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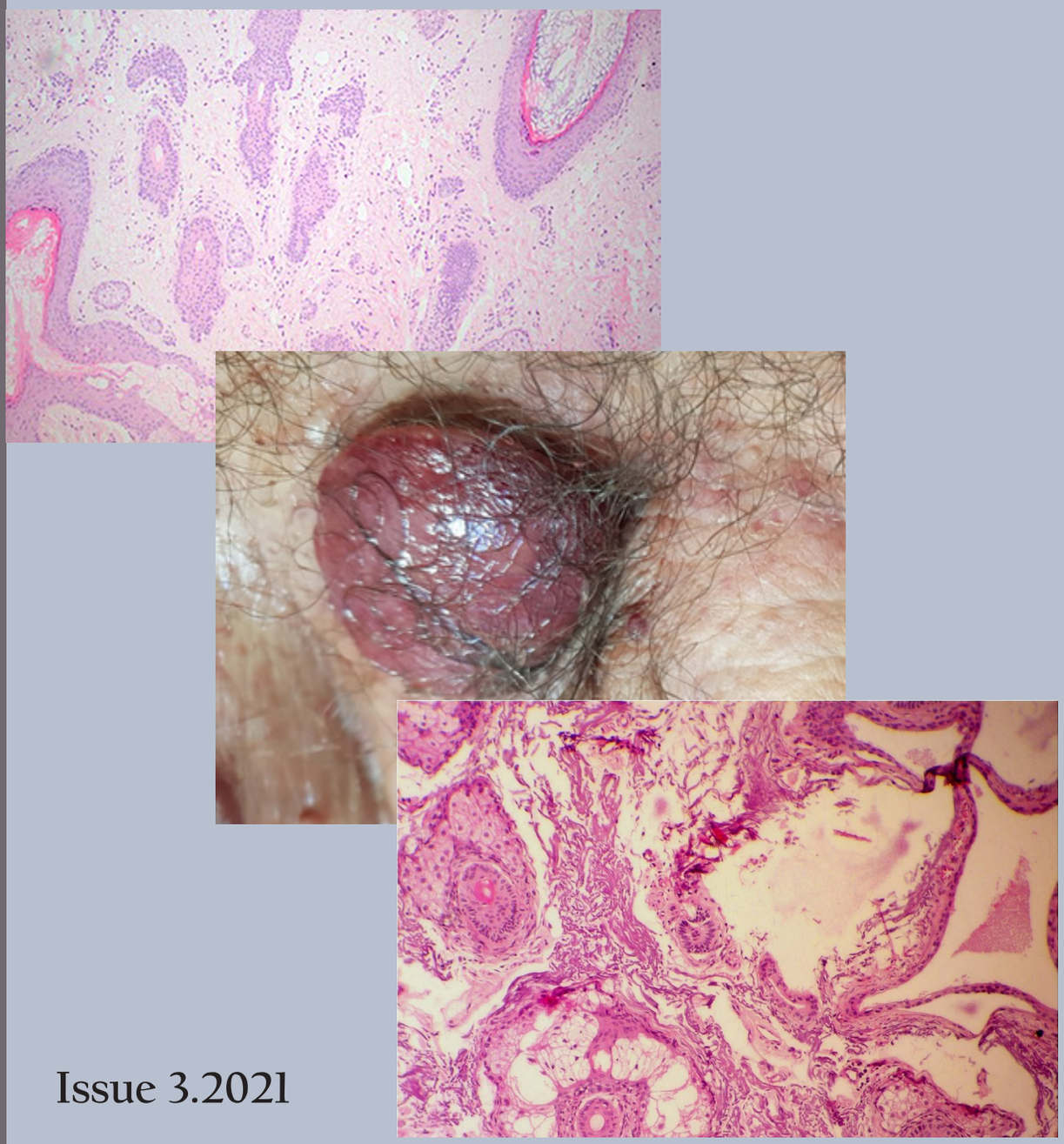

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Editorial Board

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Original Article

Heat dermabrasion with needle diathermy combined with 35% TCA peeling as an innovative therapy for acne scarring in patients with a dark complexion

