin	*Acinetobacer baumannii*
9. Pemphigus vulgaris	Blood	*Pseudomonas aeruginosa* *Klebsiella Pneumoniae*
10. Superficial pemphigus	Blood	*Pseudomonas aeruginosa*
	Skin	*Pseudomonas aeruginosa* *Staphylocoque cohnii*
11. Pemphigus vulgaris	Blood	*Yeasts* *Coagulase-négative Staphylococcus* *Acinetobacer baumannii*
	Skin	*Acinetobacer baumannii*

Table 4 lists all dermatoses that had led to death.

DISCUSSION

Epidemiological data related to deaths in dermatology departments is sparse. Indeed, few studies have been done on this subject, which makes it difficult to compare our results to other models. However, the dermatology department of Ibn Sina University Hospital of Rabat remains a good reflection of skin pathology in Morocco, since it constitutes a reference center that drains patients from a large region of the kingdom. A mortality rate of 2.6% over a period of five years may, therefore, be considered relatively low, especially since 36.8% of the deceased patients were recruited by the emergency, indicating an immediate risk. For comparison purposes, the mortality rate for patients with dermatologic diseases in ICUs is estimated to be as high as 27.5% [2]. Nearly half of the deceased patients (42.1%) were between 71 and 90 years old. This is consistent with studies on mortality risk factors in autoimmune bullous disease and severe toxidermia, where an advanced age was recognized as one [3].

Pemphigus was the condition that caused the most deaths in our series (47.3%). However, we must specify that it was one of the most frequent reasons for hospitalization in our department [4]. The average skin area affected was significant (59.6%), and mucosal involvement was found in the majority of the patients (thirteen of the eighteen patients with pemphigus). These last two factors were probably the cause that precipitated the onset of nosocomial infections of cutaneous origin [5], the main causes of death in our series. The higher frequency of sepsis in our center probably reflected inadequate hygiene measures. This underlines the importance of specialized care for this group of patients in intensive care units adapted to those for severe burns, with intense cooperation between the staff and the dermatology department [5]. Indeed, low mortality rates were reported in centers in which patients with toxic epidermal necrolysis (TEN) were treated in the burn unit [6].

Among the six cases of BP, five died from medical complications of known comorbidities, yet unrelated to the dermatosis. Two of these patients developed in-hospital stroke. Three were bedridden (due to stroke damage, senile dementia, or Parkinson's disease), which

Table 3: Deaths unrelated to dermatitis

	Sex	Age	Comorbidities	Cause of Hospitalization	Cause of Death
1	F	23	None	Pyoderma gangrenosum	Peripartum cardiomyopathy
2	F	66	None	Pemphigus (cured) + dysphagia	Aspiration pneumonia after dysphagia
3	M	85	None	Pemphigus vulgaris	Nosocomial pneumonia
4	M	78	Hypertension Steroid-induced diabetes Chronic renal failure Stroke	Bullous pemphigoid	Post-stroke aspiration pneumonia
5	M	60	None	Acro-lentiginous melanoma	Acute myeloblastic leukemia
6	M	40	Long-term systemic glucocorticoid therapy	*Epidermolysis Bullosa Acquisita*	Miliary tuberculosis
7	F	90	Hypertension Diabetes	Bullous pemphigoid	Stroke
8	M	88	Senile dementia	Bullous pemphigoid	Hyperkaliemia (acute renal failure)
9	F	78	Parkinson's disease	Bullous pemphigoid	Cardiorespiratory arrest
10	M	60	Hypertension Stroke	Pemphigus vulgaris	Respiratory distress
11	M	72	Hypertension Diabetes Chronic heart disease Chronic renal failure	Bullous pemphigoid	Septic shock after catheter-related bloodstream infections
12	M	56	Hypertension Diabetes Chronic heart disease	Superficial pemphigus	Cardiogenic shock
13	F	80	None	Pemphigus vulgaris	Pulmonary embolism
14	M	88	Diabetes complicated by peripheral arterial obstructive disease	Pemphigus vulgaris	Acute coronary syndrome
15	M	78	Chronic renal failure	Psoriatic erythroderma	Viral pneumonia (due to H1N1)
16	M	70	Diabetes	Squamous cell carcinoma	Viral pneumonia (due to SARS-CoV-2)

Table 4: Overview of all dermatoses that led to death between 2017 and 2021 in the dermatology department of Ibn Sina Hospital in Rabat

Cause of Hospitalization	Number	Percent (%)	Cause of Death			
			Related to the dermatological condition	Unrelated to the dermatological condition	Treatment complication	Unknown
Pemphigus	18	47.3	10	6	1	1
Bullous Pemphigoid	6	15.7	1	5	0	0
Severe toxidermia	4	10.5	4	0	0	0
Mycosis fungoid/Sézary syndrome	3	7.8	3	0	0	0
Malignant cutaneous tumor	2	5.2	0	2	0	0
Generalized psoriasis	2	5.2	1	1	0	0
Hypereosinophilic syndrome	1	2.6	1	0	0	0
Pyoderma gangrenosum	1	2.6	0	1	0	0
Epidermolysis bullosa acquisita	1	2.6	0	1	0	0
Total	38	100	20	16	1	1

is a classic mortality factor in BP [7]. They had all received short courses of oral corticosteroids at home and had only consulted the dermatologist after at least one month. This could explain the decompensation of their serious comorbid conditions in addition to the systemic inflammation in their autoimmune setting. This downward trend in the frequency of deaths directly related to BP was previously reported by Journet-Tollhupp [8], yet is difficult to interpret because of the small sample size. Nevertheless, it is important to note that dermatologists must be especially cautious with patients affected by BP, especially in the presence of neurological, cardiac, and renal comorbidities [9,10].

CONCLUSION

This study has shown that life-threatening dermatological disorders are numerous. Among these conditions, autoimmune bullous dermatosis and severe toxidermia, such as TEN and DRESS syndrome, were found to be the most lethal. An advanced age, the surface area of the skin lesion, mucosal involvement, associated comorbidities, and the development of sepsis may be considered poor prognostic factors. We recommend prompt referral of such conditions to specialized centers for early and adequate management, ideally in burn ICUs in the

case of bullous dermatosis, in order to improve their vital prognosis.

Statement of Human 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.

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Our Dermatology Online

Brief Report

Laser and IPL hair depilation in pilonidal disease

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ABSTRACT

Background: Pilonidal sinus disease (PNS) is a chronic inflammatory disease of the natal cleft occurring in young adults. We report our experience with laser hair removal using Nd: YAG laser and IPL for the treatment of pilonidal cysts. **Materials and Methods:** Twelve patients presenting with pilonidal disease with or without a history of surgery were examined and treated from October 2016 to October 2021. All patients had modifiable risk factors. Treatments were performed with intense pulsed light (IPL) in nine patients and Nd: YAG laser at a wavelength of 1064 nm in five patients, and occasionally both were used in two patients. The number of treatments ranged from three to five, performed at four-to-eight-week intervals. **Results:** Progressive hair depilation of the gluteal cleft was achieved in all patients. None of the patients have required further surgical treatments to date. No side effects were reported. All patients experienced a partial or complete remission of the pilonidal disease. **Conclusion:** Laser hair depilation is a promising therapy in the prevention and management of pilonidal disease.

Key words: Pilonidal sinus; Laser depilation; Intense pulsed light; Nd: YAG

INTRODUCTION

Pilonidal sinus corresponds to a pseudo-cystic cavity containing hair, most often located in the natal cleft. It may manifest as pilonidal disease, in the form of acute infection (abscess), or chronic, persistent discharge of one or more sinuses [1]. There are two hypotheses regarding the etiopathogenesis of this entity: the congenital and the acquired theory [2]. The acquired theory, which is retained by most authors, states that, following repeated microtrauma, the broken free hairs penetrate and migrate under the skin, creating a fistulous pathway and behaving like foreign bodies, which triggers an inflammatory reaction with the resultant long-term, low-grade infection [2,3]. The risk factors include the male sex, a family history, obesity, and hirsutism [1]. Its benignity contrasts with the importance of its morbidity leading to an alteration in the quality of life with major socio-professional repercussions. The difficulty of its management is related to the high risk of recurrence, estimated to be 30% [2]. Although surgery is still considered the gold-standard treatment, it has a high recurrence rate and a prolonged healing time. Therefore, search is still ongoing for more optimal management alternatives [3].

PATIENTS AND METHODS

This was a retro-prospective study conducted between October 2014 and October 2021, including twelve patients presenting pilonidal disease with or without a history of surgery. Patients presenting with an acute pilonidal abscess were not excluded from the study; however, they received oral antibiotic therapy and were scheduled for laser treatment 2–3 weeks after the resolution of the inflammatory process. Nine patients were treated with an intense pulsed light (IPL) device (Nordlys by Ellipse) with HR 600 to 950 nm filters and the following parameters: 11–13.5 J/cm^2, 40 ms. Five of our patients were treated with laser epilation with Nd: YAG laser (Fotona Dynamis XP) with a spot size of 9 mm and the following parameters: fluence 10–18 J/cm^2, pulse duration of 1.6–3 ms. A dynamic

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cooling system was employed during the laser session. In two patients, the first treatment was performed with IPL before using Nd: YAG laser. With both procedures, hair was removed in a round area of 5 cm around the affected sinus. Treatments were performed at 4-to-8-week intervals for the first three to four treatments and then every 8-to-16 weeks until the remission of infection and the removal of most of the hair.

During each treatment session, the natal cleft was shaved with the application of a topical anesthetic agent (Figs. 1a and 1b). Laser depilation of the natal cleft with an appropriate wavelength not only for the patient's skin type, yet also the degree of pigmentation of the area to be treated, was performed. The primary end point was assessed immediately with clinical and dermoscopic evaluations. In the cases with ulcerations or loss of substance, a preparation with hair and debris removal was performed (Figs. 1a and 1b). After the session, topical fusidic acid with a primary dressing made of saline-soaked compresses and a secondary absorbent dressing were applied. The patients' pain tolerance and side effects were evaluated during the session and during the follow-up before every other session.

The study was conducted according to the principles of the Declaration of Helsinki and informed consent was obtained from all patients for the treatment and release of photographic images for scientific purposes.

RESULTS

Twelve patients (eight males and four females), aged 15 to 29 years (avg.: 22 yrs. +/- 7), came to our department with a history of pilonidal sinus disease in the natal cleft. Five of the patients underwent surgical treatment before admission. All patients had risk factors (Table 1). None had a family history of pilonidal sinus. Progressive hair depilation of the gluteal cleft was achieved in all patients. Pain tolerance was evaluated with the EVA scale with an average of 6/10. To date, none of the patients has experienced more acute abscesses or infections in the epilated area. All patients experienced a partial or complete remission of the pilonidal disease. Complete healing was achieved in 91% of the patients (only two patients have an active lesion with serosal discharge with ongoing treatment) (Figs. 2a and 2b). None of the patients has required further surgical treatment to date. No side effects were reported. Table 2 summarizes our results.

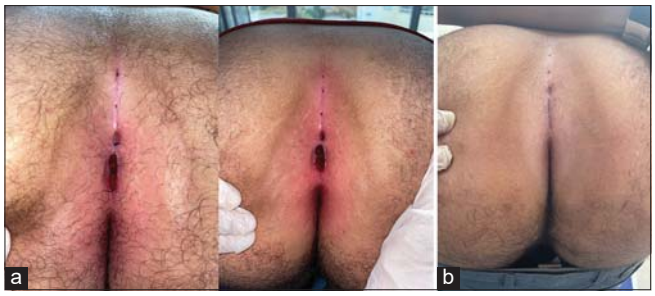

Figure 1: Preparation phase: (a) the shaving area to be treated 5 cm from the midline and removing hair debris from the sinuses; (b) after a month with one session treatment with Nd: YAG laser.

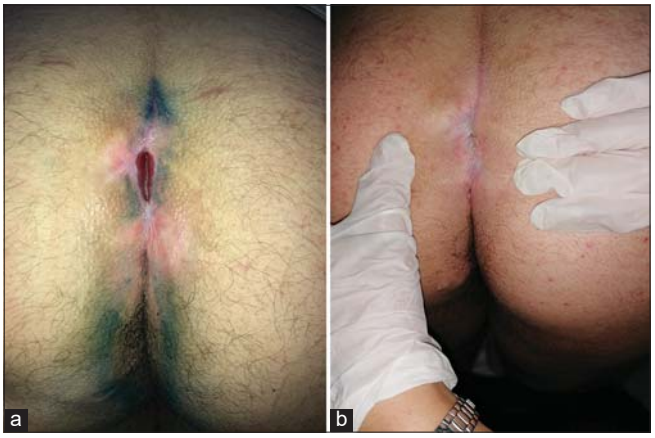

Figure 2: (a) After several unsuccessful treatment sessions of methylene blue and before hair removal; (b) complete remission after three IPL sessions.

Table 1: Risk factors of pilonidal disease.

Variable	Patients
Mean age	22 yrs.(15–29 yrs.)
Gender	
F	4 (33.3%)
M	8 (66.6%)
Tobacco use	
Yes	3 (25%)
Passive smoking	5 (41.6%)
Obesity	3 (25%)
Excessive pilosity in the gluteal area	8 (66.6%)
Prolonged sitting	7 (58.3%)
Deeper natal cleft	3 (25%)
Family history of pilonidal disease	None

DISCUSSION

Pilonidal sinus disease (PNS) is a chronic inflammatory disease of the superior natal cleft that affects approx. 26 per 100,000 adolescents and young adults [4]. It is most common in males (at a ratio of 3–4: 1) and in Caucasians. It occurs most commonly in hirsute individuals [5]. The risk factors include obesity, hirsutism, poor hygiene, repeated microtrauma and friction, and a deep intergluteal cleft [2,6]. A case-controlled study on the risk factors of pilonidal sinus

Table 2: Session parameters and results of laser epilation treatments in pilonidal disease.

Patient	Past Surgery	Laser Parameters	No. of Laser Treatments	Interval (Weeks)	Remission
1	Yes	IPL: 12.5 J, 40 ms	3	4	COMPLETE
2	No	Nd:YAG: 18 J, 3 ms	5	4–8	COMPLETE
3	Yes	IPL: 12.3–13.5 J, 40 ms	3	4–8	COMPLETE
4	No	IPL: 12.7–13 J, 40 ms Nd:YAG: 10 J, 1.6 ms	3 3	4–8	COMPLETE
5	Yes	IPL: 12.5–13.4 J, 40 ms	3	4	COMPLETE
6	No	IPL: 13.4 J, 40 ms Nd:YAG: 10 J, 1.6 ms	3 2	4	PARTIAL
7	Yes	IPL: 13.2 J, 40ms	3	4	COMPLETE
8	No	IPL: 12.3 J, 40ms Nd:YAG: 10–15 J, 1.6 ms	1 2	4	PARTIAL
9	No	IPL: 12.3–13.5 J, 40 ms	3	4	COMPLETE
10	No	Nd:YAG: 10 J, 1.6 ms	2	4	COMPLETE
11	No	IPL: 11 J, 40 ms	3	4	COMPLETE
12	Yes	Nd:YAG: 15 J, 1.6 ms	2	4	COMPLETE

disease in preparatory school students conducted by Faraj et al. reported that sitting on hard surfaces for long periods of time should be considered a risk factor for developing PNS among secondary school students [7]. A prolonged sitting posture was indeed found in 58% of our patients due to their occupation (six students, one driver). The results of our study are consistent with those in the literature as at least one of these risk factors was reported by all of our patients (Table 1). Pilonidal disease may manifest itself in different forms depending on the degree of the inflammatory reaction. The asymptomatic form (3.2% of cases) presents as one or more non-inflammatory orifices located in the natal cleft 4–8 cm above the anal margin. The course of the disease may also start in the form of an acute abscess in 45% to 50% of cases, with painful swelling and, in some cases, a lateral extension and fever. The subcutaneous collection may be evacuated spontaneously through a secondary drainage orifice. The chronic form manifests itself by a continuous intermittent suppuration of the intergluteal fold that may or may not follow an abscess. Secondary and lateral orifices may communicate with one of the medial fossae with discharge of serositis or pus, which may persist [8]. The histopathological features are those of an epidermal lined dermoid cyst or a sinus tract. The cystic cavities are lined with granulation tissue with a mixed inflammatory infiltrate, hair, and keratin debris [5]. The treatment may be divided into surgical and non-surgical techniques. Surgical treatment remains the first-line therapy for pilonidal cysts, yet it is associated with significant postoperative morbidity and a high recurrence rate, estimated at 30% [2,9,10], hence the importance of prevention by managing the modifiable risk factors, particularly excessive pilosity. Laser epilation is a highly effective method of reducing hair growth and various laser devices have been tested for the treatment of pilonidal cysts, especially postsurgical relapse. According to the Clinical Practice Guidelines for the Management of Pilonidal Disease of the American Society of Colon and Rectal Surgeons (ASCRS), laser epilation has a strong recommendation grade based on low-quality evidence [11]. It has been stated that, compared to surgical treatment of recurrences, laser depilation is an efficient and cost-effective method for preventing recurrence and reducing morbidity and loss of man-hours [12]. In a study conducted by Dragoni et al. which carried out an ultrasound evaluation at the beginning and end of treatment with Nd: YAG laser to further confirm treatment success, all patients experienced the disappearance of their pilonidal cysts. None of the patients presented recurrence of the disease during the follow-up [13]. Intense pulsed light (IPL) has also been successfully employed. A study done by Shafigh et al. including thirty patients noted a reduced recurrence rate estimated at 13.3% during a follow-up of 2.5 years on average, which shows that this hair removal technique still has its role as a safe, nearly painless alternative [14,15]. Our study supports what has been reported in the literature and illustrates that laser hair removal could potentially be a less invasive alternative to surgery in pilonidal disease by possibly avoiding the need for surgery and postoperative comorbidity. Laser hair removal could eventually play

a role in preventing recurrences in patients requiring surgical management.

CONCLUSION

Despite its benign nature, pilonidal sinus disease is characterized by a high recurrence rate and a significant alteration in the quality of life of the patients. The role of excessive pilosity in the etiopathogenesis, yet also in the recurrence of PNS, is clearly established. Laser hair depilation is a promising therapy in the prevention and management of pilonidal disease.

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

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Our Dermatology Online

Brief Report

Dermatophagia: A case series from a dermatology clinic

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ABSTRACT

Objective: Psychocutaneous diseases, such as dermatophagia, are skin manifestations of psychological distress. Cases of this nature are not well documented. Therefore, this study aimed to record cases of skin biting and perform a complete clinical evaluation. **Methods:** This descriptive case study enrolled sixteen patients treated in a dermatology and psychiatry clinic in Baghdad, Iraq, from 2014 to 2021. All patients with self-inflicted skin disease induced by skin biting were enrolled. A complete medical history was collected and a clinical examination and psychiatric assessment were performed. **Results:** Out of the sixteen patients who had demonstrated self-skin biting (dermatophagia), ten were males and six were females, with a median age of twenty years, ranging from 14 to 45 years. All patients accepted responsibility for their illness. The type of skin manifestation was nail-biting in seven (46.66%) patients, consisting of five (33.3%) patients with nail dystrophy due to proximal nail fold biting and two (13.33%) patients with nail deformity due to grinding of the distal part of all nail plates. Six (40%) patients presented with skin nodules on the dorsal side of their hands, a single nodule in one patient, and multiple in five patients. Two patients (13.33 %) revealed dermatitis-like, pigmented patches on the dorsal aspect of the hand and fingers. Psychological evaluation revealed the absence of psychosis and brain disorders. **Conclusion:** Dermatophagia is an emerging form of psychological health problem that has not been well documented. However, diverse dermatological manifestations localized in the hands, such as nail dystrophy, skin nodules, and chronic, dermatitis-like plaques, have been reported.

Key words: Dermatophagia; Dermatology clinic; Case series; Self-harm; Skin biting

INTRODUCTION

Historical Background

The association between mental disturbances and physical health has been known for centuries. Ancient literature indeed referred to such phenomena, particularly in ancient Mesopotamia and the eastern Mediterranean region. Arab Muslim scholars established the notion of *psychosomatic disorders* (7–10th century), clarifying the cause–effect link between emotional conditions and some medical illnesses that manifested through physical signs [1]. The quote "the sorrow which has no vent in tears may make other organs weep," attributed to Henry Maudsley (1867), metaphorically represents the concept of psychosomatic disorders. He was considered an authority on the link between the body and mind [2]. The proverb "the skin is a mirror of the soul" was conceptualized by numerous researchers in dermatology and psychiatry. Additionally, other terms, such as *skin-ego*, coined by Didier Anzieu, are interpreted as the skin creating an opening for mental problems: *psyche of the skin* [3]. The association between the skin and the nervous system is related to their common embryonic origin; they develop together and remain intimately interconnected and interactive throughout life [3,4].

Psychopathology

Psychological distress may manifest through skin lesions in different presentations, ranging from mild dermatitis to dangerous forms of deliberate self-harm (DSH), mainly skin cutting, burning,

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and complicated excoriation. DSH (intentionally injuring one's own body without a suicidal intent) is commonly encountered in emergency departments, dermatological or other hospital settings, and psychiatric clinics, where psychiatric assessment usually reveals underlying depression, anxiety, obsessive-compulsive disorder (OCD), and/or substance abuse. According to the Diagnostic Statistical Manual of Mental Disorders (DSM-5) and research findings, DSH is a core symptom of borderline personality disorder and occurs within the course of other psychiatric disorders. It may be fatal, representing 1.9% of the violence-related death toll in the eastern Mediterranean region [5]. In contrast, psychocutaneous disorders are usually not life-threatening conditions with a chronic course; however, such clinical presentations may overlap, requiring a robust dermatology–psychiatry liaison. The actual prevalence of non-dangerous self-harm has not been adequately reported in the literature. Previous studies have focused on patients who presented to the hospital for immediate physical treatment, while the number of patients in the non-clinical population has been higher [6,7]. Self-inflicted skin lesions (SISLs) are variable clinical presentations of psychocutaneous diseases. Dermatologists and physicians label such lesions as factitious skin disorders (dermatitis artefacta), usually disregarding the underlying psychopathology or psychiatric referral [8]. SISLs are virtual clusters of psychocutaneous diseases presenting with various psychological and dermatological conditions, one of which is compulsive skin biting. Dermatophagia (from Greek *δερματοφαγια*) is derived from the words *derma* (*δερμα*, *skin*) and *phago* (*φαγω*, *I eat*). The word denotes the eating of the skin, irrespective of whether or not one bites it. Studies on dermatophagia describe patients whose behavior consists solely of compulsive biting or gnawing on their skin, yet not ingesting. Other synonymous terms have also been employed, such as compulsive skin-picking and body-focused, repetitive behaviors [8,9]. Dermatophagia often affects the skin around the fingers and, less commonly, other exposed body parts. People who bite or, sometimes, ingest their skin are rarely encountered in psychiatric settings, possibly because they are unaware of their condition or are avoiding the social stigma of being "mentally ill." However, severe and prolonged skin biting may predispose patients to dermatological complications and irreversible disfigurement. Moreover, this repetitive, compulsive act heightens anxiety and discomfort by trapping the patient in a vicious circle [9,10].