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ABSTRACT

Background: Numerous techniques have been introduced to correct acne scarring, such as acid and laser peeling and mechanical and CO_2 dermabrasion. **Objective:** The aim was to find a new, simple, and cheap technique for improving and correcting acne scarring. **Patients and methods:** This interventional therapeutic study started in 2013 and lasted until 2020. A total of 250 patients with acne scarring were included, with the age ranging from 20 to 45 years. Most scar severity ranged from moderate to severe. The common types of scars were boxcar, icepick, and mixed. After local xylocaine anesthesia, direct heated needle diathermy was applied to the whole skin that included the scars and two passing were done superficial and deep, followed by a TCA peel. These patients were given topical antiseptic washing agents with oral antibiotics and 10 mg prednisolone once a day to be seen again after two weeks. Scoring was done to assess the reduction rate in the scars during follow-up periods. **Results:** Reduction rate scores after four months were as follows: a moderate score in 10 (4%) patients, a marked score in 140 (56%) patients, and an excellent score in 100 (40%) patients. No important complications were observed apart from temporary hyperpigmentation. Patients with active acne lesions also had a full remission following the dermabrasion. Full satisfaction was expressed by 225 (90%) patients, while partial by 25 (10%). **Conclusion:** This simple, easy, clean, and cheap innovative technique for dermabrasion was conducted on an outpatient basis with two-week downtime, showing marked (56%) to excellent (40%) reduction rates in acne scars within one session.

Key words: Heat dermabrasion; Diathermy; TCA peeling; Acne scarring

INTRODUCTION

Acne is a common chronic inflammatory skin disease experienced by most adolescents and young adults with a prevalence of over 90% among adolescents [1]. The pathogenesis of acne lesion formation and scarring involves the interplay of a variety of factors, including follicular hyperkeratinization, excess sebum production, inflammation mediated by *Propionibacterium acnes*, and other normal skin flora and immunological reactions [2].

Acne Scars

Acne lesions may result in permanent scarring with a marked impact on the quality of life. Scars affect a high percentage of patients with acne vulgaris. Genetic factors, disease severity, and delay in treatment are the important factors influencing scar formation [3,4].

Clinical Classification

Acne scars are classified into three basic types according to the depth, width, and three-dimensional structure [5].

1. Icepick scars: narrow (less than 2 mm in diameter), deep, sharply marginated, and depressed tracks extending into the dermis or subcutaneous tissue.
2. Boxcar scars: oval to round depressions with sharply demarcated vertical borders; wider at the surface than icepick scars; may be shallow (0.1–0.5 mm) or

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deep (≥ 0.5 mm), with its diameter varying from 1.5 to 4.0 mm.
3. **Rolling scars:** occur from dermal tethering of otherwise relatively normal-appearing skin; usually wider than 4 to 5 mm in diameter.

Other clinical entities included in this classification are hypertrophic scars, keloidal scars, and sinus tracts.

Treatment of Acne Scars

The treatment of acne scars may be classified into topical, procedural, surgical, and laser.

Topical Agents for Acne Scars

1. Topical retinoids: Topical retinoids, including tretinoin, tazarotene, and adapalene, work in several ways of anti-inflammatory action by decreasing the potential for the development of acne scars [6].
2. Topical antimicrobial agents: These agents produce anti-inflammatory action through decreasing populations of *Propionibacterium acnes*. Benzoyl peroxide also exhibits moderate comedolytic action [7].
3. Topical corticosteroids: Intralesional steroid injections treating hypertrophic and keloidal acne scars are well established [4].

Procedural Methods for Acne Scars

1. Peeling

The peeling methods for the treatment of acne scars include superficial peeling, medium-depth peeling, and deep peeling.

Superficial peels include salicylic acid (25% to 30%), glycolic acid (70%), pyruvic acid (40% and/or 50% to 60%), trichloroacetic acid (TCA) (20% to 30%), and the combination of salicylic acid or Jessner's peel with TCA. Superficial peels are used to enhance destruction limiting it to the epidermis and upper dermal layers [8].

TCA is the most common chemical substance used as a medium-depth peel. A 35% concentration of TCA peels the skin down to the papillary dermis [8]. The mechanism of action of the TCA peel is not clear but the following mechanisms may be coming into play: decreasing the size of sebaceous glands involved in acne pathogenesis, altering the microflora of the skin by reducing the number of bacteria, mainly *Propionibacterium acnes* and others that have a role in the pathogenesis of acne vulgaris, and revising the immunological reaction correlated with the acne formation and scarring [9].

Sharquie et al. have used TCA peel 35% and 88 % lactic acid peel effectively in the treatment of active acne vulgaris with or without scarring without acne therapy [10-12].