MATERIALS AND METHODS

This descriptive case study was conducted at the Dermatology Outpatient Clinic of Baghdad Teaching Hospital in Baghdad, Iraq, from 2014 to 2021. A consultant dermatologist—the first author—oversaw all patients with SISLs who visited the clinic. Fifteen patients who met the diagnostic criteria of compulsive skin biting were enrolled in the study, and one extra male patient from the Psychiatric Outpatient Clinic presented with serious DSH, totaling sixteen patients. After completing their dermatological examinations and checking medical records, a consultant psychiatrist subjected the patients to a semi-structured DSM-5 interview [11]. The included patients consented in writing to participate in the study and had their skin lesions photographed without revealing their identities. They received a full explanation of the study's goal and were assured confidentiality and the freedom to approve or disapprove their pictures. Formal approval was obtained from the research committee attached to the Iraqi Council of Medical Specialization. A complete physical examination further confirmed the dermatological findings. Patients with skin pathologies related to medical diseases were excluded. Psychiatric assessments were carefully conducted to exclude psychotic disorders, primarily schizophrenia, and organic causes, such as acute brain syndrome, substance abuse, autism spectrum disorder, and intellectual disability (autophagia). A significant number of patients refrained from psychiatric referrals and denied having psychiatric issues. The assigned psychiatrist—the second author—visited the dermatological setting to encourage a positive attitude toward treatment. Two registrars assisted both authors—the consultant dermatologist and consultant psychiatrist—in the multidisciplinary team at the dermatology clinic.

Ethics Statement

The study was conducted under the ethical standards of the responsible committee on human experimentation (institutional and national) and in accordance with the 2008 revision of the Declaration of Helsinki of 1975.

RESULTS

Fifteen patients with a median age of twenty years, ranging from 14 to 45 years, were diagnosed with dermatophagia by the consultant dermatologist and psychiatrist—the authors. Nine males and six females visited the dermatology outpatient clinic seeking

treatment for skin lesions caused by self-picking and biting of their hands. Most of them visited the clinic concerned about their cosmetic appearance. All patients accepted responsibility for their illness. Seven patients (46.66%) presented with excessive nail-biting, consisting of five (71.4%) patients with linear nail dystrophy due to proximal nail fold biting (Fig. 1). Two (28.57%) patients harshly bit the distal part of all nail plates, causing whole nail deformities (Fig. 2a). Six patients (40%) presented with dome-shaped, pigmented nodules on the dorsal sides of both the hands, a single nodule in one patient and multiple in five patients (Fig. 2b). The other two patients (13.33%) had hyperkeratotic pigmented plaques affecting the dorsum of the hand in one patient (Fig. 2c) and scaly, dermatitis-like lesions affected the fingers in the second patient (Fig. 2d). Psychiatric assessments revealed that none of the patients had brain lesions, neurodevelopmental disorders, or intellectual disabilities. Psychotic or bipolar disorder features were absent and none of them had a history of substance abuse. Therefore, we examined the patient with DSH for comparison purposes. The patient with DSH who attended the psychiatric outpatient clinic for treatment was selected. His chief complaint was repeated, self-inflicted cutting with a sharp razor. He described his action as "killing the inner pain" and expressed the feeling of immediate relief after seeing his blood. He denied suicidal intents or attempts. An examination revealed large, surgical scars on both arms and other superficial skin lacerations. A detailed psychiatric assessment revealed symptoms of depression with characteristics of borderline personality disorder; there was no history of alcohol or substance abuse. He presented with a classical form of DSH with dangerous wounds and superficial laceration (Fig. 3).

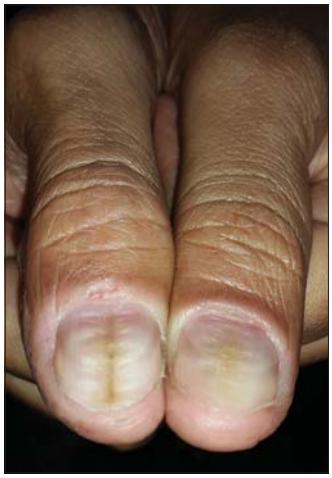

Figure 1: Linear nail dystrophy.

DISCUSSION

Self-inflicted skin lesions in their variable clinical presentations are usually encountered by physicians, general practitioners, and dermatologists, who are aware that many people with such problems do not seek medical treatment. A number of studies have classified skin biting disorders as a form of OCD, while others have included them in the domain of DSH or disorders of impulse control. However, this classification is still debated, owing to variations and sometimes contradictory findings and psychopathology [12].

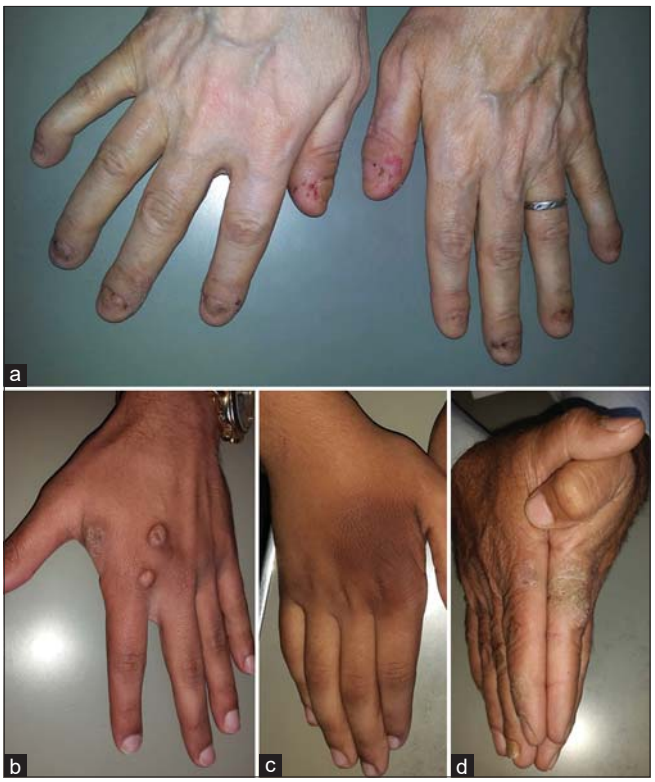

Figure 2: (a) Complete nail dystrophy following nail destruction. (b) Multiple skin nodules. (c):Hyperkeratotic pigmented plaques affecting the dorsum of the hand.(d) Scaly hyperkeratosis.

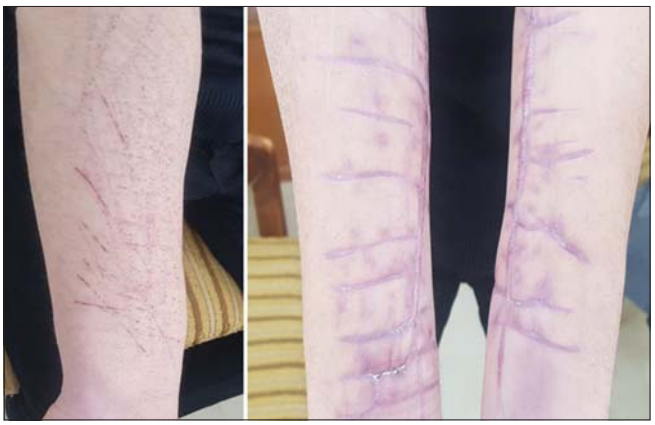

Figure 3: Deep wounds and lacerations (DSH).

Skin biting, such as dermatophagia, gnawing, or eating skin debris, is an internationally underreported SISL. There are no available data from Iraq, apart from a case study by Sharquie et al. and a single case report [13,14]. Inconsistent with numerous psychocutaneous disorders such as dermatitis artefacta and trichotillomania, all fifteen patients in the present study with dermatophagia did not deny their role in the occurrence and exacerbation of their lesions, contrary to what has been reported in other studies [8,10,12-14]. In addition, some patients reported local infections preceding the skin lesions, while others showed calluses caused by chronic friction and accumulation of keratinocytes [15,16]. Patient 16 was a typical example of a severe and dangerous presentation of DSH. Simple forms of DSH mimicking SISL, such as superficial lacerations or burns, may be managed in a dermatology clinic; otherwise, it will be ignored and remain undetected. Therefore, a tactful empathetic approach is important for successful dermatological and psychiatric management [17]. Dermatophagia may occur in people with organic brain pathologies, such as Alzheimer's disease, autism spectrum disorder, and intellectual disability [18]. Occasionally, intermittent dermatophagia may be associated with dissociation, parasuicide, and post-traumatic stress disorders [8,9]. In the same context, mental disorders may precipitate or exacerbate existing dermatological problems, and psychotropic medications may cause allergic dermatitis [8-10,19]. In the same context, psychiatric disorders may precipitate or exacerbate an existing dermatological problem, and psychotropic medications may cause allergic dermatitis [12]. On the other hand, most patients suffering from episodic forms of OCD do not fulfill the diagnostic criteria of classical OCD according to the DSM-5. They are more likely to be categorized between psychopathies (dermatitis artefacta) and DSH [19,20].

The treatment of patients with DSH includes symptomatic therapy, such as topical steroids for patients with skin-biting rash, and other supportive management. Psychiatric management begins with psychoeducation and rapport building, which play a significant role in drug compliance and follow-up. In our study, a typical antidepressant medication—selective serotonin reuptake inhibitors (SSRI)—was administered to patients who presented with symptoms of OCD, anxiety, and underlying depression, together with cognitive behavioral therapy in scheduled sessions run by the clinical psychologist during the follow-up process. Unfortunately, most patients were not ready to provide a detailed history of lesion onset and causative factors. However, the team administering treatment found that inner tension, bouts of anxiety, and depressive symptoms either predisposed individuals to or resulted from compulsive skin biting, which is similar to the results reported in developed countries, despite cultural differences[8,19,20]. This study calls for further, large-scale research on psychocutaneous diseases in Iraq to bridge the data gap and help engineer a specialized unit for better medical care.

CONCLUSION

Self-inflected skin lesions are emerging psychocutaneous disorders that are mostly treated by dermatologists without a psychiatric referral and many patients refrain from medical consultation. Fifteen patients with dermatophagia presented with diverse cutaneous manifestations, mostly nail dystrophy, skin nodules, and dermatitis-like features, limited to the hands. All patients were diagnosed and treated by the dermatologist and psychiatrist. All patients revealed symptoms of OCD with underlying anxiety and depression. Establishing a rapport and liaison management may help patients overcome psychiatric and skin problems and achieve healing. The lack of data mandates extensive future studies in Iraq and other countries.

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

Efficacy of propranolol in severe segmental infantile hemangioma of the face

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ABSTRACT

Infantile hemangioma (IH) is the most common benign vascular tumor of childhood. Most of IHs regress spontaneously, yet some require a more rapid intervention. Herein, we report the case of a two-month-old female who was brought in for consultation by the mother with a voluminous segmental IH of the face in respiratory distress. The infant was hospitalized, after taking advice from other specialists and performing a pre-treatment check-up, the patient was administered oral propranolol. Respiration returned to normal after several hours. The evolution was marked by the regression of the hemangioma and positive drug tolerance. Our observation shows the value of early diagnosis and the need for the rapid management of severe segmental IH of the face treated with oral propranolol. Apart from the efficacy of propranolol in the treatment of IH, we report the difficulties due to the unavailability of the adapted syrup form for infants in Guinea.

Key words: Segmental hemangioma; Infants; Propranolol

INTRODUCTION

Infantile hemangioma (IH) is the most common benign vascular tumor of childhood [1,2]. The growth of hemangiomas is characteristic: invisible at birth, then proliferation from 2–6 weeks with rapid growth for 3–9 months, followed by a plateau phase and finally spontaneous regression from about the second year for several years [3-5]. Depending on its volume and/or topography, hemangiomas may lead to complications that warrant specific therapeutic management [3]. If there is a vital, functional, and/or esthetic risk, first-line treatment is based on propranolol, which is rapidly effective and well-tolerated in children [4,6]. Herein, we report the case of a two-month-old female brought by her mother for a large segmental hemangioma of the face, which we treated with propranolol tablets.

CASE REPORT

The patient was a two-month-old female who had been seen in consultation for tumor-like lesions on the face, which had been progressing since birth and with dyspnea. The history revealed that she was the fourth of four siblings, born to a 27-year-old mother from a full-term pregnancy and eutocic delivery. A physical examination revealed a dark red tumor cupboard with sharp edges, of geographical contour and firm and elastic consistency, sitting on the right hemiface with palpebral edema, preventing the opening of the right eye, overflowing on the right side of the neck with spaces of healthy skin. The half-mucous membranes and labial mucous membranes were the sites of the same lesions. In view of these localizations, we requested a multidisciplinary consultation. The ophthalmologic consultation concluded that there was sub-palpebral injury with an amblyogenic risk. The

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otolaryngology consultation revealed a localization of the hemangioma lesions in the right nasal fossa causing the respiratory difficulty. The rest of the otolaryngology examination was without particularity. On pediatric consultation, the anthropometric parameters were normal, yet noted the presence of dyspnea with a respiratory frequency of 67 cycles per minute. In view of this clinical presentation, we retained the diagnosis of severe segmental infantile hemangioma of the face in the proliferative phase (Figs. 1a and 1b), and the infant was hospitalized. The assessment, including cardiac ultrasound, blood glucose, and blood count, was normal. Treatment with propranolol tablets crushed in a small amount of water was immediately initiated at a dose of 1 mg/kg/day two times a day (May 2019). The hours following the administration of propranolol were marked by the disappearance of dyspnea. We increased the dose to 2 mg/kg/day two times a day at the second week of treatment. The infant was discharged after two weeks of hospitalization. The dose of propranolol was increased and maintained at 3 mg/kg/day starting from the third week of treatment. The infant returned for blood pressure and glycemic control once weekly for the next month and then once every two weeks. We noted a rapid regression of the palpebral hemangioma with a decrease in palpebral edema in the early months (Figs. 2a and 2b). At the fourth month of treatment, the hemangioma almost regressed and a discreetly hyperpigmented macular cupboard remained in place (Figs. 3a and 3b) with no adverse effects.

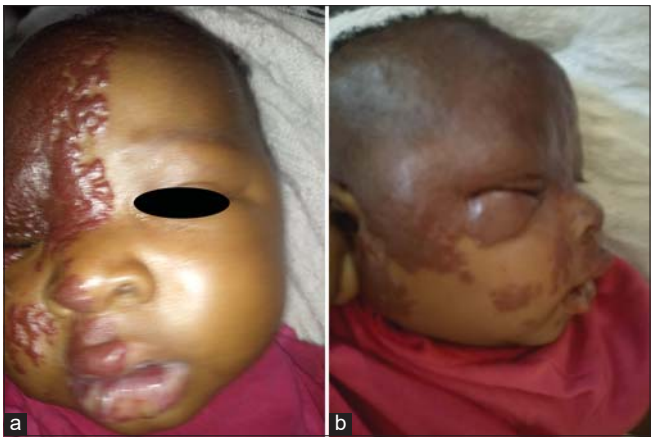

Figure 1: (a) Infantile hemangioma from the front before treatment. (b) Infantile hemangioma in profile before treatment.

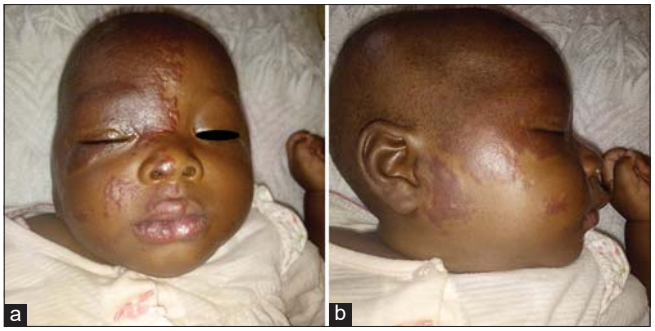

Figure 2: (a) Infantile hemangioma from the front during treatment. (b) Infantile hemangioma in profile during treatment.

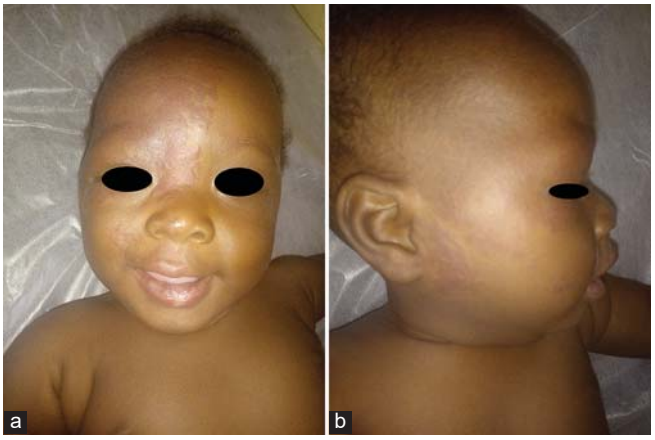

Figure 3: (a) Infantile hemangioma from the front after treatment. (b) Infantile hemangioma in profile after treatment.

DISCUSSION

Our observation illustrates the value of early diagnosis and the need for making early therapeutic decisions in the case of severe segmental infantile hemangioma of the face in the proliferative phase with a vital, functional, and esthetic risk, which has progressed favorably under oral propranolol. Infantile hemangioma (IH) is the most common tumor in children in all locations [1,7,8]. Despite its benign and spontaneously favorable evolution, its prognosis may sometimes be severe in terms of function (palpebral or labial localizations), aesthetics (thoracic localization in young females), but also vital (bleeding, damage to the respiratory axis) [7]. The growth of IH is rapid, usually during the first three months, yet may last until the sixth or eighth month in superffcial forms, and until the ninth or twelfth month in deep involvement forms. In rare cases, particularly in segmental IH, it may extend to the twenty-fourth month [4]. IH eventually stabilizes spontaneously, then a regression over several months or years is observed. The involution is slow and progressive and results in the appearance of central bleaching of the superficial lesions and sagging of the subcutaneous components [2,4,9]. There is little known about the regulators of hemangioma proliferation and involution. During the growth phase,

angiogenesis is stimulated by the basic fibroblast growth factor (bFGF) and the vascular endothelial growth factor (VEGF). In this proliferation phase, histology reveals active endothelial and interstitial cell division; in the involutional phase, however, apoptosis of these groups of cells is observed [4,10-13]. There are four main indications for the treatment of childhood hemangiomas. Those with a topography and/or volume that may be life-threatening, those that may entail a functional risk (periorbital region), those that may be painful in the case of ulcerated hemangiomas, and those that have an especially high risk of mutilating sequelae with major long-term aesthetic repercussions, particularly in periorificial localizations [10]. Our case concerned the palpebral region with a limitation of the opening of the right eye, which may lead to amblyopia, damage to the mucous membrane and the labial half-mucous membrane hindering sucking (functional risk), damage to the right nasal fossa leading to respiratory difficulty (vital risk), and facial localization and the size and appearance of the lesions (aesthetic risk). All infants with this type of hemangioma must be treated imperatively with oral propranolol, which is the first-line treatment, rapidly effective and well-tolerated in children, as several authors indicate [4,5,13-15]. Since the publication in the New England Journal of Medicine in 2008 [16], reporting the efficacy of propranolol on eleven complicated cases of IH, this fortuitous discovery prompted physicians in different countries to test this treatment on complicated IH. Thus, a multitude of retrospective [17], prospective [14], and multicentric [18] studies have been published after this original article confirming the treatment's efficacy on complicated IH. Noukeu et al. [3] described a case of favorably evolving sub-palpebral hemangioma under oral propranolol. Yilmaz et al. [1] reported, in their study on 25 cases of complicated hemangiomas, 18 parents (21, 86%) with a highly favorable perception and 3 parents (21, 14%) with a favorable perception of the efficacy of treatment and the evolution of IH. Our observation is related to the data in the literature [4,5,9,13,15,19], which reports that the initiation of treatment should be early and progressive (with a starting dose of 1 mg/kg/day increased in steps to reach an effective dose of 2–3 mg/kg/day). As the oral solution of propranolol is unavailable in our country, we used the tablet form to be dissolved in water in a fraction equivalent to the infant's dosage. The compliance of the parents allowed us to obtain a satisfactory result.

CONCLUSION

Propranolol transformed the prognosis and management of severe segmental facial IH. Therapeutic success is nevertheless based on early treatment. Although the oral solution of propranolol is not yet available in our country, the tablet remains a therapeutic alternative with satisfactory results. The HEMANGIOL 3.75 mg/mL oral solution (propranolol) specialty received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on February 20, 2014, and a marketing authorization (MA) on April 23, 2014, accompanied by a risk management plan (RMP) and risk minimization measures in Europe. A study on a larger sample would be necessary to assess the efficacy and tolerance of this presentation of propranolol.

Statement of Human and Animal Rights

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

Statement of Informed Consent

Informed consent was obtained from both parents to be included in the study

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Our Dermatology Online

Case Report

Leukocytoclastic vasculitis induced by medications displaying colocalizing lesional deposits for CD15, myeloperoxidase and HLA-DPDQDR: A Yin and Yang?

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ABSTRACT

Leukocytoclastic vasculitis is an inflammatory disease of small blood vessels; circulating immune complexes are part of the disease. A 57-year-old female presented with a sudden appearance of palpable purpura with petechial hemorrhages on the lower limbs after taking multiple medications. Skin biopsies were stained for H&E, direct immunofluorescence (DIF) and immunohistochemistry (IHC). The DIF revealed strong staining with multiple immunoglobulins and other markers in small dermal blood vessels, including those around skin appendices The IHC was positive for myeloperoxidase. CD15, myeloperoxidase and HLA-DPDQDR on the upper dermal blood vessels, as well as on inflammatory cells and debris around the vessels. These findings have not been previously documented and may indicate that circulating immune complexes activate the neutrophils.

Key words: Leukocytoclastic vasculitis; CD15; myeloperoxidase; HLA-DPDQDR; direct immunofluorescence; immunohistochemistry

Abbreviations: Hematoxylin and eosin (H&E); immunohistochemistry (IHC); direct immunofluorescence (DIF); basement membrane zone (BMZ); 4',6-diamidino-2-phenylindole (DAPI)

INTRODUCTION

Leukocytoclastic vasculitis is an inflammatory condition that affects the small blood vessels of the skin but can also affect other organs. In half of the cases leukocytoclastic vasculitis is idiopathic, and infections including viruses and drugs are the most common triggers for secondary leukocytoclastic vasculitis [1,2]. The disease equally affects both sexes. The lesions usually are accompanied by a burning rash predominantly in the lower extremities often associated with pain; other areas of the skin can be affected [1,2]. The most common cutaneous manifestation is a palpable purpura; other lesions include livedo reticularis, bullae, small papules, ulcers, and livedo reticularis. When the lower extremities are affected, is important to search for arthralgias or arthritis involving the knees or ankles [1,2]. Systemic symptoms can occur including fever, arthralgias, fatigue, and malaise in 50 to 60% of patients; thus, is important to perform laboratory studies to rule out other causes.

Histologically leukocytoclastic vasculitis is characterized by deposition of neutrophils, fibrinoid necrosis and neutrophilic debris ("leukocytoclasia") in small dermal postcapillary venules [1,2].