2. Dermabrasion

Dermabrasion is a skin-resurfacing technique that surgically abrades or planes the epidermis and the upper part of the dermis with an abrasive surface. Dermabrasion completely removes the epidermis and reaches the level of the papillary or reticular dermis, enhancing the remodeling of the skin's structural proteins [13].

The growing number of applications of dermabrasion have been accompanied by the development of the procedure from the utilization of sandpaper in the mid-twentieth century to electrically powered tools with wire-brush tips or diamond fraises of varying shapes, sizes, and textures. The technique has culminated in its application to a variety of lesions, including facial scars secondary to acne, trauma, and surgery [14,15].

It may also be employed to effectively manage surgical or traumatic scars, irregular scarring from skin grafts, photodamage, some benign tumors, rhinophyma, perioral rhytides, and actinic ketosis [16]. Dermabrasion has been used to manage superficial malignancies such as superficial basal cell carcinoma and squamous cell carcinoma *in situ* [17].

A novel and safe technique involving heat dermabrasion accompanied by needle diathermy was introduced by Sharquie for the treatment of different types of acne scars and nose volume plastic surgery for a bulky nose under local anesthesia within one session with minimal or no adverse effects [18-23].

3. Microdermabrasion

This is a type of mechanical exfoliation or micro-resurfacing procedure that uses a mechanical medium for exfoliation along with adjustable suction, removing the outermost layer of dead skin cells from the epidermis [24,25].

Laser for Acne Scars

Laser resurfacing includes devices employing ablative, non-ablative, and fractional ablative technologies. The three approaches differ widely in the way of inducing thermal damage, varying degrees of efficacy, downtime, and adverse effect profiles. The fractional laser technology, introduced by Manstein et al. in 2004, represents a major advantage over the older, conventional ablative methods (CO_2 and Er:YAG lasers) [26]. Nonetheless, ablative lasers had the advantage of their predictability in the depth of tissue ablation and thermal denaturation [27].

Laser and Light for Acne Scars

The following are used in the treatment of acne scars [28,29].

1. CO_2 laser: 10,600 nm, ablative and fractional CO_2.
2. Er:YAG: 2940 nm, ablative and fractional Er:YAG.
3. Er:Glass: 1540/1550 nm, non-ablative and fractional.
4. Pulsed-dye laser: 585 nm for hypertrophic scars and keloids.
5. IPL: for erythematous and hyperpigmented macular scars.
6. Nd:YAG: 1064 nm for mild scarring.
7. Diode laser: 1450 nm for mild scarring.

The aim of the present study is to find a new simple and effective technique for dermabrasion with direct diathermy heat combined with 35% TCA peeling.

PATIENTS AND METHODS

This clinical, interventional, therapeutic study took place from January 2013 through July 2020 and was conducted by one author (KS).

Two hundred fifty patients with acne scarring were enrolled in the study, 143 (57.2%) females and 107 (42.8%) males. Their age ranged from 20 to 45 years with a mean ± SD of 26 ± 5.101 years. Twenty-five (10%) patients had associated active acne lesions in addition to acne scarring.

Sharquie's scoring [9,30,31] (Table 1) was used to grade the severity of the acne scars. These were divided into mild, moderate, and severe that involved most of the face, commonly the cheeks, sides of the face, nose, and forehead. No treatment for active acne lesions was administered. The common types of scars were boxcar, icepick, and mixed; five (2%) patients had undulating rolling scars.

The study followed the principles of the Declaration of Helsinki and formal written consent was taken from each patient before starting the therapy and after explaining in full detail the nature of the disease, its course, the method of its treatment, the complications, the follow-up period, the prognosis, and the need for before-and-after photos with the twelve-megapixel camera of a Samsung Galaxy Note 9 smartphone at the same place and distance and in the same illumination. Statistical analysis was done with the chi-square test and *t*-test.

Sharquie's scoring [11,12] was used to evaluate the reduction rate of acne scars (Table 2).

Patient satisfaction from the response to treatment was assessed as follows:

1. full satisfaction,
2. partial satisfaction,
3. no satisfaction.

All patients were of Fitzpatrick's skin types III and IV.

The exclusion criteria were the coexistence of pregnancy and lactation, the use of any topical or systemic treatments in the previous one month, any other dermatoses involving the face, and an allergy to a medication, as well as a history of recurrent herpes simplex infection, diseases such as diabetes mellitus, and epilepsy, drugs interfering with the clotting system, immune-compromised patients, and unreliable patients.