CASE REPORT

We describe a 57-year-old female who presented with a sudden appearance of hemorrhagic petechiae

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and plaques, comprising a clinical violaceous and erythematous palpable purpura (Fig. 1). No arthritis or arthralgias were detected. The patient described itchiness and burning sensations on the lesions. The patient was taking clonidine HCL 0.2 mg/day, atenolol 100 mg/day, tramadol HCL 50 mg/day, cyclobenzaprine 10 mg/day, and furosemide 10 mg/day for a constellation of clinical high blood pressure, depression and localized aches and pains. The patient did not exhibit general symptoms, and the possibility of ulcerative colitis was excluded. Laboratory tests including a complete blood count, erythrocyte sedimentation rate, biochemistry profile with liver and renal functions, urinalysis and C-reactive protein were negative. A skin biopsy for hematoxylin and H&E and PAS staining, as well as direct immunofluorescence (DIF) immunohistochemical (IHC) staining were performed. These procedures were performed as previously described [3]. The H&E tissue sections demonstrated an early subepidermal blister with eosinophils and occasional lymphocytes present within the blister lumen. Neutrophils were rare, but leukocytoclastic debris was noted within the lumen. Within the dermis, a moderately florid, superficial, perivascular infiltrate of lymphocytes, histiocytes, neutrophils, neutrophilic debris and rare eosinophils was identified (Fig. 1a). No frank vasculitis was seen. The DIF revealed deposits of FITC conjugated anti-human IgG, anti-kappa, anti-lambda, anti-human complement C3 and C4, anti-human fibrinogen and anti-human albumin (all these positive +++; the scale used was + weak positive, through ++++ strong positive) in 1) most of the upper dermal vessels, 2) some of the vessels communicating with the deep dermal vessel system, 3) mesenchymal/endothelial cell junctions, 4) small vessels around the piloerector muscle basement membrane area and 5) small vessels around eccrine sweat glands. The PAS displayed strong positivity around all the small dermal vessels, including those feeding the skin appendices.

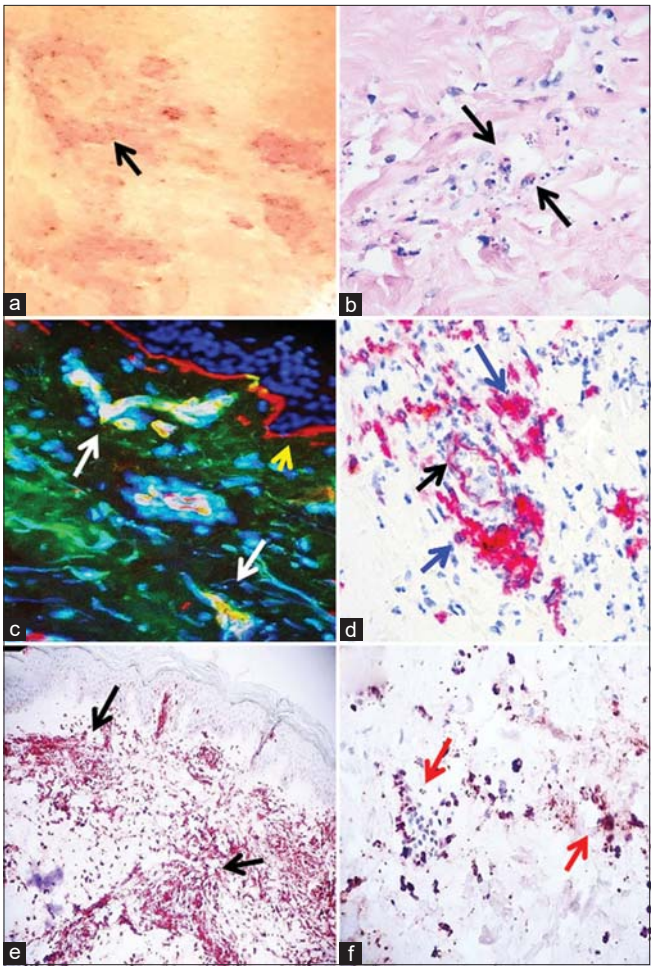

Figure 1: (a) Clinical purpuric lesions featuring some circinate rings, primarily present on the lower extremities (black arrow). (b) H&E stain highlighting dermal vessels surrounded by nuclear debris and a few eosinophils and neutrophils (black arrows) (400X). (c) DIF stain, showing positivity against an upper dermal vessel using FITC conjugated anti-human fibrinogen (white/yellow staining; white arrows) (400X). Note the red linear staining with Texas red conjugated Collagen IV on the basement membrane zone of the skin (yellow arrow). The nuclei of the cells were counterstained in blue with 4',6-diamidino-2-phenylindole (DAPI). (d) through (f) IHC staining. (d) Highlights positive staining with HLA-DPDQDR on individual cells (fuchsia staining; blue arrows) and on a dermal blood vessel (fuchsia staining; black arrow) (400X). (e) and (f) Highlight double positive staining with CD15 colocalizing with myeloperoxidase; seen as dark brown/magenta in punctate staining around the vessels and correlating with leukocytoclastic debris. In (e) black arrows (100X). In (f) red arrows (400X).

In our workup, we employed both single- and double-color IHC staining, performed with the Leica Bond MAX automated system (Buffalo Grove, Illinois, USA) using a Novolink™ detection and Compact Polymer™ technology as previously described [2]. For primary staining, we used the Bond Max refined red detection DS9390, an alkaline phosphatase linker polymer, and fast red chromogen (red staining). For secondary staining, we used the Bond Max refined brown detection DS9800, a horseradish peroxidase linker polymer, and DAB chromogen (brown staining). Positive and negative controls were consistently performed. The following antibodies were used from Novocastra-Leica for IHC: HLA-DPDQDR antigen, clone CR3/43, polyclonal rabbit anti-human antibodies: myeloperoxidase, and BOND™ Ready-to-Use Primary Antibody CD15 (MMA) Catalog No: PA0473 (Leica Biosystems Newcastle, Newcastle Upon Tyne, United Kingdom). We also utilized CD8 and CD68; cells both were positive in few cells around the vessels. Figure 1c shows positive staining of the vessels using FITC conjugated anti-human fibrinogen. Figure 1d

shows an IHC stain, showing positive expression of HLA-DPDQDR on the upper dermal vessels as well as on the inflammatory cells surrounding the vessels. Figures 1e and 1f document simultaneous positivity on IHC staining for myeloperoxidase and CD15.

The clinical and microscopic findings established a diagnosis of leukocytoclastic vasculitis. The patient was re-evaluated by her treating physician to decrease her medication dosages, and to remove the Tramadol. The patient was ordered to rest, elevate her legs and apply ice packs to the affected areas. Loratadine 10 mg/day and Celebrex® (Celecoxib) 200 mg were provided with topical steroids. After treatment, the patient's skin lesions improved. Repeat DIF and IHCs were performed after 15 days of treatment and were both within normal limits.

DISCUSSION

Leukocytoclastic vasculitis has been associated with numerous etiologic factors including drugs, autoimmune diseases, collagen vascular diseases, infections, foods and their preservatives, hair dyes and malignancies among other causes [1,2]. Although the exact pathogenic mechanism remains to be elucidated, circulating immune complexes are believed to be involved [1,2]. Neutrophils are innate immune cells that generate significant cell debris in cases of leukocytoclastic vasculitis.

In our case, both immunoglobulins and complement were seen in lesional small dermal blood vessels, including those supplying skin appendices. The simultaneous positivity on lesional skin biopsies from a leukocytoclastic vasculitis patient with simultaneous deposition of CD15, myeloperoxidase and HLA-DPDQDR represents a new and interesting finding. We reviewed multiple databases including all the years in the PubMed database and could not find previous documentation. The findings were also positive on vessels supplying skin appendices.

We do not know why the IHC positivity for CD15, myeloperoxidase and HLA-DPDQDR occurred simultaneously. It is accepted that HLA-DPDQDR is classically related to a non-innate, more specialized immune response with lymphocytes. We noted only a few CD8 and CD68 positive cells around the vessels. We speculate that HLA-DPDQDR expression may play an unknown role in exposing neutrophilic and/or endothelial cell molecules that were previously not exposed to the immune system. Thus, this finding warrants more investigation.

Antigen presentation by major histocompatibility complex (MHC) proteins is essential for adaptive immunity. The MHC Class II-encoded HLA-DPDQDR antigens play a crucial role in the human immune response. Their constitutive expression has been classically restricted to several immunocompetent cells defined as antigen-presenting cells. In our case, the expression of the gene at the lesional protein level may suggest a generic predisposition towards a vasculitis in this patient [4].

CD15 antigen (also known as Lewis x, or Le^x) is a characteristic marker for human myeloid cells and mediates neutrophil adhesion to dendritic cells [5, 6]. CD15 protein can be found in the cell membranes and the cytoplasm's of granulocytes and epithelial cells in a variety of tissues. Acute funisitis, a granulocyte-related inflammation of the umbilical cord, is associated with chorioamnionitis and perinatal adverse events. Thus, CD15 immunohistochemistry has been a powerful tool for studying the patterns of clinically relevant umbilical vasculitis, especially in cases that were indeterminate according to morphology alone [5]. To account for our observed presence of CD15, we found a published study that showed that antibody blockade of Lewis X (Le^x) blocked chemotaxis [5, 6]. It is known that glycans and endothelial glycan-binding proteins are critical for initial transepithelial migration of neutrophils out of the vasculature. We suggest that the body and the immune system could be trying to counterbalance, and limit neutrophilic flow out of the vasculature to limit secondary vessel damage. Often, the body and the immune system work with balancing mechanisms to avoid further damage.

It was recently demonstrated that although intracellular neutrophil elastase functions as a host defense factor against pathogens, its leakage into spaces induces degradation of host connective tissue components. The authors used a model of pneumococcal pneumonia and were able to demonstrate in cell cultures that expression of HLA class II molecules was decreased in THP-1-derived macrophages treated with supernatants from dead neutrophils [6]. Based on this data and given our findings, we suggest that the neutrophil and CD15 response may be one of "protection" against a specific antigenic response present in this kind of vasculitis; and thus could help the immune system to avoid a further "chronic" immune response via B and T lymphocytes [7].

Neutrophils are known to be effector cells of innate immune responses. However, when stimulated by interferon-γ (IFN-γ) to express HLA-DR, neutrophils acquire accessory cell functions for superantigen-mediated T cell activation [8]. The data was demonstrated by inducing *in vitro* HLA-DR expression on neutrophils. The findings in our case may represent a parallel example of what could occur *in vivo*.

We conclude in our case that the demonstration of HLA-DP, DQ, and DR antigens on blood vessels, as well as in the inflammatory infiltrate and cellular debris in the vessel walls may support the concept that the vessels (through their interactions with certain molecules) may play an active role in leukocytoclastic vasculitis. A larger series studying the presence of CD15, myeloperoxidase and HLA DP, DQ, and DR antigens is needed, and could lead to better diagnostic and/or therapeutic tools for this disorder. We also noted involvement of mesenchymal/endothelial cell junctions, small vessels around the piloerector muscle basement membranes and small vessels around the eccrine glands. We suggest that the constellation of these features may represent a non-traditional, expanded leukocytoclastic vasculitic process.

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 patient gave their consent for images and other clinical information to be included in the publication. The patient understood that their names and initials will not be published, and due effort was made to conceal their identity.

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Our Dermatology Online

Case Report

Metastatic brain melanoma in a patient with Noonan syndrome with multiple lentigines

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ABSTRACT

Metastatic melanoma of unknown primary origin often presents a major diagnostic and therapeutic challenge to the clinician. Herein, we present a case of metastatic brain melanoma of unknown primary origin in a patient with generalized lentiginosis and features of Leopard syndrome, which is the first case reported to date as of reviewing the literature. This case presents features suggestive of Leopard syndrome. Clinicians must be aware that a malignancy may occur even in the absence of the complete clinical picture of Leopard syndrome.

Key words: Noonan syndrome with multiple lentigines; Malignant melanoma; Brain metastasis; Cerebral hematoma

INTRODUCTION

LEOPARD syndrome (LS), currently termed *Noonan syndrome with multiple lentigines* (NSML), is a complex, dysmorphogenetic, multisystemic disorder of autosomal dominant heredity and variable penetrance and expressivity [1,2]. Its prevalence remains unknown. Gorlin et al. [3] first introduced the acronym LEOPARD to describe the following manifestations: lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness. The most common gene associated with NSML is PTPN11, identified in 50–85% of patients with NSML [4,1]. Other related mutations include the RAF1 (< 5%), BRAF, and MAP2K1 (< 1%) genes. In 5% of these cases, genes are unknown [5].

Lentigines are seen in more than 90% of cases of NSML and represent the most prominent finding of the syndrome. Other cutaneous manifestations include axillary freckling, café au lait macules, and localized hypopigmentation. Although it is unknown whether the pigmented lesions seen in NSML may progress to a malignancy [6], there are four reports of LS associated with a melanoma [1,7-9].

Herein, we present another case of melanoma in a patient with incomplete signs of NSML.

CASE REPORT

A 63-year-old female was admitted to the neurosurgery unit of our hospital with loss of consciousness. According to her medical history, she had arterial hypertension present for four years, treated with captopril and hydrochlorothiazide.

The patient underwent computed tomography revealing a cerebral hematoma, which was evacuated surgically (Fig. 1a). In the debris of the liquid, a proliferation of HBM45 positive cells was found. The histological picture was compatible with the diagnosis of metastatic brain melanoma of unknown primary origin.

Laboratory investigation and thorough physical examination followed to determine the location of the primary melanoma. Full blood count and liver tests were within the normal ranges. The levels of follicle-stimulating hormone, luteinizing hormone, thyrotropin, 17-hydroxycorticosteroids, and 17-ketosteroids were normal. No abnormality was found on chest

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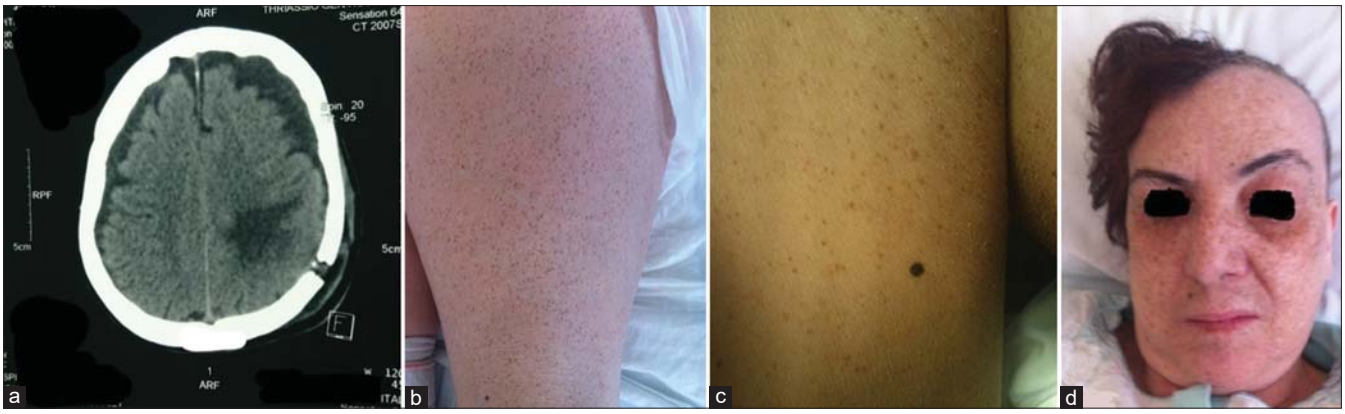

Figure 1: (a) Cerebral hematoma. (b) Lentigines on the left leg. (c) Lentigines and café noir spots. (d) Hypertelorism, triangular face, posteriorly-rotated ears, mandibular prognathism.

radiography, skeletal radiography, electrocardiogram, and echocardiography. Liver and abdominal ultrasonography scans were also normal. Ophthalmological examination revealed ocular hypertelorism. ENT and gynecological examination were normal.

A skin examination revealed multiple lentigines disseminated across the entire body, including the face, trunk, and sun-exposed areas (Figs. 1b and 1c). The lesions were flat, polygonal, irregularly-shaped, brown to dark brown macules (café noir spots), ranging in size from 1 to 3 mm, sparing the oral mucosa (did not cross the vermilion border of the lips), conjunctiva, and genitalia. Several café au lait spots were also on the trunk. The rest of the skin examination was unremarkable. The patient did not report any history of mole removal or shape or color changes in any of her moles. No family history of multiple lentigines syndrome or other inherited condition was mentioned.

According to maxillofacial examination, the patient also had mandibular prognathism, posteriorly-rotated, low-set ears, and a triangular face (Fig. 1d). The height of the patient was 1.72 m. Genetic analysis to detect mutations in the PTPN11 gene was performed yet the patient proved negative. The genetic analysis of the RAF1, BRAF, and MAP2K1 genes was not performed. The clinical findings raised suspicion of an incomplete Leopard syndrome.

The patient died six months later from disseminated metastatic melanoma.

DISCUSSION

NSML belongs to RASopathies, a group of rare genetic conditions with mutations in the genes of the RAS-MAPK pathway, including cardiofaciocutaneous syndrome, neurofibromatosis type 1, Costello syndrome, Legius syndrome, Noonan syndrome (NS), and Noonan-like syndromes (NSML, Noonan syndrome with loose anagen hair).

The diagnosis of NSML is established either clinically or by the identification of a heterozygous pathogenic variant in one of the four genes PTPN11, RAF1, BRAF, and MAP2K1. The clinical diagnosis includes multiple lentigines plus two of the following cardinal features: cardiac abnormalities (hypertrophic cardiomyopathy), a short stature, pectus deformity, and dysmorphic facial features [5]. In the absence of lentigines, three of the cardinal features plus a first-degree relative with NSML are required [10]. Additional features occurring in NSML are a variable degree of cognitive deficits, sensorineural hearing loss, cryptorchidism, skeletal anomalies, and café au lait macules.

It is now well-known that NSML has overlapping clinical features with other syndromes of the RASopathies group, and the genotype–phenotype relationship is commonly complicated [11], creating a dilemma in the final diagnosis.

The clinical findings in our patient included disseminated lentigines sparing the mucous membranes, several café au lait spots on the trunk, and facial dysmorphism (ocular hypertelorism, mandibular prognathism, posteriorly-rotated, low-set ears, a and triangular face), accounting for two cardinal features and one additional. The absence of a mutation in the PTPN11 gene in association with the clinical manifestations was not sufficient to establish the diagnosis of Leopard syndrome in this patient. However, this is not the first reported case of LS with incomplete clinical signs [12].

Four previous cases of NSML associated with melanoma have been described so far. Seishima et al. first reported a 62-year-old Japanese female who presented a somatic BRAF mutation in the melanoma on the left heel and a germline PTPN11 mutation [7]. Cheng et al. reported a 24-year-old female who developed a scalp melanoma and had a germline heterozygous PTPN11 missense mutation [8]. Colmant et al. reported a 62-year-old male with NSML and a mutation in the PTPN11 gene who developed four superficial spreading melanomas (three were achromic or hypochromic) and three atypical lentiginous hyperplasias [1]. García-Gil et al. reported a 44-year-old male with NSML confirmed by the genetic study of a mutation in heterozygosity in the PTPN11 gene who developed a melanoma at the dorsal level of the trunk [9].

Orrego-González et al. [13] described a twelve-year-old female with NSML and a mutation in the PTPN11 gene who presented acute hemorrhage of the right thalamus. CT angiography did not show the source of bleeding (arteriovenous malformations or aneurysms). Recently, Athanasiou et al. [14] have reported a nine-year-old male with Noonan syndrome and a heterozygous missense mutation in the PTPN11 gene who had two intracranial pseudoaneurysms leading to episodes of intracerebral hemorrhage, which were successfully treated with endovascular embolization.

In all cases with NSML and melanoma development, the patients had a heterozygous mutation in the PTPN11 gene. Despite the low number of reported cases, an increased risk of melanoma in NSML patients has been reported [9]. The PTPN11 gene codes SHP-2, a cytoplasmic protein tyrosine phosphatase that participates in the regulation of the activity of the RAS signaling pathway. It has been hypothesized that the suppression of SHP-2 may favor tumorigenesis through the abnormality of the STAT3 pathway, which is involved in the pathogenesis of melanoma [15].

CONCLUSION

Our patient proved negative against the detection of a mutation in the PTPN11 gene, thus the development of her melanoma was, apparently, not associated with the aforementioned hypothesis. It is possible that another pathway may be implicated in the development of melanoma in patients with NSML, yet this remains unclear.

Orrego-González et al. [13] suggested that the phenotype of NSML could be broader, probably including the development of intracerebral hemorrhage. Our patient's cerebral hematoma, although attributed to the metastatic brain melanoma, possibly confirmed that intracerebral hemorrhage has not been correlated with PTPN11 mutations in the literature.

Our case highlights the need for future studies to develop a definite, clinical algorithm for the diagnosis of NSML and to help to distinguish this entity from the other syndromes of the RASopathies group.

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

Merkel cell carcinoma of an atypical presentation: A case report and literature review

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ABSTRACT

Merkel cell carcinoma (MCC) is a primary cutaneous neuroendocrine carcinoma. It is a rare and aggressive tumor characterized by a high frequency of local recurrence, regional nodal metastasis, distant metastasis, and a low survival rate. Its diagnosis is challenging due to its rarity and it may be clinically mistaken for other skin cancers. It requires an incisional biopsy and confirmation by histology and immunohistochemical staining. This case illustrates an uncommon presentation of MCC in a 53-year-old young adult in an unexposed area of the right gluteal region. It is a rare cutaneous tumor that should be diagnosed and treated precociously given the aggressive nature of MCC and the limited therapeutic options for metastatic tumors. Herein, we urge physicians to suspect this diagnosis in front of any rapidly growing skin tumor, even in an unusual location, to provide the patient with appropriate treatment and improve the overall survival rate.

Keywords: Merkel cell carcinoma; Unexposed skin areas; Neuroendocrine tumors; Cytokeratin-20 Introduction

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive primary cutaneous neuroendocrine carcinoma [1]. It is characterized by a high frequency of local recurrence, regional nodal metastasis, distant metastasis, and a low survival rate [2]. Its incidence has increased over the last thirty years. It affects elderly Caucasian males in their seventies and eighties and occurs in sun-damaged skin, commonly on the head and neck. It may present at an earlier age in immunocompromised patients, such as organ transplant recipients, HIV-infected individuals, and those with B-cell lymphoid malignancies [3]. Merkel cell polyomavirus (MCPyV) causes up to 80% of MCC tumors in North America and Europe, yet an advanced age, exposure to UV radiation, and an immunosuppressed state are important risk factors. It most often presents itself as an erythematous or violaceous nodule or plaque and its clinical presentation is non-specific and varied [4]. Its diagnosis is challenging due to its rarity and it may be clinically mistaken for other skin cancers. It requires an incisional or excisional biopsy and confirmation by histology and immunohistochemical staining. This paper reports an uncommon case of rapidly progressive Merkel cell carcinoma diagnosed in a 53-year-old young adult in an unexposed area of the right gluteal region.

CASE REPORT

Herein, we report the case of a 53-year-old patient, a chronic smoker, with no notion of immunosuppression or a history of radiotherapy. He presented with an ulcerated and budding lesion in the right gluteal region (Fig. 1), increasing in size progressively and rapidly, evolving for the previous seven months. A biopsy was performed, suspecting the diagnosis of sarcoma,

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squamous cell carcinoma, or high-grade B lymphoma. Histological analysis of the skin specimen after HES staining revealed a proliferation of blue, round cells infiltrating the dermis and hypodermis (Figs. 2a – 2c). The tumor cells were monotonous with round and vesicular nuclei with finely granular and salt-and-pepper chromatin patterns. Numerous mitotic figures were observed as well as reduced eosinophilic cytoplasm. On immunohistochemical staining (Figs. 3a and 3b), the tumor cells stained for low-molecular-weight cytokeratins (AE1/AE3 and CK20) with a characteristic perinuclear, dot-like pattern for CK20, as well as chromogranin A and synaptophysin. Lymphoid markers, TTF1 and CK7, were negative. In the light of these morphological and immunohistochemical findings, the diagnosis of Merkel cell carcinoma was reached. A large surgical excision (Fig. 4) was performed with clear margins followed by radiotherapy.

DISCUSSION

Merkel cell carcinoma is a primary cutaneous neuroendocrine carcinoma first described by Friedrich Sigmund Merkel in 1875 as a nondendritic, non-keratinocyte, epidermal "tastzellen" (or "touch cell") that functions as a tactile skin receptor [5]. It most commonly arises in the elderly and has a predilection for the upper body, although the trunk and lower limbs may be involved as well. Its clinical differential diagnosis is nonspecific. The prognosis of the tumor has been variable. However, in most cases, these are aggressive neoplasms with a tendency to recur and eventually metastasize. It affects elderly Caucasian males in their seventies and eighties and occurs in sun-damaged skin, commonly on the head and neck [6,7]. This is different from our patient, who was younger (53 years old), did not have immunosuppression, and his tumor had developed in a non-sun-damaged skin area (gluteal region). This unusual clinical presentation was a source of clinical misdiagnosis, thinking instead of sarcoma, high-grade B-cell lymphoma, or squamous cell carcinoma. The biopsy that was communicated to us revealed skin tissue in which the dermis was infiltrated by a proliferation of round, blue cells with typical histopathologic and immunohistochemical characteristics of Merkel cell carcinoma. Histologically, Merkel cell carcinoma is composed of nests of round, blue, small-to-medium, monotonous cells. They characteristically display a fine, granular, salt-and-pepper chromatin pattern with reduced cytoplasm. Mitotic figures and apoptotic bodies are frequent [1,8]. Immunohistochemically, the tumor cells are positive for neuroendocrine markers (chromogranin A, synaptophysin, and CD56), epithelial markers (CK AE1/AE3, EMA), and CK20 typically stains in a perinuclear, dot-like pattern due to the clumping of the intermediate filaments. TTF1 and lymphoid marker staining is negative, which distinguishes them from small-cell lung carcinoma and lymphoma, respectively [1,9]. The antibody anti-MCPyV detects the presence of MCPyV large T antigen of Merkel cell polyomavirus

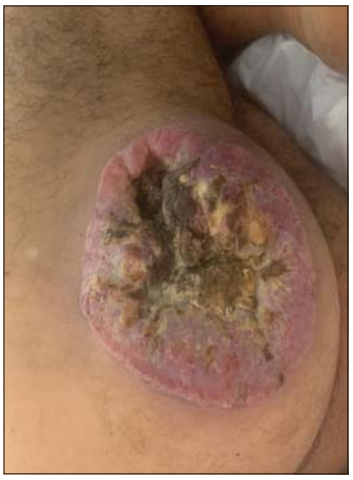

Figure 1: Ulcerated and budding lesion in the right gluteal region.

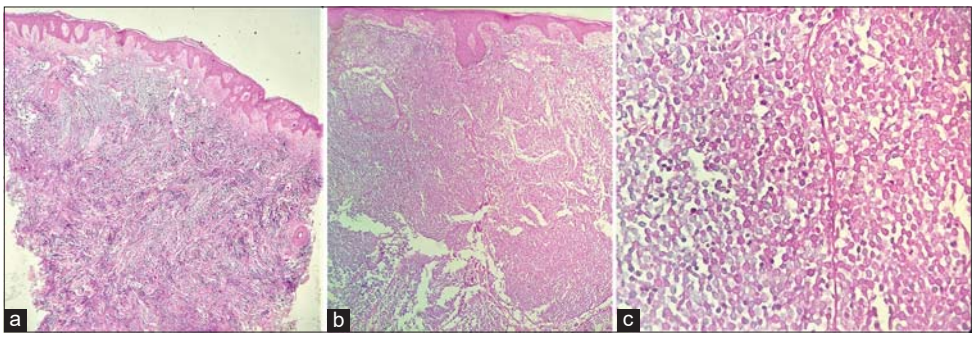

Figure 2: (a) Dermis infiltration by the small, round, blue cell, undifferentiated tumor (H&E, 40×). (b) Dermis infiltration by nests of small, round, blue, monotonous cells (H&E, 100×). (c) Tumor cells displaying a fine, granular, salt-and-pepper chromatin pattern with reduced cytoplasm and frequent mitotic figures and apoptotic bodies (H&E, 400×).

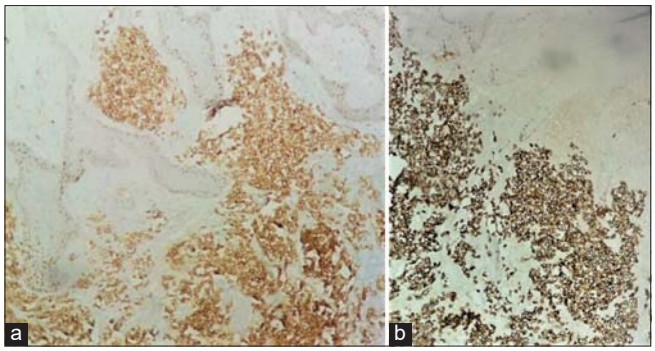

Figure 3: (a) Tumor cells immunostaining for chromogranin A. (b) Tumor cells immunostaining for cytokeratin 20 in a perinuclear, dot-like pattern.

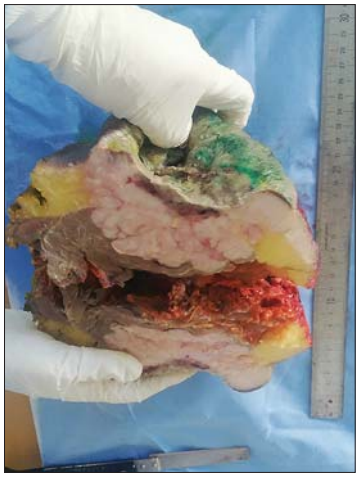

Figure 4: Surgical excision specimen: the macroscopic appearance of an ulcer, a budding tumor, with a whitish and homogeneous pattern.

with nuclear staining. Unfortunately, we did not have this antibody to confirm MCPyV in our gluteal Merkel cell carcinoma [10]. Surgical management with clear margins is the gold standard of treating Merkel cell carcinoma, as well as adjuvant radiotherapy [11]. The sentinel lymph node (SLN) is recommended for all patients to detect lymph nodal involvement and indicate a regional lymph node dissection. However, the current NCCN recommendations [12] on management and treatment remain based on clinically detectable nodal involvement because of conflicting evidence on the survival benefit of SLN in patients without clinical nodal involvement. Chemotherapy is reserved for metastatic cases with single or combined agents. While immunotherapy has revolutionized the management of Merkel cell carcinoma, preliminary data from non-randomized trials in patients with metastatic or recurrent locoregional MCC demonstrated that anti-PDL-1 agents and anti-PD-1 agents improve the rate of a prolonged response when compared to chemotherapy [13].

CONCLUSION

This case illustrates an uncommon presentation of Merkel cell carcinoma in a 53-year-old young adult in an unexposed area of the right gluteal region. It is a rare primary cutaneous tumor that should be diagnosed and treated precociously given the aggressive nature of MCC and the limited therapeutic options for metastatic tumors. Herein, we have urged physicians to suspect this diagnosis in front of any rapidly growing skin tumor, even in an unusual location, to provide the patient with appropriate treatment and improve the overall survival rate.

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Our Dermatology Online

Case Report

Generalized eruptive keratoacanthomas of Grzybowski in the practice of a dermatologist: A case report

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ABSTRACT

The article deals with a case of the clinical observation of a rare disease: generalized eruptive keratoacanthomas of Grzybowski. The disease pattern is characterized by the presence of small, generalized, itchy papules on the skin of the face, eyelids, trunk, extremities, genitals, and oral and laryngeal mucosae. The authors present a case of their own clinical observation of multiple eruptive keratoacanthomas of the Grzybowski type in a fifty-year-old patient seeking medical advice from a dermatologist. The duration of the disease was 2.5 years and its occurrence was preceded by repeated visits to countries with excessive insolation, which may be considered an etiological factor in the development of the disease. The diagnosis was verified by the disease pattern and pathomorphological studies on a biopsy of the affected skin.

Keywords: Generalized eruptive keratoacanthomas of Grzybowski; Disease pattern; Medical detection; treatment

INTRODUCTION

Generalized eruptive keratoacanthomas of Grzybowski is an extremely rare atypical form of keratoacanthoma, a benign epithelial skin neoplasm. The disease pattern is characterized by the presence of hundreds or thousands of small, generalized, itchy papules on the skin of the face, eyelids (with the formation of ectropion), trunk, extremities, genitals, and oral and laryngeal mucosae. The disease develops over the age of forty, has a relapsing course, and is characterized by possible spontaneous involution of individual elements with the formation of areas of depigmentation or atrophic scars. The influence of ultraviolet radiation, chemical carcinogens, human papillomavirus, and immunosuppressive therapy are assumed to be etiopathogenetic factors in the development of the disease [1-5].

Herein, we present a clinical observation of generalized eruptive keratoacanthomas of Grzybowski diagnosed by the staff of the institute for the first time.

CASE REPORT

A fifty-year-old patient turned to the Ural Research Institute of Dermatovenereology and Immunopathology to establish a diagnosis with complaints about numerous itchy papules on the skin of the face, trunk, and extremities, severe dryness and tightness of the skin up to eversion of the lower eyelids. Sleep disturbance due to itching and tightening of the skin was present. The patient had been ill for 2.5 years, when he began to notice the periodic appearance of single neoplasms described above on the skin of the face, chest, and right forearm, spontaneously disappearing after 2–3 months with the formation of flat, atrophic scars. During the previous several months, he noted a significant deterioration in the course of the disease: generalization of the rashes, increased intensity of itching, and tightening of the skin. Retrospectively, the patient was found to have visited countries with excessive insolation 6–7 months before the onset of the disease: Costa Rica, Cuba, Nicaragua, and Thailand.

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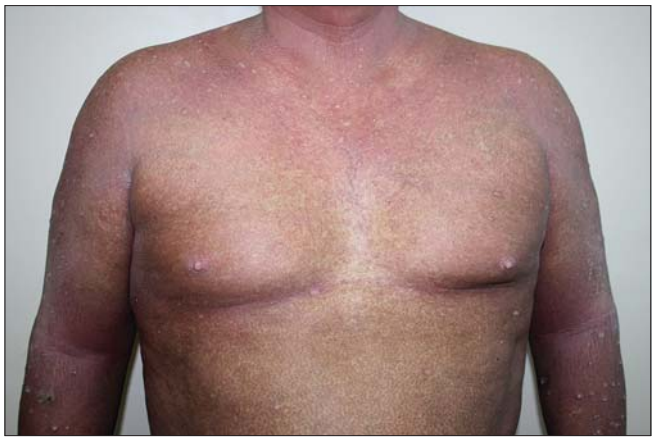

Figure 1: Multiple keratoacanthomas on the skin of the trunk and upper limbs.

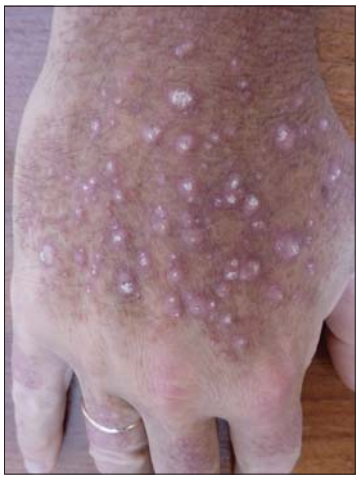

Figure 2: Multiple keratoacanthomas on the skin of the right hand at different stages of development.

The general condition of the patient was satisfactory. No pathological changes were found in the internal organs.

Status specialis: The skin process is generalized. On the skin of the face, trunk, and extremities, hundreds of erythematous nodules with a diameter of 1 to 8 mm are observed; the nodules have a smooth surface or are covered in the central part with gray, horny crusts, which are easily removed with a spatula without bleeding (Figs. 1 and 2). In the place of the nodules that have undergone spontaneous involution, areas of skin depigmentation are formed. On the skin of the lateral surface of the neck, there is a dome-shaped knot with a diameter of 1.7 cm and, in its central part, there is a crater-shaped depression (pseudo-ulcer) surrounded by a dense roller up to 3 mm wide, pink in color (Fig. 3). Ectropion of the upper and lower eyelids of both eyes is noted. The eyelashes on the lower eyelid are absent. The oral mucosa is without specific changes.

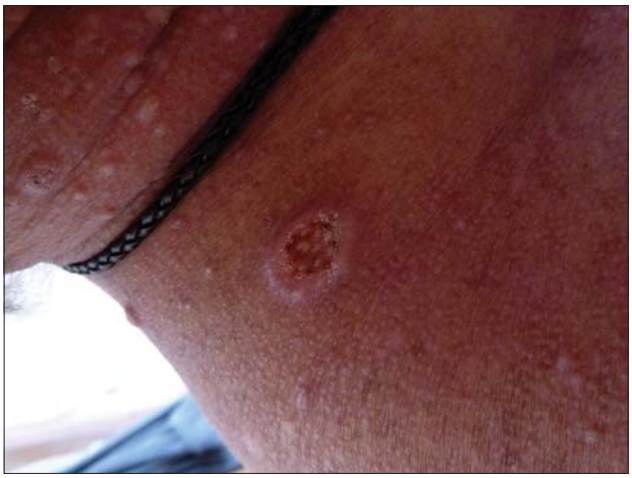

Figure 3: Crater-shaped keratoacanthoma with a central pseudo-ulcer on the skin of the lateral surface of the neck.

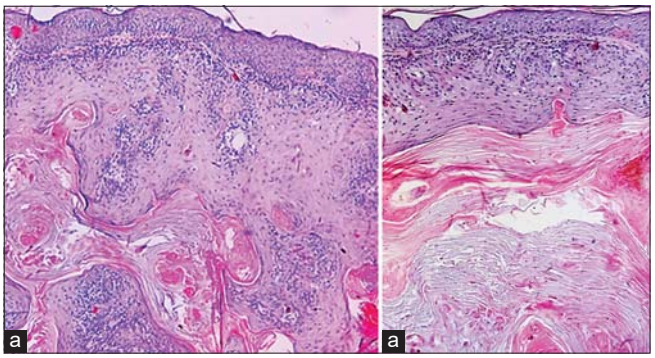

Figure 4: Pathomorphological examination of skin biopsy: (a) The epidermis with submerged papillomatous and acanthotic outgrowths (H&E, 50×); (b) signs of atypical keratinization of the "horny pearls" type and massive, hyperkeratotic, concentric foci (H&E, 100×).

No abnormalities are revealed in the clinical blood analysis and clinical urine test. In a biochemical blood test, there is an increase in total bilirubin to 27.1 μmol/L. Blood tests for viral hepatitis, HIV, and a complex of serological reactions to *Treponema pallidum* are negative.

Pathomorphological studies of the skin biopsy (Figs. 4 a and 4b): There is hyperparakeratosis with the formation of "horny pearls" submerged in epidermal outgrowths, which do not have a clear border with the underlying dermis, and foci of dyskeratosis. The length of the epidermal processes reaches the level of the pilosebaceous appendages. Quite a dense mononuclear infiltrate is determined in the stroma of the keratoacanthoma and the underlying dermis. The morphological picture corresponds to a developing keratoacanthoma.

On the basis of the clinical and pathomorphological data, the patient was diagnosed with generalized

eruptive keratoacanthomas of Grzybowski. Various treatment options were discussed with the patient and the appointment of acitretin (Neotigason) at a dose of 35 mg/day was recommended under the control of a biochemical blood test and dynamic observation by the dermatologist. The flattening and regression of most small keratoacanthomas and the disappearance of itching were noted a month after the first administration of Neotigason. Inspired by the improvement in the skin process, the patient independently increased the dose of Neotigason to 70 mg/day, which resulted in pronounced side effects of systemic retinoids (cheilitis, xerosis, peeling of the palms and soles, brittle nails, nosebleeds, blepharoconjunctivitis) as well as in an increase in total (73.3 μmol/L) and indirect bilirubin (64.1 μmol/L) in biochemical blood analysis. All these served as the basis for the discontinuation of the drug. The patient was referred to the gastroenterologist and ophthalmologist for an in-depth examination to establish a possible concomitant pathology. Then, communication with the patient was lost and there was no possibility of dynamic observation.

DISCUSSION

The diagnosis of the disease is established on the basis of the clinical picture and the data from pathomorphological studies on a skin biopsy. Differential diagnosis is performed with squamous cell skin cancer, ulcerative basal cell carcinoma, molluscum contagiosum, Kyrle disease, multiple keratoacanthomas of the Ferguson–Smith type, cutaneous metastases of internal cancers, Muir–Torre syndrome, etc. [1,3].

The treatment of generalized eruptive keratoacanthomas of Grzybowski does not exclude relapses of the disease and is performed with aromatic retinoids or cytostatics. In some cases, intralesional injections of interferon-α, applications of cytostatic drugs, electrocoagulation, cryo- and laser destruction, photodynamic therapy, and surgical tumor excision are employed [6-9].

CONCLUSION

The presented clinical case demonstrates the complexity of the diagnosis of generalized eruptive keratoacanthoma of Grzybowski due to the rare occurrence of this nosology and emphasizes the importance of consolidating the clinical experience of leading dermatologists and pathomorphological studies on skin biopsies.

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 the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that his name and initials will not be published and due efforts will be made to conceal their identity.

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Our Dermatology Online

Case Report

Morphea overlapping borderline leprosy: An unusual association

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ABSTRACT

Leprosy, or Hansen's disease, is a chronic infectious disease with a low transmission rate, affecting the skin, peripheral nerves, eyes, and mucous membranes of the upper respiratory tract, yet it may also be systemic. Cases of borderline leprosy are the acute or subacute stages of the disease. They are immunologically unstable and reflect the gradual variation in resistance against the etiological agent. Localized scleroderma or morphea is a fibrosing disease of the skin and underlying tissues that results from the disrupted function of growth factors (platelet-derived growth factor, i.e., PDGF) and receptor expression (as in the case of transforming growth factor β, i.e., TGF-β). Herein, we report a female patient with borderline tuberculoid leprosy (BT) who, during multidrug treatment (MDT), developed an indurated lesion of morphea exactly on the surface of an infiltrated patch.

Key words: leprosy; morphea; overlapping; borderline leprosy

INTRODUCTION

Leprosy, or Hansen's disease, is a chronic infectious disease with a low transmission rate, affecting primarily the skin, peripheral nerves, eyes, and mucous membranes of the upper respiratory tract, yet it may also be systemic. It is caused by *Mycobacterium leprae* and, in some cases, by *M. lepromatosis* [1]. Worldwide, it is an outstanding cause of morbidity due to the physical handicap and social stigma [1,2].

Cases of borderline leprosy are the acute or subacute stages of the disease. They are immunologically unstable and reflect the gradual variation in resistance against the etiological agent. Most progress to lepromatous leprosy. These patients develop infiltrated nodular or annular/circular plaques, which resolve with central atrophy. Some patients develop symmetrical neuropathy and areas of anesthesia [1,3].

Localized scleroderma or morphea is a fibrosing disease of the skin and underlying tissues that results from the disrupted function of growth factors (platelet-derived growth factor, i.e., PDGF) and expression of receptors (as in the case of the transforming growth factor β, i.e., TGF-β). There is an imbalance between collagen production and destruction found more frequently in females [1,4].

Herein, we report a female patient with borderline tuberculoid leprosy (BT) who developed an indurated lesion clinically and histologically compatible with morphea exactly on the surface of an infiltrated plaque during multidrug treatment (MDT) for multibacillary leprosy.

CASE REPORT

This was a 52-year-old female, a housewife from Merida, in the Yucatan peninsula of Mexico. Her

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medical history was non-contributory. She complained of a two-month history of a "growing hematoma" and lesions on the abdomen. An examination found three erythematous, well-demarcated, infiltrated plaques with a nodular appearance on the abdominal wall. The largest plaque was approx. 15 × 8 cm while the smallest, with an annular morphology, was 7 × 5 cm. There were no sensory abnormalities on the initial neurological examination (Fig. 1).

A skin biopsy of the initial lesion revealed an inflammatory infiltrate of epithelioid histiocytes surrounded by lymphocytes, forming granulomas around neural and adnexal structures. Occasional histiocytes with a foamy appearance were observed (Figs. 2a and 2b). The presence of acid-fast bacilli (AFB) was confirmed, with a bacteriological index of 1+ and a morphological index of 33%. Additionally, PCR identified *M. leprae*. The patient was classified as having borderline tuberculoid leprosy (BT). MDT was commenced with a good response and a significant improvement in the lesions.

After six months of follow-up, the patient complained of tenderness in the larger plaque. An examination revealed increased peripheral erythema associated with hardening and central hyperpigmentation (Figs. 3a and 3b). A second biopsy was performed, showing atrophy of the epidermis with diffuse hyperpigmentation of the basal layer. There was a lymphoplasmacytic interstitial infiltrate between the collagen bundles as well as around the eccrine glands and other adnexal structures. Loss of appendageal structures was also observed. Increased dense hyalinized collagen bundles with a sclerodermiform appearance extended to subcutaneous cellular tissue and were confirmed by Masson's trichrome stain (Figs. 4a and 4b). The diagnosis of morphea was established.

The patient was treated with 0.05% desonide cream twice a day applied to the indurated lesion for two months with an improvement. Over time, both the lesions of leprosy and those of morphea resolved with residual dyschromia (Fig. 5).

DISCUSSION

Patients with borderline leprosy have dynamic immunity with fluctuations in the course of the disease. These oscillations are the result of interactions

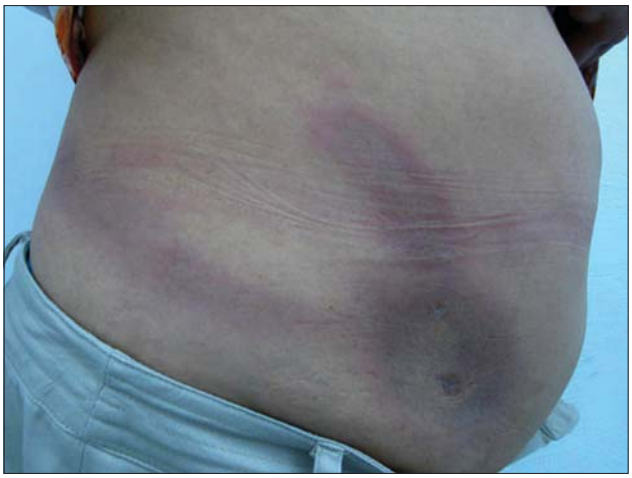

Figure 1: Erythematous, well-demarcated, infiltrated plaques on the abdominal wall.

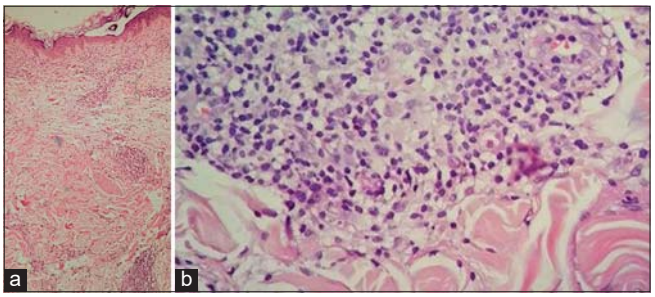

Figure 2: (a and b) Inflammatory infiltrate of epithelioid histiocytes surrounded by lymphocytes arranging granulomas around neural and adnexal structures (H&E; 10× and 40×).

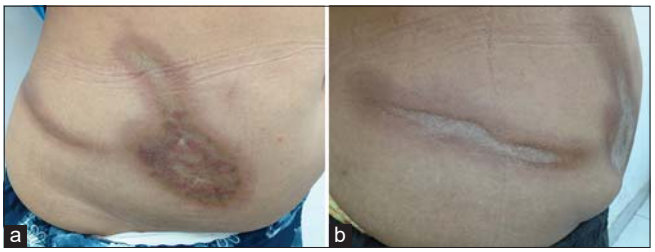

Figure 3: (a and b) Morpheaform aspect of the larger plaque during MDT.

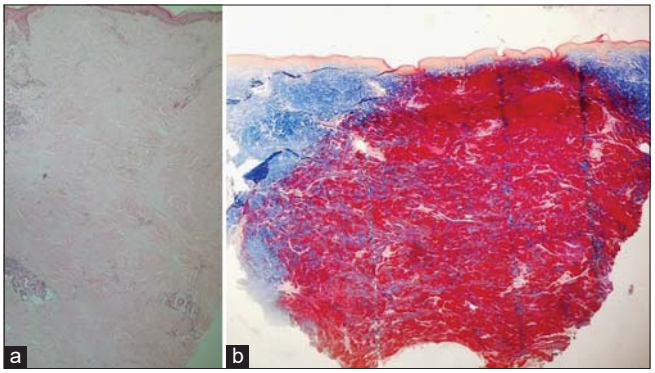

Figure 4: (a and b) Inflammatory, lymphoplasmacytic, interstitial infiltrate around the eccrine glands with hyalinized collagen bundles (H&E; 10×) (Masson's trichrome stain; 10×).

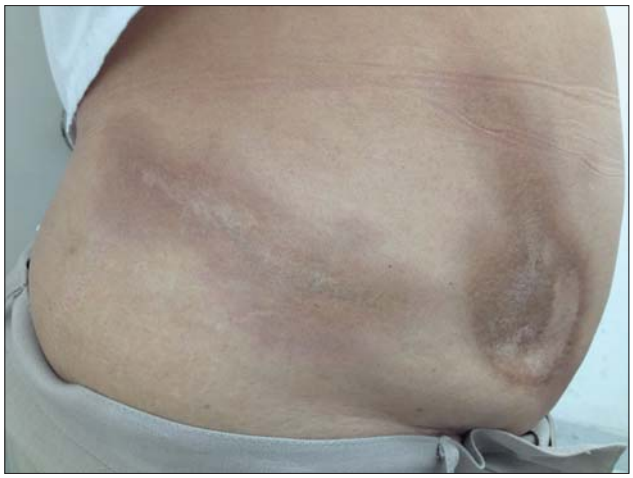

Figure 5: The remaining dyschromic plaque after MDT.

between multiple inner factors of the patient and the mycobacterium. Th1-type cytokines play a major role in the tuberculoid pole (IFNɣ, IL-2, IL-22, IL-15, and TNFα), as opposed to Th2-type, which are predominant in the lepromatous pole (IL-4, IL-10) with the formation of immune complexes [1,5,6].

It is well known that, after beginning adequate treatment, the immune response fluctuates. There is the reactivation of the cellular response with the production of inflammatory mediators associated with tissue damage [6].

Another group of cells that play an important role in the immune response against mycobacteria are Th17 cells, which perform a regulatory function. Depending on the closest pole they reside in, they trigger the synthesis of IL-17A, IL-17F, IL-21, and IL-22, which results in the recruitment of neutrophils and the activation of macrophages or the production of transforming growth factor β (TGF- β). Likewise, in patients with tuberculoid leprosy and in those with a type-1 reaction, a marked increase in ICAM-1 expression in keratinocytes and lymphocytes is classically seen [1,7].

Finally, lymphocytes may differentiate into Th9 and Th22 cell lines in the presence of IL-4 and TGF-β. These Th9 lymphocytes produce high amounts of IL-9, IL-10, and IL-21, which promote cytotoxicity against *M. leprae*; meanwhile, Th22 lymphocytes are characterized by the production of IL-22 and fibroblast growth factors, which are predominant as the patient approaches the lepromatous pole [7].

The pathogenesis of morphea is unknown. There is a functional disfunction of fibroblasts leading to increased synthesis of collagen and other extracellular matrix proteins [6]. Vascular damage, autoimmune factors, and skin fibrosis have been postulated as a result of triggering factors, such as physical damage, radiation therapy, trauma, and bacterial or viral infections, in which epitope extension or lymphocyte microchimerism takes place. Occasionally, a relationship with *Borrelia burgdorferi* infection was demonstrated by the presence of the microorganism in tissue samples or in antibodies against it [1,6].

The pathogenesis of fibrosis involves the presence of profibrotic factors that act on fibroblasts. These mediators, such as TGF-β, are secreted by lymphocytes, macrophages, and mast cells. Overexpression of receptors for TGF-β promotes increased levels of connective tissue growth factor (CTFG). Together, they increase levels of collagen and decrease the production of collagenases [1,6,8-10].

Overall, the immune response led by mononuclear cells results in the disruption of endothelial cells following microvasculature damage. There follows the production of chemotactic cytokines such as selectins, vascular adhesion cell molecules (VCAMs), intercellular adhesion molecules (ICAMs), interleukin (IL) -1, IL-2, IL-4, IL-6, and IFNɣ, and an active TH1 response. The consequence is the increase in the production of abnormal collagen with the deposition and storage of extracellular matrix components [1,10], different from lipomembranous changes seen in vascular or connective tissue diseases (systemic sclerosis), due to the interruption of blood supply with thickening and hyalinization of vessel walls [11].

In addition to platelets themselves, the hypersecretion of platelet-derived growth factor (PDGF) has been observed in different cell lines, such as fibroblasts, macrophages, epithelial cells, and nerve cells. Platelet-derived growth factor (PDGF) has a paracrine and autocrine chemoattractant and mitogenic effect in fibroblasts, resulting in the increase of collagen and the production of extracellular matrix components. Cells that express receptors for PDGF include fibroblasts, smooth muscle cells, capillary, and neuronal endothelial cells [12].

The histology of morphea is variable and depends on the stage of the disease. Overall, the epidermis is normal or atrophic. Incipient stages show thickening

of collagen and edema in the dermis associated with perivascular lymphoplasmacytic infiltrates, loosening of the adnexal structures, and vessels with wall thickening and luminal narrowing.

In the late stages, the inflammatory infiltrate tends to disappear, and the dermis shows thickening with dense collagen and reduced elastic tissue. There is a general loss of the adnexal structures and the presence of only some sweat glands in the deep sclerotic areas [1,13]. In some cases, there is a perineural distribution of these infiltrates without sensory abnormalities. The latter explains the disposition of lesions in a dermatomal pattern [14].

Comments

The immune response in dimorphic leprosy comprises a dynamic and oscillating spectrum with fluctuations both during the evolution of the disease and during treatment. Thus, cellular involvement and pro-inflammatory cytokines vary greatly depending on the predominant pole of the disease.

Acute reactions may appear in approx. 20% of cases, especially during pharmacological treatment with a greater release of mediators associated with tissue damage. These mediators include IFNɣ, IL-1 (typical of the tuberculoid pole) and IL-22 (which actives macrophages secreting TGF-β), ICAM-1, fibroblast growth factors (shared with scleroderma and which may be triggered in response to infectious processes). IL-1, IL-2, and IL-4 activate PDGF and CTGF, resulting in the chemoattractant effect on fibroblasts, with the excessive formation of collagen and a decrease in the production of collagenases.

It is likely that the coexistence of these two entities was provoked by either an infectious stimulus in a patient with a genetic predisposition or as a result of the immune adjustment activated by MDT. A significant inflammatory response may result from both, driven mainly by macrophages and the production of a dynamic cytokine profile. Furthermore, a potential cross-reaction with the stimulation of fibroblasts and profibrotic factors (microchimerism) cannot be excluded. The sclerotic changes may also be due to a physical injury with microvascular lesions, intercurrent infections, or stress (not reported in our patient) [15, 16].

In fact, some authors have previously reported several cases of leprosy mimicking connective tissue diseases with features of systemic lupus erythematosus, with the resolution of both disorders after MDT [17, 18]. In our patient, all lesions resolved with topical steroid therapy after concluding MDT. Some authors report the use of steroids with or without methotrexate, vitamin D analogs, colchicine, retinoids, antimalarials, pentoxifylline, broad-band UVA, phototherapy, Salazopyrin, or immunomodulators, systemic retinoids, and immunosuppressive drugs in resistant cases [19, 20]. In conclusion, we postulate that the fibrosing process resolved after the disappearance of the antigenic stimuli constituted by the bacilli and the cessation of the treatment-derived inflammation.

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Our Dermatology Online

Case Report

Dowling–Degos disease: An association with hidradenitis suppurativa

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ABSTRACT

Dowling–Degos disease is one of the genodermatoses presenting with acquired reticulate pigmentation of the flexures, black-dot papules, and pitted scars. Numerous associated conditions and multiple variants of the disease have been reported in the literature. Several gene mutations play a role in the pathogenesis of the disease giving rise to multiple phenotypic expressions. Herein, we discuss a case in three generations of a family affected with the disease and shed light on the associations and various expressions of the disease.

Keywords: Reticulate pigmentation; Hidradenitis suppurativa; Autosomal dominant inheritance

INTRODUCTION

Dowling–Degos disease (DDD), also termed reticular pigmented anomaly of the flexures, is a rare genetic disease with an autosomal dominant mode of inheritance with different phenotypic expressions [1]. It usually presents after puberty with reticular pigmentation of the flexures, particularly the axillae, groin, and submammary folds, blackhead comedo-like papules, and perioral, acneiform, pit-like scars [2]. DDD results from a mutation in more than one gene [3]. It is associated with numerous conditions, such as hidradenitis suppurativa (HS) [4], multiple epidermal cysts [5], keratoacanthoma [6], squamous cell carcinoma, and malignant melanoma [7].

CASE REPORT

A 39-years old diabetic male presented with a painful ulcer on the posterior surface of the upper part of the right thigh persistent for five days. An examination revealed an irregular ulcer, around 1.5 × 2 cm in diameter, with its edge macerated, around 2 cm in depth, and with a reddish base. It was surrounded by an erythematous zone, mostly representing a ruptured cyst (Fig. 1a). There were also multiple cysts, nodules, and scars resembling HS on the buttocks persistent for fifteen years (Fig. 1b). Similar lesions were located on the back of the scalp and neck (Fig. 1c). In addition to these lesions, multiple pitted, acneiform scars were present on the face, involving the nose, paranasal areas, nasal bridge, cheeks, and forehead (Fig. 2a). Reticulated confluent hyperpigmented patches and discrete macules at its periphery, hyperpigmented keratotic papules, black, comedo-like lesions, and multiple linear, atrophic scars were present in the axillae and groin, with the presence of a solitary cyst in the right axilla (Figs. 2b – 2e). Also, numerous atrophic scars and blackhead comedones were found on the upper back and dorsal surfaces of both elbows (Figs. 3a – 3c). These skin features appeared at the age of fifteen years. The hair, nail, and mucus membranes were normal. The family history was positive for other members of the family (Fig. 4). A histopathological examination of the pigmented macule on the axilla revealed a normal stratum corneum with a basket-weave pattern. The other layers of the epidermis were slightly thin. There was a suprapapillary thinning of the epidermis. The rete ridges were thin, branched, elongated, and with basal pigmentation, with an antler-like appearance. There was mild lymphocytic infiltration of the dermis and some melanophages (Fig. 5). The patient was treated with systemic and

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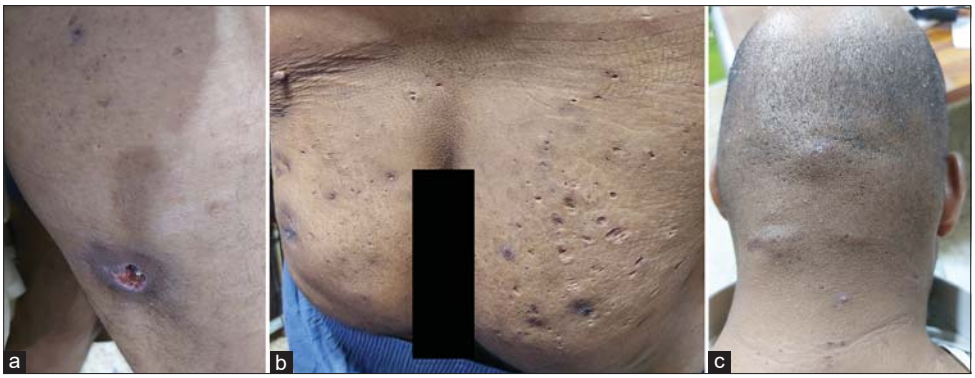

Figure 1: (a) Ulcer on the upper part of the thigh. (b) Multiple atrophic scars and cysts on the buttock. (c) Multiple cysts on the back of the scalp and scars on the back of the neck.

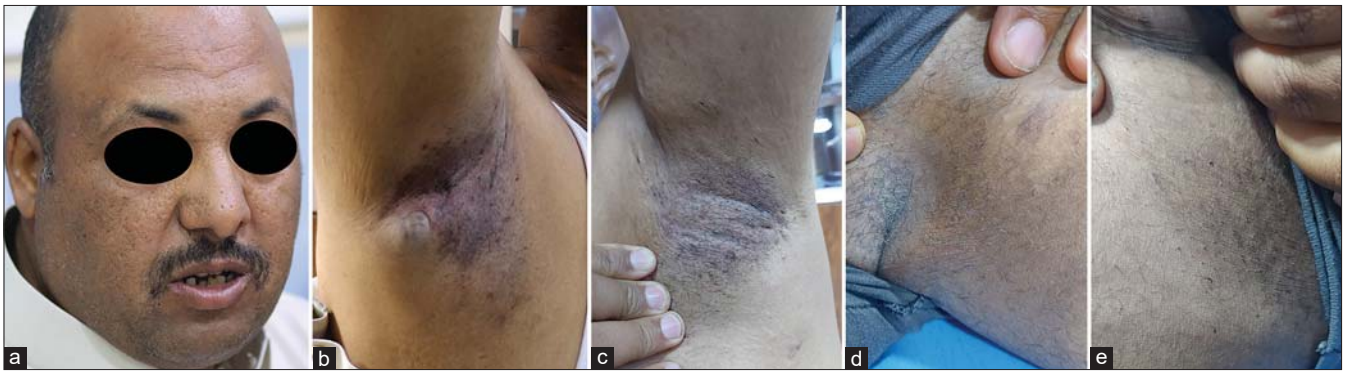

Figure 2: (a) Multiple pitted, acne-like scars on the face. (b) Reticulated hyperpigmentation of the right axilla with a cyst. (c) Reticulated hyperpigmentation of the left axilla. (d-e) Reticulated hyperpigmentation of the right and left groin.

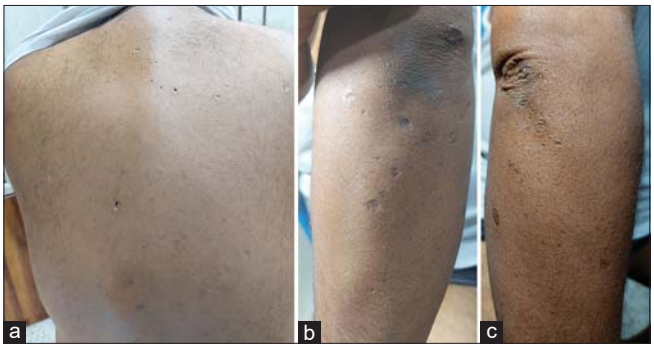

Figure 3: (a) Multiple pitted, acne-like scars on the back. (b-c) Multiple atrophic scars of the elbows.

topical antibiotics as an acute treatment for the ruptured, infected cyst. Thus, a diagnosis of DDD was reached based on the clinical manifestations, mode of inheritance, and histopathological characteristics. Informed consent was taken from the patient and the study was approved by the ethical committee.

DISCUSSION

DDD (OMIM #179850) is a genetic dermatosis manifesting with discrete, light brown or black, acquired macules arranged in a reticular form [7,8]. It usually appears first in the intertriginous areas, especially the axillae and groin, then progresses slowly [9]. In most reported cases, the involvement is of the face with acneiform pitted scars, usually located around the mouth [2,10,11]. In this case, most of the face was involved, the nose, paranasal areas, nasal bridge, forehead, and cheeks, while the perioral areas were spared. These manifestations were also observed by Gupta et al. [7] and Singh et al. [12]. This could be explained by a certain genetic mutation giving rise to this specific phenotypic expression.

DDD usually appears after puberty and, although inherited as autosomal dominant, females are more frequently affected [10,13]. In this family, the disease appeared at an age of fifteen years, thus an earlier onset may be determined by a specific mutation, although the disease was reported even in a newborn by Zuo et al. [10].

DDD results from mutations of more than one gene [3]. Such mutations affect keratin 5 (KRT5) and the POFUT1, POGLUT1, and PSENEN genes [4,9,14]. The PSENEN gene is linked to DDD associated with

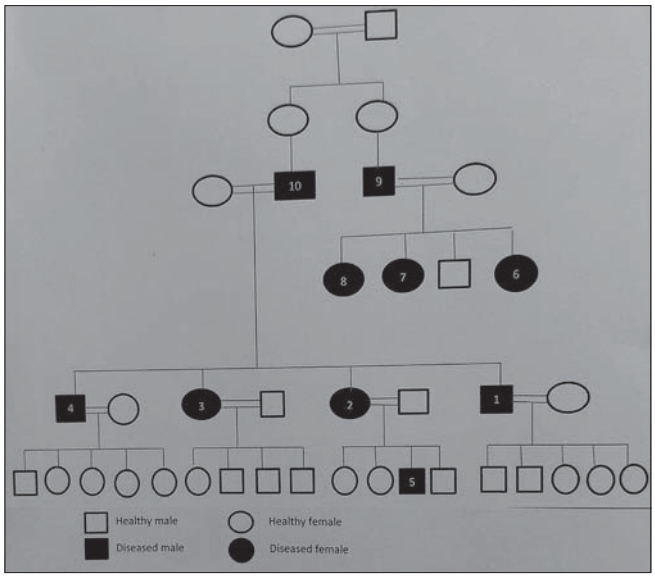

Figure 4: Family pedigree.

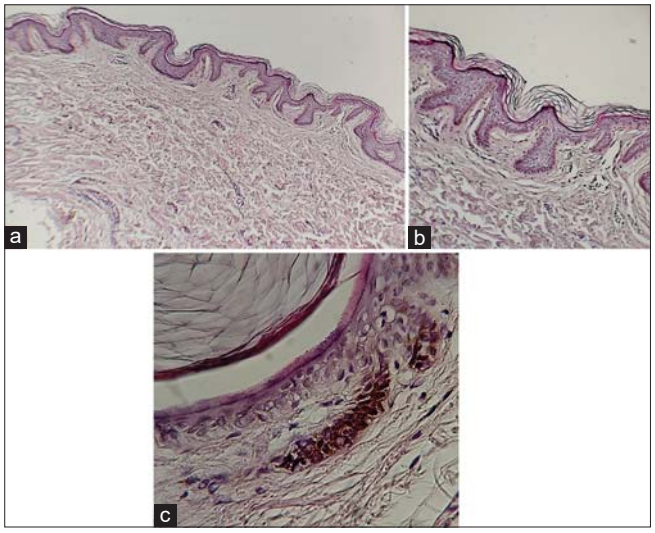

Figure 5: Histopathological examination of the hyperpigmented macule on the axilla (a: H&E, 4×; b: 10×; c: 40×), revealing branched, elongated, and antler-like rete ridges, basal hyperpigmentation, and mild perivascular lymphocytic infiltrate.

HS [14]. The POFUT1, POGLUT1, and PSENEN genes ameliorate the NOTCH signaling pathway, which is essential in keeping the integrity of the hair follicle sheath and other skin appendages [3,10,15,16]. It also plays an essential role in the maintenance of the homeostasis of cutaneous cells and controls the growth, maturation, and differentiation of keratinocytes and melanocytes [14].

Numerous dermatoses are associated with DDD [5-7]. One of these is HS, in which the involvement of the follicular unite is an important step in its pathogenesis [4,5]. It has been found that defects in the NOCH signaling pathway lead to disturbances in epidermal and follicular maturation [17]. The POFUT1 and POGLUT1 genes play a role in the regulation of the NOTCH pathway [18]. Hence, interactions among these different pathways may result in the appearance of HS in this disease. In our case, there was the involvement of the back of the neck and scalp with multiple cysts and previous scars. As recently described by Eugenia et al., the involvement of the nape area in a patient with HS is more likely to be associated with DDD [19]. Some diseases ought to be differentiated from DDD, such as Haber's syndrome, acanthosis nigricans, neurofibromatosis type 1, prurigo pigmentosa, Galli–Galli disease, and the follicular variant of DDD, reticulate acropigmentation of Kitamura, acropigmentation of Dohi, and dyschromatosis universalis hereditarian [8,11,13], yet clinical and histopathological criteria may exclude these dermatoses.

Numerous options are employed for the treatment of the disease, such as the depigmenting agents hydroquinone and retinoids. Also, laser is employed, such as Er: YAG, and a combination of Q-switched Nd: YAG and fractional CO_2 lasers, yet these modalities produce limited effects [20].

CONCLUSION

As reported in the literature, DDD resembles a spectrum of diseases, not one single, with localized and generalized forms at the ends of the spectrum, in between numerous varieties and associations. An early-age onset, the involvement of the nape of the neck and the back of the scalp, sparing of the perioral areas in some members, and association with HS in others, require genetic studies to detect the underlying defects giving rise to the variable phenotypic expressions.

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

Spinular follicular keratosis of Siemens associated with wooly hair in two sisters: Trichoscopic description and anatomopathological correlation

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ABSTRACT

Spinular follicular keratosis (SFK) is a rare X-linked inherited disorder of keratinization characterized by diffuse follicular hyperkeratosis and progressive scarring alopecia of the scalp, eyebrows, and eyelashes. Trichoscopy is a non-invasive dermatological tool that has improved the differential diagnosis of hair pathologies. In fact, dermoscopic models have been developed for several entities of scalp diseases, allowing early diagnostic confirmation and rapid action without the need for histopathology, as well as good follow-up for patients and signs of pathological activity. To date, the specific trichoscopic signs of KFSD have not been developed. Herein, we report the case of KFSD of Siemens in two sisters associated with wooly hair. We employed trichoscopy as a highly useful tool for diagnosis, then performed an anatomopathological study to confirm the diagnosis and explain the signs found on trichoscopy.

Key words: Spinular follicular keratosis; Trichoscopy; Anatomopathology; Wooly hair; Isotretinoin

INTRODUCTION

Spinular follicular keratosis (SFK) is a rare X-linked hereditary disease. It is a keratinization abnormality involving the hair follicle, characterized by progressive scarring of the scalp, eyebrows, and eyelashes associated with skin involvement. Other organ involvement has been reported, such as ocular involvement [1]. Approx. fifty cases have been reported in the literature. Although Siemens syndrome is highly rare and its clinical manifestations are peculiar, anatomopathological confirmation remains mandatory. Trichoscopy is a non-invasive dermatological tool that has improved the differential diagnosis of hair pathologies. In fact, dermoscopic models have been developed for several entities of scalp diseases, allowing early diagnostic confirmation and rapid action without the need for histopathology, as well as good follow-up for patients and signs of pathological activity. To date, the specific trichoscopic signs of KFSD have not been developed.

Herein, we describe a case of KFSD proven by pathology in a patient in whom trichoscopy served an important role in helping to achieve a differential diagnosis with respect to non-scarring alopecia, showing the typical signs of scarring alopecia and selecting the most appropriate place to perform a scalp biopsy.

CASE REPORT

This case was a six-year-old female from a second-degree consanguineous marriage who presented with progressive alopecia and generalized asymptomatic skin lesions present since birth. The prenatal and postnatal histories were normal. Her younger, four-year-old sister presented the same symptomatology, involving scalp

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hair loss without eyebrow involvement, yet at a less advanced stage (Figs. 1a and 1b).

A scalp examination revealed obvious hypotrichosis composed of a diffuse rarefaction of the density of scalp hair, follicular prominence, short, thinned hair giving an aspect of uncombable wooly hair (Figs. 1b and 1c). There was also hypotrichosis, follicular prominence, and scaling of the eyelashes (Fig. 1d). The traction sign was negative in the eyebrows, lashes, and scalp. The trunk, arms, and thighs showed extensive, tiny follicular keratotic papules of normal skin color, typical of keratosis pilaris (Figs. 2a and 2b). A dermoscopic examination revealed an inflammatory background, dilated white spots, diffuse disappearance of the pilar orifices, with localized, homogeneous peri-pilar pigmentation (Fig. 2c). The remaining hair holes gave rise to highly fine, scattered hairs, with the emergence of a single hair per hole, leukotrichial hairs, and broken or bent hairs. The nails, teeth, and mucous membranes were normal. She also had bilateral fissural plantar hyperkeratosis, predominantly next to the calcaneum (Fig. 2d). A skin biopsy of the scalp showed follicular hyperkeratosis with follicular ostia dilated by keratotic plugs protruding on the surface and a significant reduction in the number of hair follicles. The remaining hair follicles had atrophic hair sheaths, with their superficial parts surrounded by lymphocytic lichenoid inflammatory infiltrate with vacuolation of the basal cells of the hair sheaths. The sebaceous glands were hypoplastic (Figs. 3a and 3b). This appearance was in favor of keratosis follicularis spinulosa decalvans of Siemens. The patient was initiated on isotretinoin with a significant improvement of the keratosis pilaris and the disappearance of the plantar keratoderma two months later and the attenuation of the inflammation.

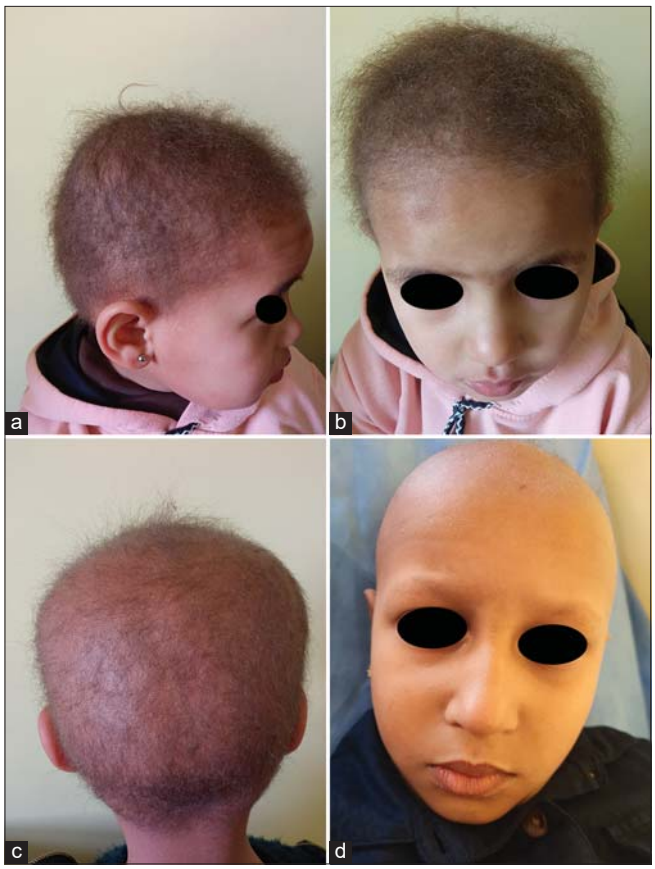

Figure 1: (a and b) Photos of the sister with diffuse hypotrichosis with follicular prominence of the scalp, without the involvement of the eyebrows. (c) Obvious hypotrichosis consisting of a diffuse rarefaction of the density of scalp hair, follicular prominence, short, thinned hair giving an aspect of uncombable woolly hair. (d) Hypotrichosis, follicular prominence, and scaling of the eyelashes.

DISCUSSION

Spinular follicular keratosis of Siemens (KFSD) is a rare genodermatosis with an autosomal dominant X-linked mode of inheritance. The condition was first described by Macleod, yet the term KFSD was employed by Siemens in 1926. The gene was mapped to Xp21.2-p22.2. Sporadic cases have also been described [1].

The main clinical features of the disease are diffuse cutaneous follicular hyperkeratosis and progressive scarring alopecia of the scalp, eyebrows, and eyelashes. The alopecia may be patchy or generalized. The less frequently reported features are atopy, palmoplantar hyperkeratosis with the predominance of the calcaneal region, clumpy hair folliculitis or wooly hair among hair abnormalities, and the unusual sign of high cuticles (or long cuticles) [2].

Severe pruritus may be present and may be related to increased levels of substance P, which has been reported in numerous inflammatory skin conditions, including alopecia, atopic dermatitis, and psoriasis [2].

Ocular abnormalities, such as photophobia, blepharitis, keratitis, corneal dystrophy, conjunctivitis, congenital glaucoma, and lenticular cataract, have been described in several patients with KFSD [3].

Nowadays, dermoscopy is an essential tool for the dermatologist to more effectively reconcile the diagnosis of several pathologies with clinical similarities, especially hair pathologies and alopecia. Since the trichoscopic model of KFSD has never been developed before, the role of trichoscopy is not diagnostic for KFSD, yet it is useful, at the beginning, to differentiate

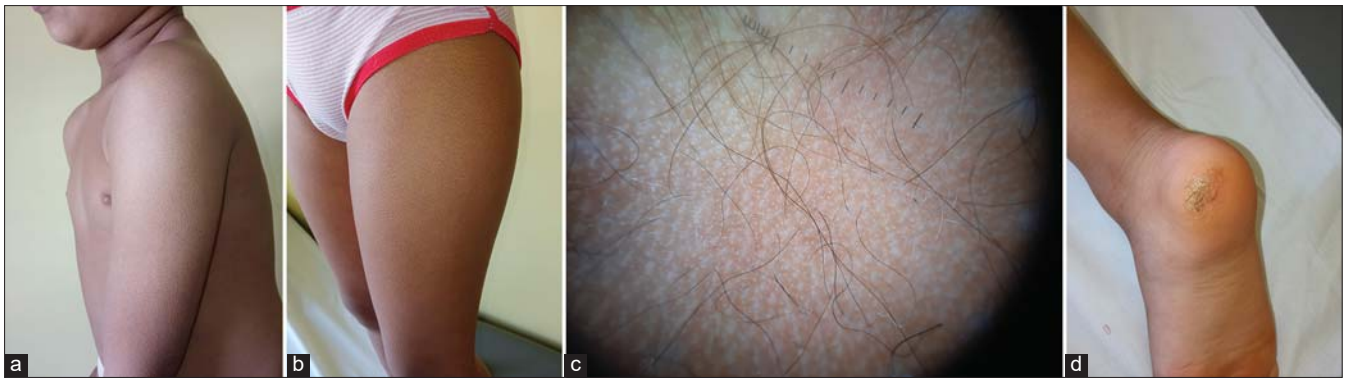

Figure 2: (a) Keratosis pilaris of the trunk and arms. (b) Keratosis pilaris of the thighs. (c) Trichoscopy showing ilated white spots, diffuse disappearance of the pilar orifices, the remaining hair holes giving rise to highly fine, scattered hairs with the emergence of a single hair per hole, leukotrychial hairs, and broken or bent hairs. (d) Fissural plantar hyperkeratosis of the calcaneum.

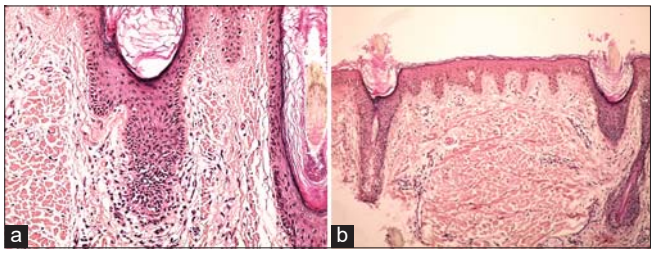

Figure 3: (a) Keratotic plugs protruding above the dilated follicular ostia, rarefaction of the hair follicles, and atrophic hair sheaths. (b) Slight lymphocytic infiltrate around an atrophic hair sheath and loose, concentric fibrosis.

between scarring alopecia and non-scarring alopecia. In 2020, Alessandrini et al. suggested the first trichoscopic description in a 26-year-old female, in whom clumpy hair, dystrophic hair, yellow spots, and follicular ostium loss were noted [4]. In our case, trichoscopy suggested the diagnosis, with the discovery of dystrophic hair composed of broken or bent hair, leukotrychial hair, loss of follicular ostia homogeneously scattered over the entire scalp and eyebrows, an erythematous background testifying dermal inflammation, and the presence of yellow dots expressing ostial dilatation with the secretion of the sebaceous glands.

The evaluation of hair loss is a diagnostic challenge for both the dermatologist and the pathologist. KFSD is a rare type of primary scarring alopecia with lymphocytic predominance. A good clinicopathological correlation is quite essential [4].

We decided to perform a biopsy to differentiate the disease from other scarring types of alopecia. Trichoscopy is crucial to select the most appropriate location for the scalp biopsy, as in other hair disorders.

Histopathologically, in advanced KFSD, the alopecia is lymphocytic [4]. However, in the early stages, the infiltrate is more neutrophilic [5]. A keratinization defect is usually observed, resulting in hypergranulosis and compact hyperkeratosis in the upper part of the infundibulum [5], which correlate clinically with follicular plugs. In the next phase of acute inflammation, spongiosis appears with a neutrophilic infiltrate in the infundibulum and the adjacent epidermis. The evolution includes the appearance of a lymphocytic infiltrate associated with perifollicular fibrosis, predominantly in the upper part of the follicle. In the terminal stages, fibrosis is observed with the presence of foreign-body granulomas surrounding the hair shafts [6].

In our case, the follicular ostia dilated by keratotic plugs protruding on the surface corresponded to keratotic papules and yellow dots on dermoscopy. The atrophic follicular sheaths surrounded in their superficial part by a lymphocytic inflammatory infiltrate in slightly lichenoid places with vacuolation of the basal cells of hair sheaths may explain both the hair dystrophy responsible for fine, brittle, wooly hair and the inflammatory background of the scalp. The loose, concentric fibrosis surrounding the hair follicles explains the white spots found on dermoscopy, representing fibrosed follicles in the terminal stage unable to produce hair.

Evidence for the treatment of keratosis follicularis spinulosa decalvans is anecdotal. Keratolytic agents and topical emollients only offer a symptomatic improvement in skin texture [6]. A combination of topical and/or intralesional corticosteroids may be employed for symptomatic relief [6]. Antibiotics such as tetracyclines, sulfonamides, macrolides, penicillins, and rifampin may be required during pustular flare-ups of the disease. Etretinol and isotretinoin may be useful,

yet have been reported to produce variable results. Oral retinoids are effective in the early phase of the disease when an active perifollicular infiltrate is present and should be continued for six to twelve months for an optimal response. Retinoids decrease epidermal proliferation and cytokine production, thereby reducing hyperkeratosis and inflammation [7].

Non-Q-switched, long-pulse ruby laser may be useful in recalcitrant KSFD.

Cases of end-stage KSFD treated with 800 nm diode laser have been reported with a striking response, with skin smoothing and the complete resolution of inflammation without the recurrence of symptoms within 2.5-year follow-up [7].

Our patient was treated with oral isotretinoin with smoothing of the skin surface and scalp and the disappearance of hon plantar hyperkeratosis over three months. Emollient creams based on 10% urea were combined with the oral treatment.

CONCLUSION

KFSD is a rare genodermatosis of the X chromosome. It consists of follicular hyperkeratosis of the skin, scarring alopecia of the scalp, the absence of the eyebrows, and corneal degeneration. Clinical and genetic heterogeneity has been described, yet the trichoscopic characteristics of this pathology have never been elaborated. The gold standard for diagnosis remains histopathology, yet trichoscopy may be highly useful for scalp biopsy site selection and patient follow-up. Through our clinical case, a novel trichoscopic description was established, as well as a correlation between dermoscopic signs and histopathology. Analytical studies of large series and novel cases are necessary to unravel the trichoscopic signs of this entity for more effective management and a more favorable aesthetic prognosis.

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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Clinical Image

Mucocutaneous leishmaniasis

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Leishmaniasis is a parasitosis caused by protozoa of the genus *Leishmania* (*L.*) transmitted by the bite of the sandfly *Phlebotomus* [1]. In Morocco, there exist three species: *L. infantum*, *L. major*, and *L. tropica*, most often responsible for the cutaneous and visceral forms. Mucosal involvement is rare and responsible for invasive, destructive, and treatment-resistant lesions [2]. Herein, we report a case of mucocutaneous leishmaniasis with different epidemiological and clinical characteristics from those of the New World.

A nineteen-year-old female patient from the South (Essaouira, Morocco), without any particular personal history, with a father treated for cutaneous leishmaniasis one year ago, consulted for cutaneous and mucosal lesions that appeared eight months previously, painless, non-pruritic, beginning with an erythematous papule that progressively increased in size, with an ulcerated surface and an infiltrated base, two on the lower lip (Fig. 1a), and ten distributed between both forearms (Fig. 1b) and both legs. Direct examination for Leishman bodies was positive on the two oral mucosal lesions and one skin lesion. HIV serology was negative. The patient received meglumine antimoniate for twenty-one days, combined with cryotherapy sessions, with a good evolution without any detectable side effects.

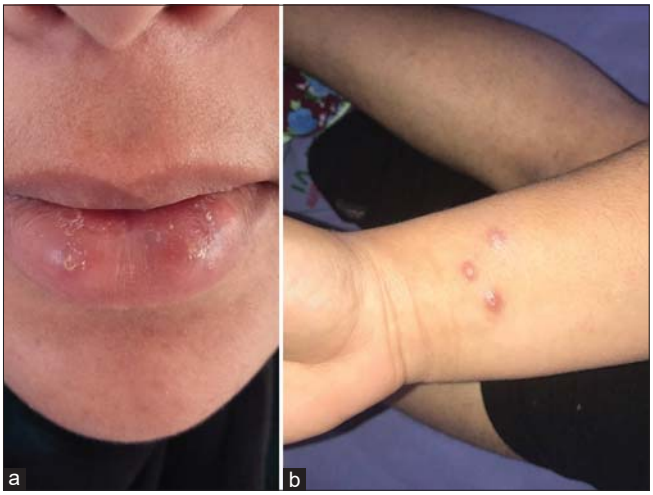

Figure 1: (a) Two papular lesions on the lower lip. (b) Three papulonodular lesions on the forearm.

Consent

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Our Dermatology Online

Clinical Image

A BCC masquerading as a fungating breast mass

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A 55-year-old female presented with a growth on her left chest that was increasing in size. The growth had been present for several years. The patient had no complaints of pain; just concerns about the presence of the mass. Upon examination, the patient had a polypoid, lobulated, violaceous, and red fungating mask measuring approx. 7.0 cm x 6.0 cm (Fig. 1a). Malignant breast disease encompasses many histologic types that include, ductal or lobular carcinoma, infiltrating ductal or lobular carcinoma, and inflammatory carcinoma. Benign masses can include fibroadenoma, intraductal papilloma, and abscess. Patient was referred to a general surgeon for removal due to the uncertain nature of this growth (Fig. 1b). Pathology was positive for a basal cell carcinoma with focal squamous cell differentiation, nodular type (Fig. 2). All resected margins were negative. Recovery was uneventful. Basal cell carcinomas located on the trunk account for only 10 percent of all cases. The majority are in sun exposed areas such as the face and neck [1,2].

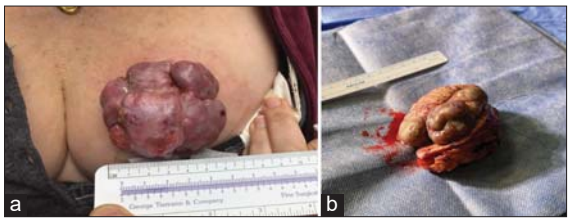

Figure 1: (a) Well demarcated lobular mass measuring 7.0 cm x 6.0 cm located on the left chest. (b) Lobulated mass after surgical removal

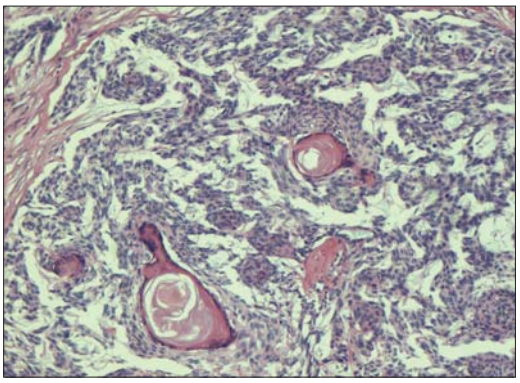

Figure 2: Well defined basaloid cells with squamous differentiation

Consent

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

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Clinical Image

A case of bullous pyoderma gangrenosum with endometrial adenocarcinoma

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Pyoderma gangrenosum (PG) is a reactive non-infectious inflammatory dermatosis falling under the spectrum of neutrophilic dermatoses. PG is generally classified into four types: ulcerative, pustular, bullous, and vegetative. Among them, bullous PG is known to be a rare type [1]. Herein, we report a case of bullous PG in a seventy-year-old female with a medical history significant for endometrial adenocarcinoma diagnosed five years previously with total hysterectomy and bilateral adnexectomy. Several years later, the patient presented a strangulated eventration treated with musculo-aponeurotic suture. Afterward, she presented purulent and hemorrhagic blisters on the abdominal wall. They were quickly progressive, painful, and necrotic with ragged, undermined edges and violaceous/erythematous borders. An abdominopelvic CT scan showed a large collection in the anterior abdominal wall without intraabdominal extension. Initially, the lesions were considered secondary to superinfection of the abdominal wall and were treated with antibiotics, drainage, and necrosectomy. As the lesions failed to improve, the patient was transferred to the dermatology department and a skin biopsy was performed, confirming the diagnosis of pyoderma gangrenosum (Fig. 1). Although systemic corticosteroids were administered at a dose of 1 mg/kg/day with the lesions starting to heal (Fig. 2), the patient died in less than two months. PG may precede, coexist, or follow diverse systemic diseases. The bullous variety is usually associated with hematologic disorders and is considered a predictor of hematological malignancies, such as acute or chronic myeloid leukemia that indicates characteristic pathophysiology specific to bullous PG. Despite being a well-recognized condition, PG is often diagnosed not early enough. Such a diagnosis should be actively

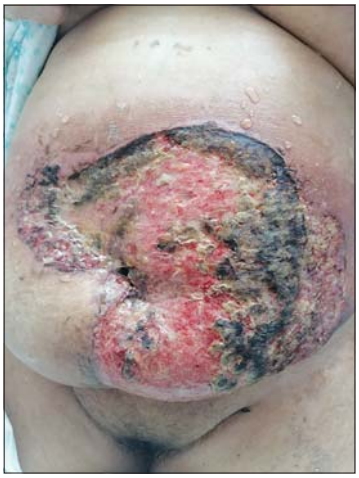

Figure 1: Post-drainage erosive and necrotic lesions with ragged, undermined edges and violaceous/erythematous borders.

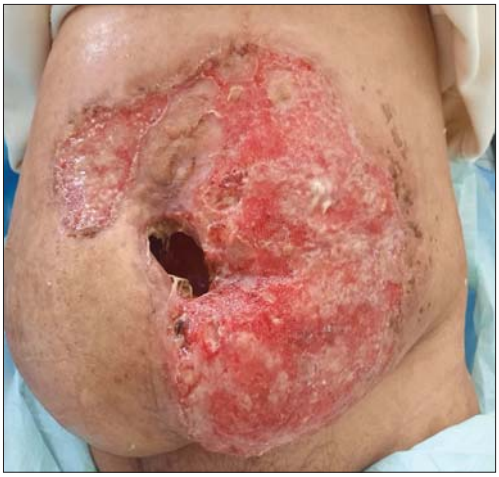

Figure 2: The lesions starting to heal after four weeks of systemic corticosteroids.

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considered when assessing ulcers, as prompt treatment may prevent the complications of prolonged systemic therapy, delayed wound healing, and scarring.

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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Clinical Image

Smegma remains a diagnostic dilemma

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A healthy, uncircumcised, two-year-old male presented with a six-month history of an asymptomatic, mobile, yellowish nodule near the base of the glans penis. An examination revealed a 1 × 0.5 cm, yellowish-white, soft, and mobile nodule between the glans and the foreskin of the penis (Fig. 1). No signs of infection or irritation were noted and the rest of the body was free of lesions. Ultrasound revealed soft tissue thickening, excluded a solid formation. The urine dipstick test was negative. Based on the clinical features, the diagnosis of a smegma cyst was reached. A smegma cyst is composed of epithelial debris, fat, and proteins and is covered by a well-formed, epithelial wall [1]. When there is no covering sac of lump, it is called the smegma pearl. Frequently located on the ventral surface of the glans, within the subpreputial space, the urethral meatus is not affected and the prepuce is partially retractable. It develops in uncircumcised patients. As phimosis resolves the inner foreskin, adhesions begin to undergo a gradual process of separation from the glans penis. Smegma may become entrapped during this process, forming smooth, palpable pearls [2]. It is neither damaging nor irritating. The differential diagnosis concerns either acquired or congenital penile cysts (e.g., trichilemmal cysts, preputial Epstein pearls, dermoid cysts, median raphe cysts, para meatal cysts, mucoid cysts, epidermoid cysts, pilosebaceous cysts, juvenile xanthogranuloma) [3]. Given the paucity of published reports, these collections are a diagnostic challenge for clinicians unfamiliar with this entity and a source of concern for parents. Smegma pearls are a benign entity. Bimanual retraction or gentle expression may be performed with a risk of paraphimosis, irritation, and recurrence [2,3]. Thus, these techniques must be discussed with the parents considering the spontaneous resolution. In the case of chronic evolution, smegma may evolve to preputial stones in adults and the elderly. No investigations or treatments are required. Only monitoring and parental reassurance are recommended.

Figure 1: Mobile, yellowish-white nodule between the foreskin and the glans penis of the uncircumcised boy.

Consent

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

Our Dermatology Online

Case Letter

Amicrobial pustulosis of the folds mimicking Hailey–Hailey disease in a patient with systemic lupus erythematosus and Sjögren's syndrome

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Sir,

Amicrobial pustulosis of the folds (APF) is a rare disease of neutrophilic dermatosis involving the scalp, ears, axillae, umbilicus, groin, and buttocks [1-3]. Herein, we describe a case of APF involving the bilateral axillae mimicking Hailey–Hailey disease in association with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SjS).

A 63-year-old female had been undergoing treatment for SLE and SjS for six years. She had been taking prednisolone at a dose of 4 mg per day on the first visit to us. She also had a history of Crohn's disease in remission. She complained of recurrent, erosive erythema on the axillae and beneath the breasts, which worsened in summer. A physical examination revealed infiltrative erythema with superficial erosions on the bilateral axillae (Figs. 1a and 1b). A laboratory examination revealed normal liver and kidney function, yet positive results for serum antinuclear antibodies (1:1280), anti-double strand DNA antibody (128 IU/mL), anti-Sm antibody (index: 6.7), anti-SS-A antibody (index: 131.5), and anti-SS-B antibody (index: 93.7). The erythrocyte sedimentation rate was high (32 mm in the first hour), and the CRP level was slightly increased (1.19 mg/dL). Bacterial cultures were positive for group G streptococci and the *Corynebacterium* species. A biopsy specimen did not reveal acantholysis of the epidermis, yet mild epidermal acanthosis without intense infiltration of inflammatory cells. Hailey–Hailey disease was excluded, and the patient was followed under treatment with topical corticosteroid ointment. During the course, the skin lesions exacerbated, and new pustules and erosive erythemas appeared on the groin and the anogenital areas (Fig. 1c). A histopathological examination revealed subcorneal neutrophilic abscesses in the epidermal and dermal perifollicular areas (Figs. 2a – 2d).

APF is a rare condition included as one of the neutrophilic dermatoses. It mainly affects the scalp and ear canals, as well as the intertriginous areas such as the axillary, groin, and perianal regions. If it involves the scalp, it typically results in alopecia [4]. APF is characterized by small, sterile pustules and erythemas and, histopathologically, subcorneal or intraepidermal neutrophil infiltration sometimes forming spongiform pustules, parakeratosis, and cellular infiltrates in the upper dermis. Pustules are both follicular and non-follicular. In the present case, we initially suspected Hailey–Hailey disease, because wet erythemas with superficial tiny pustules were observed on the skin folds such as the bilateral axilla and anogenital areas. However, the initial biopsy did not show acantholysis of the epidermal cells. A second biopsy revealed subcorneal neutrophil infiltration, follicular epithelial infiltration forming neutrophilic abscesses, as well as neutrophil infiltration around the follicles in the dermis.

APF is known to occur in patients with autoimmune diseases such as SLE. Marzano et al. proposed the diagnostic criteria for APF, which require association with one or more autoimmune disorders, positive antinuclear antibody at more than 1:160, and the presence of one or more serum autoantibodies [5]. In the present case, although the activity of APF and

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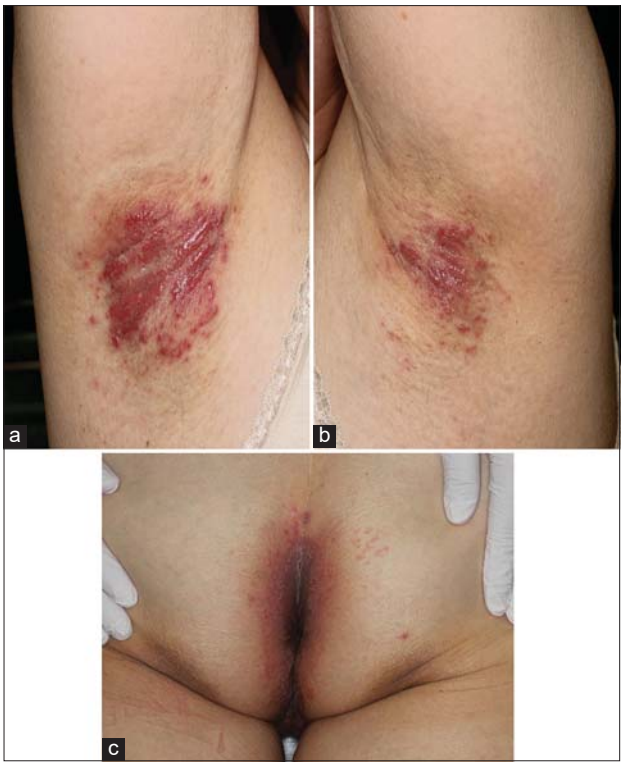

Figure 1: (a and b) Infiltrative erosive erythema on the bilateral axillae. (c) Erosive erythema and scattered papules in the intergluteal region.

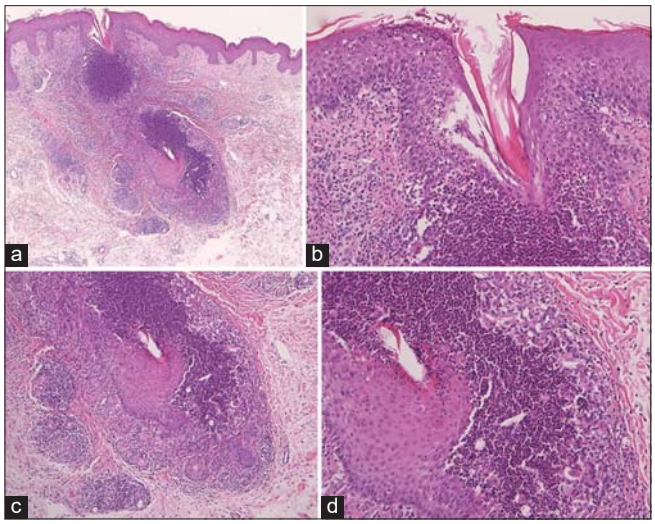

Figure 2: (a) Neutrophil infiltration in the follicular epidermis (40×). (b) Subcorneal neutrophil infiltration and follicular pustule (200×). (c) Prominent neutrophilic abscess in the dermis (100×). (d) Higher magnification showing giant cells outside the neutrophilic abscess (200×).

SLE/SjS was not parallel in behavior, the patient's previous history of Crohn's disease, as well as the presence of concurrent SLE and SjS, may have suggested the risk of developing APF. In addition, APF has recently been suggested to be a spectrum of autoinflammatory disorders, and several cases of APF in association with neutrophilic dermatoses, such as palmoplantar pustulosis and pyoderma gangrenosum, have been reported [6,7]. APF is a type of neutrophilic dermatosis and needs differentiation from Hailey–Hailey disease.

Consent

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

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Case Letter

Neutrophilic urticarial dermatosis of the extremities: Report of one case

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Sir,

Neutrophilic urticarial dermatosis (NUD) is a recently described entity part of the spectrum of neutrophilic dermatoses (ND). It is often associated with inflammatory diseases or neoplasms, such as hemopathies.

Herein, we report the case of a 67-year-old patient with a history of pulmonary tuberculosis, treated and declared cured, chronic obstructive pulmonary disease, operated prostatic adenoma, smoking at a rate of 50 pack-years, weaned four months ago, alcoholism, and cannabis use, weaned sixteen years ago. The patient presented with non-itchy, slightly infiltrated, maculopapular, erythematous-to-purplish plaques, which were present only in the extremities of the upper and lower limbs (Figs. 1a – 1c). The rash had persisted for almost ten years in relapses or remissions and progressed against a background of fever, polyarthralgia, and asthenia.

There was a biological inflammatory syndrome, with increased ESR and CRP, ferritinemia, and an inflammatory profile on protein electrophoresis.

Histology revealed a perivascular neutrophilic infiltrate without associated vasculitis (Fig. 2). Thus, the diagnosis of urticarial neutrophilic dermatosis was established. An entire paraneoplastic assessment was requested and returned unremarkable. The patient was treated with indomethacin with a regression of the lesions.

Neutrophilic urticarial dermatosis (NUD) is a rare variant, falling within the spectrum of neutrophilic dermatoses.

The concept of NUD was recently proposed by D. Lipsker et al. [1] to designate a rash distinct from common urticaria or urticarial vasculitis by its slightly

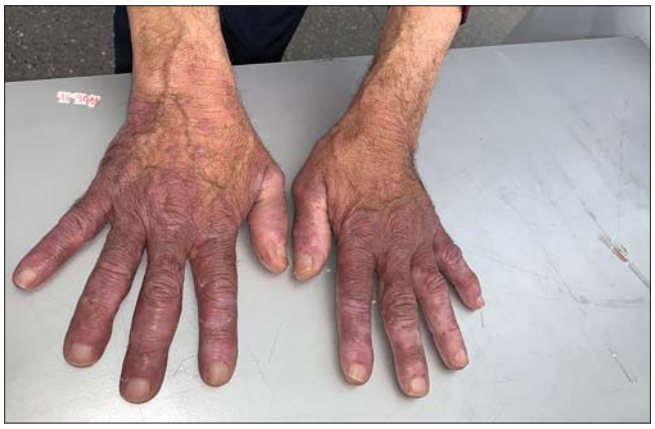

Figure 1a: Erythemato-purplish, maculo-papular plaques involving the back of hands.

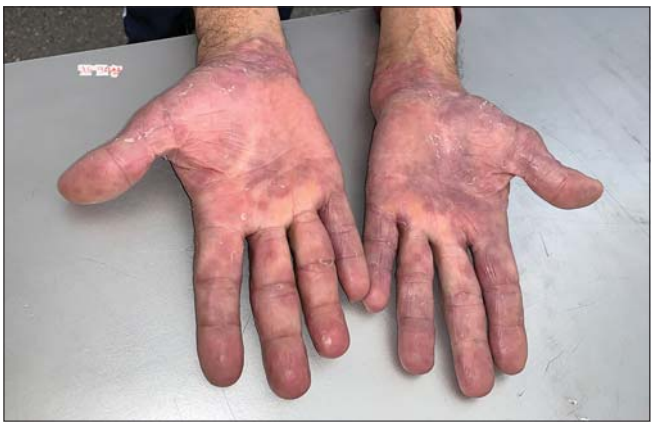

Figure 1b: Erythemato-purplish, maculo-papular plaques involving the palms of the hands.

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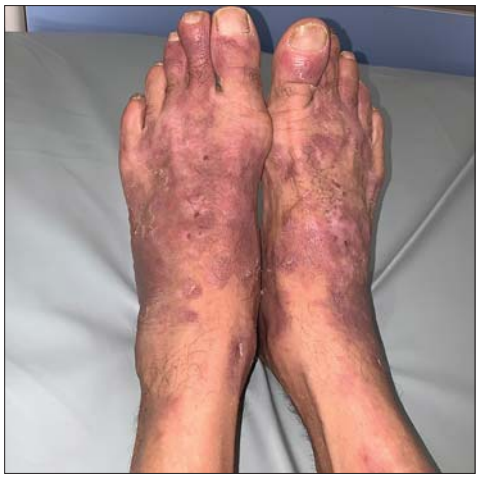

Figure 1c: Lesions on the feet.

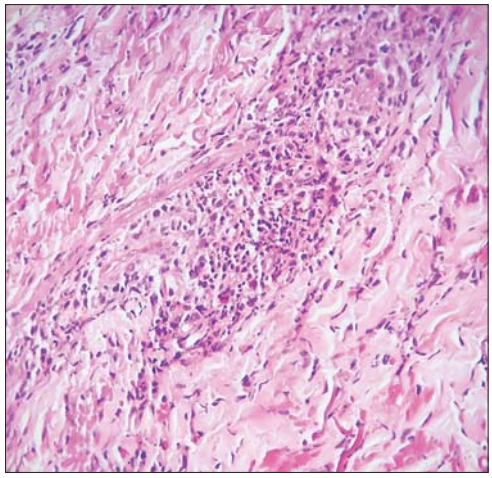

Figure 2: Histological aspect of neutrophilic urticarial dermatosis.

raised and non-itchy character as well as by a pink-red color. All these clinical characteristics were found in our patient. The localization of lesions reduced to the extremities of the upper and lower limbs was a peculiarity of our present case.

NUD is often associated with inflammatory diseases, such as systemic lupus, Still's disease, and juvenile idiopathic arthritis, and neoplastic diseases, such as hemopathies (myeloids, lymphoids) and solid tumors (digestive, pulmonary, testicular, mammary) [2]. These diseases were absent in our case.

Histologically, NUD is characterized by a perivascular and interstitial neutrophilic infiltrate, known as the "single file" or "en file indienne" [2], without vasculitis or dermal edema; all of these histological elements consolidated the diagnosis of this entity in our patient.

The treatment adopted for this case based on indomethacin allowed the lesions to regress rapidly. It should be noted that colchicine [3], dapsone, and general corticosteroid therapy may also be relevant therapeutic options.

Herein, we reported a case of neutrophilic urticarial dermatosis (UND) with an acral localization. It is imperative to keep in mind the need for usual supervising to search for an associated neoplasia or connectivitis.

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

Artificial pearl-induced penile annular lichen planus

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Sir,

Annular lichen planus is an uncommonly reported variant of lichen planus, especially on the penis [1]. Herein, we report a case of penile annular lichen planus induced by artificial pearls.

A 42-year-old, circumcised male presented to our hospital with asymptomatic, annular lesions of the glans penis. Around one month prior to presentation, he reported a history of inserting artificial pearls inside his penis by stainless steel. He denied a history of drug intake or a personal history of hepatitis C. A physical examination revealed multiple, reddish-purple, annular plaques with central atrophy on the glans penis (Fig. 1a). Inguinal lymph nodes and other mucocutaneous lesions were absent.

On the day of the visit, a rapid plasma reagin (RPR) test, *Treponema pallidum* hemagglutination (TPHA) test, and hepatitis C antibody test were all negative. Fungal microscopy of the glans penis was negative. A patch test was not performed due to its unavailability.

A histological examination revealed a lichenoid reaction pattern characterized by a combination of degeneration of the basal layer of the epidermis and a band-like lymphocytic infiltrate obscuring the dermal–epidermal junction. There was irregular, epidermal hyperplasia forming a characteristic saw-tooth appearance with wedge-shaped hypergranulosis (Fig. 2a). The basal layer of the epidermis exhibited vacuolar degeneration. The inflammatory infiltrate was chiefly lymphocytic and formed a dense band in the superficial dermis (Figs. 2b and 2c).

The diagnosis of annular lichen planus was confirmed and tacrolimus 0.1% was applied twice a day for two weeks. The lesions resolved significantly (Fig. 1b).

Annular lichen planus is one of the rarest variants of lichen planus, accounting for 3–7% of cases. The lesions present as ring-formed, violaceous plaques with or without central atrophy on the intergious sites, the penis and the scrotum [2].

The pathogenesis of lichen planus remains unknown. However, it is related to virus infection (hepatitis C), drugs (antimalarials, ACEIs, thiazide diuretic, NSAIDs, quinidine, beta-blockers, tumor necrosis factor-alpha inhibitors, gold), and contact allergens (mercury, copper, and gold) [3]. Our patient presented the annular lesions on the glans penis after one month of penile implants; therefore, it could be linked to the etiology.

The differential diagnosis of a penile annular lesion includes annular psoriasis, granuloma annulare, dermatophyte infection, and annular secondary syphilis [4]. Annular psoriasis is characterized by annular, erythematous plaques with scaling borders and central clearing, especially a positive Auspitz's sign. Therefore, annular psoriasis was excluded due to the negativity of the Auspitz's sign and the non-scaling borders of the lesions. Fungal microscopy and syphilis tests were negative. The diagnosis of a dermatophyte infection and annular secondary syphilis were also excluded. Granuloma annulare is histologically characterized by necrobiotic degeneration of dermal collagen surrounded by an inflammatory reaction, while the band-like lymphocytic infiltration at the dermal–epidermal junction is commonly seen in annular lichen planus.

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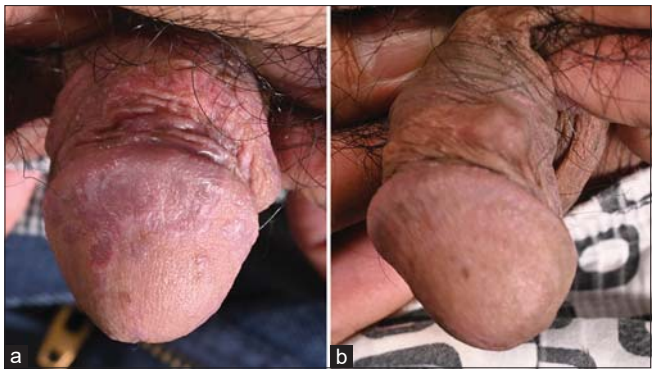

Figure 1: Annular lichen planus: (a) multiple, reddish-purple, annular plaques with central atrophy; (b) after two-week treatment with tacrolimus 0.1%.

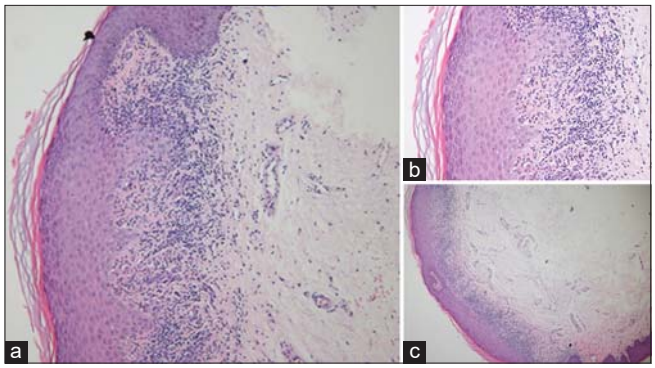

Figure 2: Histological findings: epidermal hyperplasia forming a characteristic saw-tooth appearance with wedge-shaped hypergranulosis (H&E, 40×); (b-c) the basal layer of the epidermis exhibiting vacuolar degeneration and the inflammatory infiltrate chiefly lymphocytic and forming a dense band in the superficial dermis (H&E, 100× and 200×).

The first-line treatment of genital lichen planus is topical corticosteroids. Alternative treatments include topical calcineurin inhibitors, topical calcipotriol, systemic corticosteroids, acitretin, isotretinoin, methotrexate, hydroxychloroquine, dapsone, cyclosporine, azathioprine, and mycophenolate mofetil [2,5].

CONCLUSION

Annular lichen planus is a rare manifestation of lichen planus, which may be misdiagnosed as other annular skin lesions.

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

Sprue-like disease possibly related to a single dose of methotrexate

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Corresponding author: Fatima Azzahra El Gaitibi, MD, E-mail: elgaitibi.fatimaazzahra@gmail.com

Sir,

Methotrexate is an antimetabolite commonly used in dermatology for inflammatory and autoimmune diseases, including psoriasis. Malabsorption secondary to treatment with methotrexate after its use in high doses and/or long-term has been described in the literature. However, only several cases of a sprue-like disease secondary to a low dose of methotrexate have been described. Herein, we report an exceptional case of a sprue-like disease after a single dose of methotrexate.

A 43-year-old female was admitted to our department with psoriatic erythroderma (Figs. 1a and 1b). Treatment with MTX was administered at a dose of 12.5 mg/week as well as folic acid supplements. Three days later, the patient developed bilateral leg edema, associated with biological malabsorption syndrome (hypoalbuminemia at 19 g/L, hypocholesterolemia at 0.98 g/L, prothrombin time at 45%, blood glucose at the lower limit of 0.7 g/L, and normocytic normochromic anemia at 9.4 g/dL). A duodenal biopsy performed three weeks later revealed no villous atrophy (Fig. 2). The discontinuation of methotrexate led to the disappearance of the leg edema and the progressive correction of biological parameters.

Three cases of non-coeliac sprue secondary to the use of methotrexate at low doses have been reported in the literature [1-3], either after relatively prolonged use (ten months) or after a single injection. A duodenal biopsy performed early or during treatment with methotrexate revealed villous atrophy. In our case, the absence of villous atrophy in the biopsy might be explained by the biopsy being performed three weeks after the injection. In fact, according to experimental studies, villous atrophy secondary to methotrexate is observed 72 hours after a methotrexate injection and regresses spontaneously in three to four weeks after the completion of treatment [3].

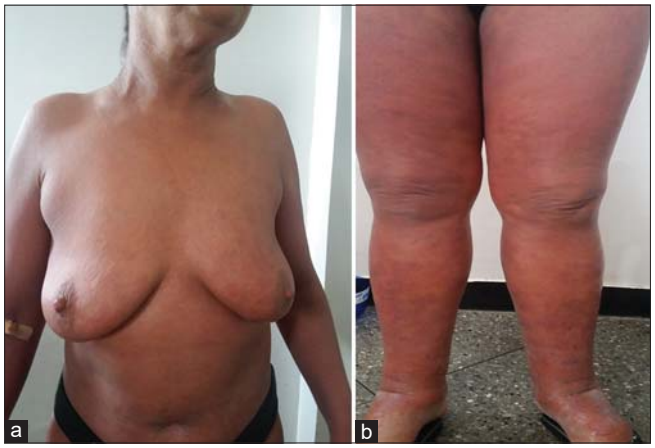

Figure 1: (a) Psoriatic erythroderma and (b) bilateral leg edema.

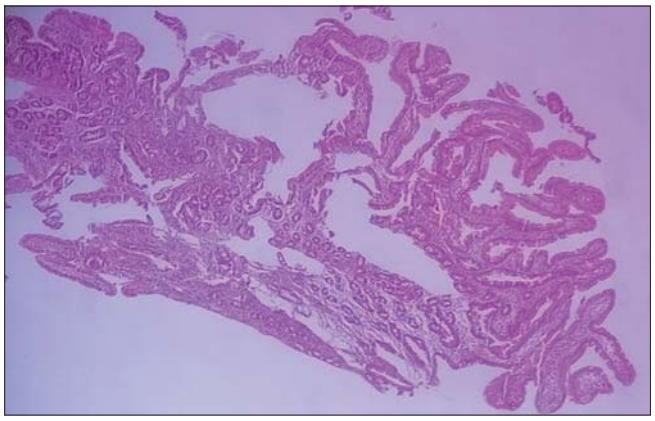

Figure 2: Duodenal biopsy.

How to cite this article: El Gaitibi FA, Khallaayoune M, Palamino H, Meziane M, Benzekri L, Ismaili N, Hassam B, Senouci K. Sprue-like disease possibly related to a single dose of methotrexate. Our Dermatol Online. 2022;13(4):465-466.

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The appearance of a sprue-like disease after a single dose of methotrexate is exceptional but possible, even in combination with folic acid supplements. The interest of a duodenal biopsy in the first days of clinical suspicion is to reduce morbidity.

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

Case Letter

Oral involvement in lupus erythematosus: A report of three cases

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Sir,

Lupus erythematosus (LE) is an autoimmune disease that may rarely affect the oral mucosa. This mucosal damage may be mistaken for lichen planus. Herein, we report three cases of oral lupus.

Observation 1: A 41-year-old female, with a seven-year history of systemic LE (SLE) treated with hydroxychloroquine, presented for recent food discomfort. An examination of the oral mucosa found an erythematous plaque on the palate (Fig. 1) and whitish macules on the cheek mucosa. A palatal biopsy was in favor of lupus.

Observation 2: A 47-year-old female presented with a clinical picture of SLE, with diffuse lichenoid ulcerations of the oral cavity (Figs. 2a and 2b). The workup confirmed SLE with severe renal impairment requiring treatment with oral methylprednisolone combined with cyclophosphamide boluses. Oral involvement improved markedly.

Observation 3: A ten-year-old child presented with photosensitivity. An examination found erythematous plaques on the cheekbones and nose and atrophic hypochromic macules with a scaly surface on the forearms. A skin biopsy concluded the diagnosis of subacute lupus (SAL). Direct immunofluorescence was negative. Four months later, at follow-up, erythematous macules were noted on the palate and on the inside of the lips with angular stomatitis (Figs. 3a and 3b). A mucosal biopsy was refused by the patient.

Oral involvement in LE is rare. In a study by Menzies et al., 50% of patients with lupus showed positive oral findings [1]. This condition is associated with a worsened health-related oral quality of life [2]. During SLE, the involvement of the oral mucosa may manifest as erosions or atrophic lesions with whitish striations, which may mimic lichen planus.

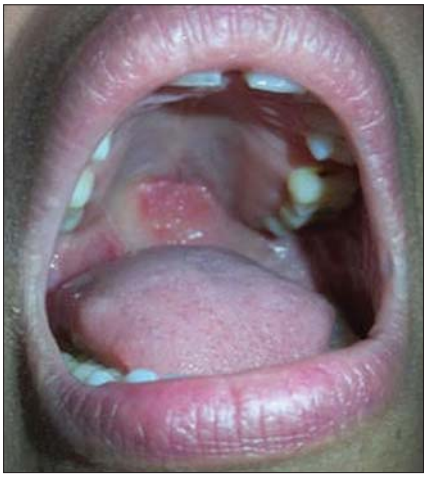

Figure 1: Erythematous patch of the palate (patient 1).

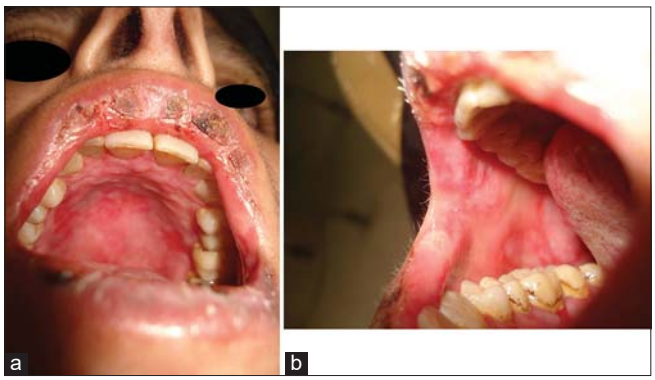

Figure 2: (a) Superficial ulcerations with a whitish, lichenoid background of the palate; erosive cheilitis (patient 2). (b) Similar lesions in the right cheek mucosa (patient 2).

How to cite this article: Rekik M, Sellami K, Baklouti M, Bahloul E, Turki H. Oral involvement in lupus erythematosus: A report of three cases. Our Dermatol Online. 2022;13(4):467-468.

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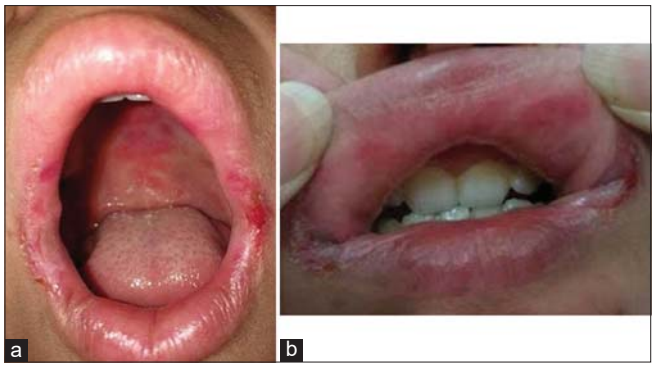

Figure 3: (a) Erythematous macules of the palate; bilateral perlèche (patient 3). (b) Erythematous macules on the inside of the lips (patient 3).

The lips, palate, cheek mucosa, and tongue could be affected [3]. Oral involvement may persist for years or occur only during relapses [4]. In SAL, the most frequent oral involvement is that of the palate with erythematous plaques, sometimes petechial or keratotic patches or erosions [5]. The labial and gingival mucous membranes could also be affected. Chronic lupus causes mucosal damage similar to that in SLE [3].

The specific involvement of the oral mucosa in LE is difficult to diagnose. It seems to be underdiagnosed. An examination of the oral cavity should be part of the clinical examination of any patient with lupus.

Consent

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

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

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Our Dermatology Online

Case Letter

Hidradenoma with an atypical localization mimicking lipoma

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Sir,

Nodular hidradenoma is a rare, benign adnexal tumor usually located in the head, neck, and extremities [1]. The difficulty of the diagnosis is due to the non-specificity of the clinical and histological presentation, often requiring a clinicopathological correlation [2]. Herein, we report a case of atypical abdominal hidradenoma mimicking lipoma.

Our patient was a 51-year-old Moroccan female operated for bowel obstruction and fibroma presenting with a slowly growing, painless, subcutaneous abdominal nodule persistent for the last two years. The nodule had gradually increased in size in a context of apyrexia and general state preservation.

A clinical examination was remarkable for a subcutaneous nodule (2.5 cm long axis) at the left iliac fossa, painless, indurated, and not fixed to the deep tissues, with slightly purplish skin (Fig. 1). The rest of the examination was featureless. In addition, dermoscopy was non-specific.

The initial diagnosis was lipoma or neurofibroma. However, the histology of an excisional biopsy revealed a lobulated, nodular tumor proliferation involving the reticular dermis, consisting of spindle-shaped round cells with clear acidophilic cytoplasm and rare mitotic activity. The proliferation associated with a fibrohyaline stroma (Fig. 2) was in favor of hidradenoma.

At two years of follow-up after surgery, no recurrence was observed.

Hidradenoma is a rare, sweat gland, adnexal tumor that arises from either eccrine or apocrine sweat glands [1]. It represents 1% of primary cutaneous tumors. Females between the age of twenty and fifty are at the biggest risk of developing these tumors [3]. Although no etiological factor has been determined, the presence of estrogen receptors in benign nodular hidradenomas and the predominance in females suggest a possible role of these hormones in the development of the tumors [1].

Clinically, it is a solitary nodule localized in the dermis or hypodermis, violaceous red or brown in color. They are of variable size and grow slowly (less than 5 mm up to 10 cm). Although most often asymptomatic, they may ulcerate, sometimes expressing a watery light or hematic discharge [1,3,4].

Studies have shown that hidradenomas are mainly located in the thorax [5,6], followed by the cervicofacial and, in some cases, plantar regions [2]. Sites of other localizations include the ankles [4], palms [6], and breasts [7]. However, to our knowledge and up to this day, no case of abdominal hidradenoma has been described.

The histopathological diagnosis is difficult because of the different clinical signs and the variable prevalence of various components, yet the clear-cell form is the most common. The histological features of hidradenoma include a cystic cavity lined with an epithelium with a hyalinized stroma and polygonal cells with clear cytoplasm [1,3,5].

Because of the potential for recurrences and the risk of transformation into hidradenocarcinoma, surgery

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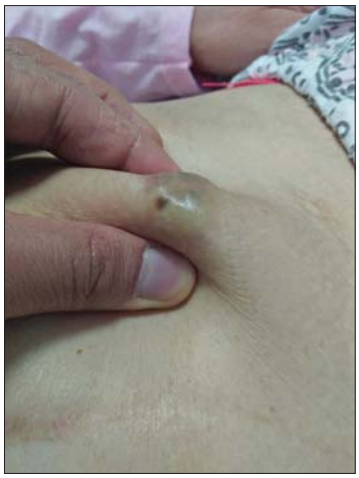

Figure 1: Subcutaneous nodule with bluish skin in the abdominal area.

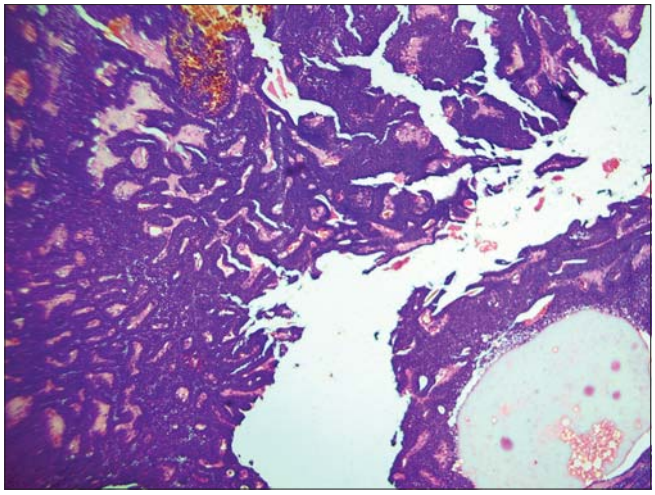

Figure 2: The tubes lined with a regular double cell base, the stroma with fibrohyaline, and the presence of eosinophilic substances inside the tubes (400×).

remains the preferred treatment with regular clinical surveillance [1,3].

In conclusion, hidradenoma is a rare adnexal tumor. It is characterized by non-specific clinical or histological morphology, with a varying localization, making a clinical and pathologic correlation essential for an accurate diagnosis. The recommended treatment is surgical excision because of the risk of malignant transformation with long-term follow-up.

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

Diltiazem-associated, photo-distributed hyperpigmentation in a patient with Sjögren's syndrome

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Sir,

Herein, we report a case of hyperpigmented macules on ultraviolet exposed areas during the intake of diltiazem hydrochloride (DTH) in a patient with Sjögren's syndrome.

A 63-year-old Japanese female with a history of Sjögren's syndrome and vasospastic angina presented to our hospital with brown, irregular macules on the neck, face, and both hands, which she first noticed one year earlier. The patient had a history of taking DTH for vasospastic angina for the previous fifteen years. A physical examination revealed pale brown macules and plaques irregularly scattered around the corners of the mouth, lower lip, and neck (Figs. 1a and 1b). In addition, there were numerous erythematous papules on the dorsal side of both hands. The oral mucosal membrane, scalp, and nails were not involved. A biopsy specimen taken from the dorsal side of a hand revealed individual cell keratinization in the epidermis, intercellular edema, liquefaction degeneration of the basal layer, and band-like lymphocyte infiltrate with melanophages in the superficial dermis (Fig. 2a). Immunohistochemistry revealed the infiltration of CD3+, CD4+, CD8+, and HLA-DR+ lymphocytes in the superficial dermis (Figs. 2b and 2c). Routine laboratory examinations of the blood cell count, serum, and urine showed no abnormalities. Other tests showed positive antinuclear antibody (1:80, nucleolar) and anti-SS-A antibody (240 U/mL; normal: < 9.9), whereas hepatitis C virus antibody, rheumatoid factor, anti-CCP antibody, and anti-SS-B antibody were negative. DTH was switched to another medicine, and ascorbic acid, calcium pantothenate, and topical steroids were initiated. In addition, we advised the patient to avoid sun exposure. Although no improvement was observed in the rash in the first four months, it disappeared at follow-up several years later (Figs. 3a and 3b).

Diltiazem-associated, photo-distributed hyperpigmentation is an uncommon, drug-induced lichenoid eruption. The clinical feature is slate-gray, reticulated hyperpigmentation on sun-exposed areas, and the histopathologic feature is lichenoid dermatitis with prominent pigmentary incontinence [1]. There have been nineteen reported cases, including our case, of diltiazem-associated, photo-distributed hyperpigmentation in the past. The period between the initiation of the drug and the onset has ranged from 1.5 months to 12.5 years; thus, many of the cases developed cutaneous lesions after taking the drug for a long time. The distribution of the skin rash was on the face in all cases, on the neck in thirteen cases, on the forearms in five cases, on the chest in three cases, and on the hands in two cases. Among these cases, eleven were black, three were Hispanic, four were Asian, and one was white [1-3]. In addition, only four cases were Japanese, suggesting the racial differences and the rarity of Japanese cases. Oiso et al. suggested that diltiazem-associated, photo-distributed hyperpigmentation is caused by impaired melanogenesis and aberrant transfer of immature melanosomes from melanocytes to keratinocytes [2]. In the present case, the patient had been taking

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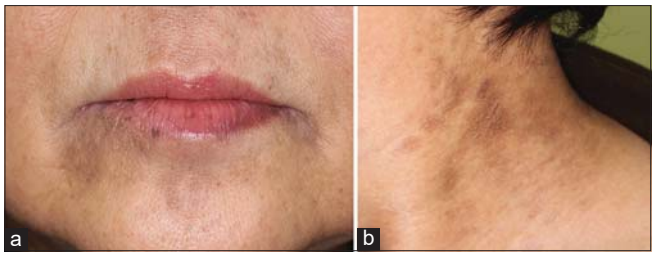

Figure 1: (a) Pale brown spots irregularly scattered on the corners of the mouth and lower lip, (b) as well as the neck.

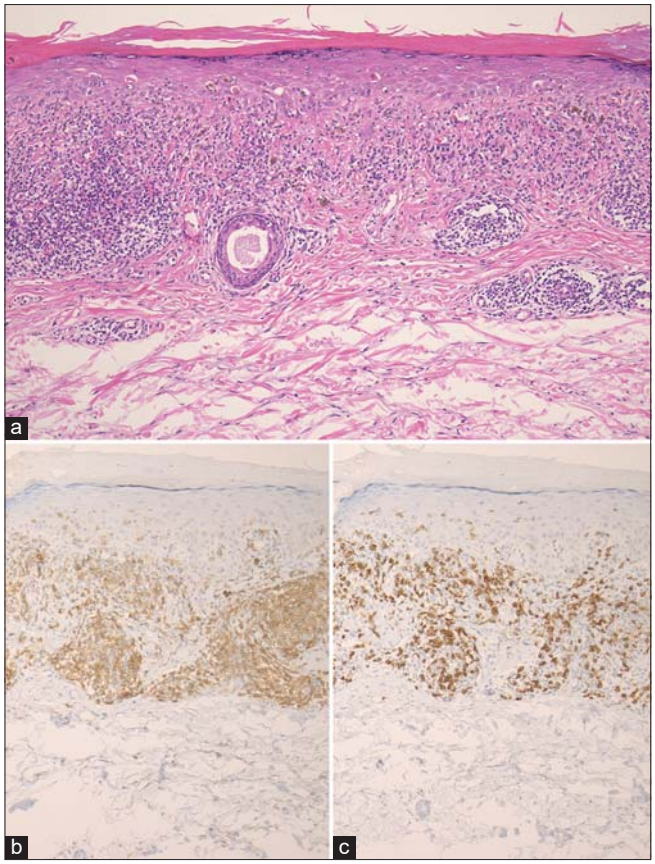

Figure 2: (a) Findings from the skin biopsy were band-like lymphocyte infiltrate with melanophages in the superficial dermis. (H&E, 100×). Immunohistochemistry revealing the infiltration of (b) CD4+ and (c) CD8+ lymphocytes in the superficial dermis.

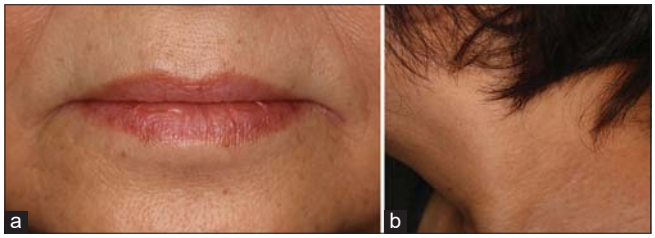

Figure 3: (a and b) The patient's eruption disappeared at follow-up.

DTH for fifteen years until the appearance of the rash, which disappeared after DTH was stopped and replaced by another medication. Unfortunately, neither patch/photopatch tests nor provocation tests were performed.

It is important to differentiate diltiazem-associated, photo-distributed hyperpigmentation from actinic lichen planus (ALP). ALP affects sun-exposed areas of the skin, and the histopathological examination reveals typical features of LP [4]. The clinical and histological findings of ALP and diltiazem-associated, photo-distributed hyperpigmentation are difficult to differentiate because of their similarities. We initially considered ALP, yet finally the diagnosis of diltiazem-associated, photo-distributed hyperpigmentation was reached due to the history of oral administration of DTH. To date, there have been no reports of Sjögren's syndrome associated with DTH-related diseases. However, Sjögren's syndrome is frequently associated with drug allergies [5], which may have contributed to the development of the skin rash in our case.

Consent

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

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

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

Our Dermatology Online

Case Letter

Pseudoepitheliomatous, keratotic and micaceous balanitis: A case report

Hasna Kerrouch, Hicham Titou, Meryem Khalidi, Rachid Frikh, Naoufal Hjira, Mohammed Boui

Dermatology venerology Department, Military Hospital Instruction Mohammed V, University Mohammed V, Rabat, Morocco

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Sir,

Pseudoepitheliomatous, keratotic, and micaceous balanitis (PKMB) is an uncommon premalignant and rare condition occurring over the glans in older men who undergo circumcision late in life [1].

It was first described in 1961 by Lortat-Jacob and Civatte, who described it as locally advancing thick hyperkeratotic plaque on the glans penis [2].

It was previously thought a benign condition, but is now believed to be premalignant [3].

Herein, We report a patient with PKMB who, having declined definitive surgery was managed with cryotherapy and lifelong followup.

A 52 year old circumcised male patient presented at the dermatology departement with a 1 year history of gradually enlarging thick scaly plaque on the glans penis. There was no history of itching, or difficulty in urination. He was an ex-smoker.

Patient was non diabetic and there was no history suggestive of sexually transmitted infections. There was no history of bleeding either spontaneously or following minor trauma. He was not taking any medication. He was treated with antiseptic applications and herbal medicines on various occasions.

Examination revealed a thick scaly plaque on the glans penis measuring about 2 cm by 2 cm (Fig. 1). The plaque was not tender or itchy, and was not obstructing the urethral meatus. The rest of the genitalia were normal.

There were no other significant skin lesions or palpable inguinal lymphadenopathy. Systemic examination was normal.

The initial differential diagnoses included PKMB, hypertrophic lichen sclerosus (LSc), genital warts, keratoacanthoma, penile intraepithelial neoplasia (PeIN), verrucous carcinoma and frank squamous cell carcinoma (SCC).

Blood counts and blood glucose were within normal limits. Serological tests for human immunodeficiency virus, hepatitis B and syphilis were negative.

Based on these findings, biopsy of the lesion was performed under local anesthesia. Histopathology of the lesion revealed epidermal hyperkeratosis, parakeratosis, acanthosis, and papillomatosis with perivascular mononuclear cell infiltrate in the dermis (Fig. 2). There was no evidence of malignancy or cellular atypia in histopathology.

Based on these clinical and histopathological findings a diagnosis of PKMB was made.

The patient declined definitive surgery and was started on cryotherapy. He had four sessions at monthly intervals to the thicker areas. There was a slight reduction in size of the plaque. He is being regularly followedup.

PKMB is a rare disease that typically occurs on the glans penis in older men [1]. Most patients are over the age of 60 and frequently have been circumcised for phimosis in adult life [1].

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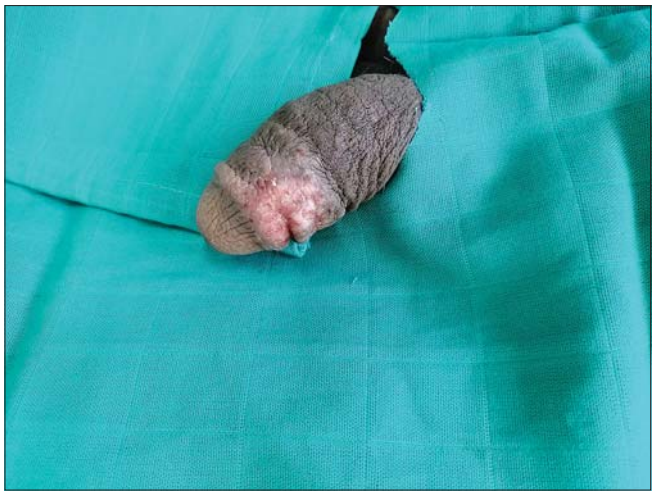

Figure 1: A Thick scaly plaque on the glans penis.

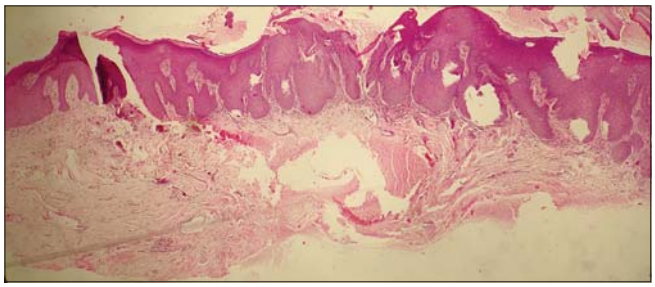

Figure 2: Epidermal hyperkeratosis, parakeratosis, acanthosis, and papillomatosis with perivascular mononuclear cell infiltrate in the dermis.

The differential diagnosis includes squamous cell carcinoma (SCC), verrucous carcinoma, keratoacanthoma, giant condyloma, penile horn, and erythroplasia of Queyrat [4].

Histopathological examination demonstrates hyperkeratosis, parakeratosis, acanthosis, elongated rete ridges, and mild lower epidermal dysplasia with a nonspecific dermal inflammatory infiltrate of eosinophils and lymphocytes [5].

Krunic et al., theorized that PKMB evolves into four stages; (a) initial plaque stage, (b) late tumor stage, (c) verrucous carcinoma, and (d) transformation to SCC and invasion [6].

Treatment is based on the stage of the lesion. The initial plaque stage can be treated with topical therapy, but advanced stages require a more aggressive approach [7]. Other treatment can be proposed such as x-ray irradiation, shave biopsy plus electrocoagulation, and carbon dioxide laser therapy [6].

Pseudoepitheliomatous, keratotic, and micaceous balanitis is a rare condition and has a characteristic appearance. Long term follow-up is needed for early detection of malignant transformation.

Consent

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

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On behalf of our **Scientex family** and **Conference committee**, we are happy to invite all our professional scholars, researchers, doctors and beloved students to be a part of the **"International Conference on Dermatology and Cosmetology"** on **May 18-19, 2023** at **Tokyo, Japan.**

The **Dermatology 2023** consists of several sessions to present researches in the category of keynote, plenary, poster, exhibitor, workshop, video presentation, e-poster and YRF.

The gathering will be oriented on the theme **"Investigate skin care issues and new technologies for better treatment".**

It is a Global platform for business delegates, B2B meetings, poster presentations, workshops, symposia, networking and more. It will offer a platform wherein you can ensure enormous exposure and networking by exhibiting products and services. Grab the opportunities and share your innovative ideas, new technologies and recent researches.

With the great support of our conference committee members and we are expecting huge response and support from the **Dermatologist,** Aesthetic and Ageing, Medicine Physicians, Trichologists and Students, Dermatology Associations and Societies, Journal Publishing Groups, Healthcare Industries, Cosmetics Companies and Clinics etc. Young Researchers, Students, Delegates, Directors and other Skin Care companies to have your gracious presence at our Dermatology and to make this congress a great successful event of the year 2023.

This Conference will be a **Hybrid event** (Physical conference as well as Virtual conference) As some attendees may not be able to fly due to the pandemic or its economic impacts.

In Japan, dermatological care is likely to receive special attention. A nationwide study was carried out by the Japanese Dermatological Association, and statistics on 67,448 cases that took part was analysed.

Tokyo, Japan is the excellent place to discuss skin care advancements in dermatology and cosmetology, so join us as we experience this stunning city.

With Thanks
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