A solution of 35% TCA consisting of 35 g (United States Pharmacopeia, USP, crystals) in 100 ml of 88%

Table 1: Sharquie's scoring to assess the scarring in acne vulgaris

Parameter		Score			
		1	2	3	4
1	No. of scars	≤ 10	11–20	21–30	> 30
2	Total area of scars	≤ 1/4	> ¼–½	> ½–¾	> ¾
3	Type of scars	Flat	Depressed	Hypertrophic	Keloid
4	Color of scars	Skin-colored	Erythematous or hypopigmented	Hyperpigmented	Bluish or grayish
5	Psychological effects	None or mild discomfort	Mild dysmorphophobia	Moderate dysmorphophobia	Severe dysmorphophobia or social withdrawal

Table 2: Sharquie's scoring to assess the reduction rate of acne scarring

Parameter	Reduction rate (%)	Score
No change	0	0
Mild reduction	1–25	I
Moderate reduction	> 25–50	II
Marked reduction	> 50–75	III
Excellent reduction	> 75–100	IV

Table 3: Reduction rates of acne scarring according to Sharquie's scoring system

Reduction rate	No. of patients	Percentage (%)	*P value
Moderate	10	4	*0.000001
Marked	140	56	
Excellent	100	40	
Total	250	100	

lactic acid was prepared and kept in amber glass flacons to be available for use.

The patients were prepared by cleansing and degreasing the whole face with 70% alcohol and waited several minutes for the alcohol to dry. The face was then wiped with an impregnated gauze with normal saline several times in two directions for further cleaning and sterilization. After local xylocaine anesthesia, direct heated needle diathermy was applied to the whole skin that included the scars and two passing were done superficial and deep until a smooth erythematous surface was reached, followed by two TCA coatings applied until uniform frosting. Immediately, frozen bag compresses were applied. The patients were told that a stinging sensation will peak for two to three minutes and vanish. The patients were given topical antiseptic washing agents with oral antibiotics and 10 mg prednisolone once a day to be seen again after two weeks. Then, the patients were given mild topical corticosteroid cream twice a day combined with oral propranolol 10 mg twice a day for one month to minimize post-inflammatory erythema. The patients were only advised to avoid sun exposure with no need to use sunblock and to be seen again for a follow-up to report on scar reduction, side effects, and relapses.

Follow-ups were scheduled at two weeks, one month, two months, four months, and six months after the interventional therapy.

RESULTS

The severity of the scars was as follows: mild in 15 (6%) patients, moderate in 50 (20%), and severe in 185 (74%).

Reduction rate scores are shown in Table 3. No important complications were observed apart from temporary hyperpigmentation that was noticed in several patients who had gone overtime. Otherwise, there was more hypopigmentation when compared with the non-dermabraded skin. The patients with active acne lesions also had a full remission following the dermabrasion, accompanied by scar reduction without anti-acne therapy. There was not much difference in the response to therapy in the different types of acne scars.

During the follow-up period, the following were observed:

1. Two weeks: erythema still present, scar reduction.
2. One month: the same scar reduction as at two weeks but with the erythema almost gone and with five (2%) patients showing hyperpigmentation.
3. Two months: the same scar reduction as before and no more pigmentation.
4. Four months: no change in scar reduction but improvements in skin texture, with the post-inflammatory hyperpigmentation vanished and with hypopigmentation in many patients.
5. Six months: no change in scar reduction but with a further improvement in skin texture and a slight improvement in hypopigmentation.

Sixty patients were also seen after 6 to 12 months with continuous improvement and no relapse. Many patients were also seen accidentally after years and showed a marked improvement and no relapse or pigmentary complications.

Figs. 1 – 6 show photos of the patients before, at the end of the session, and during the follow-up period.

Full satisfaction was expressed by 225 (90%) patients, while 25 (10%) expressed partial satisfaction. The downtime was around two weeks.

DISCUSSION

Acne is a common chronic inflammatory skin disease experienced by most adolescents and young adults with a prevalence of over 90% among adolescents [1]. The pathogenesis of acne lesion formation and scarring involves the interplay of a variety of factors, including follicular hyperkeratinization, excess sebum production, inflammation mediated by *Propionibacterium acnes*,

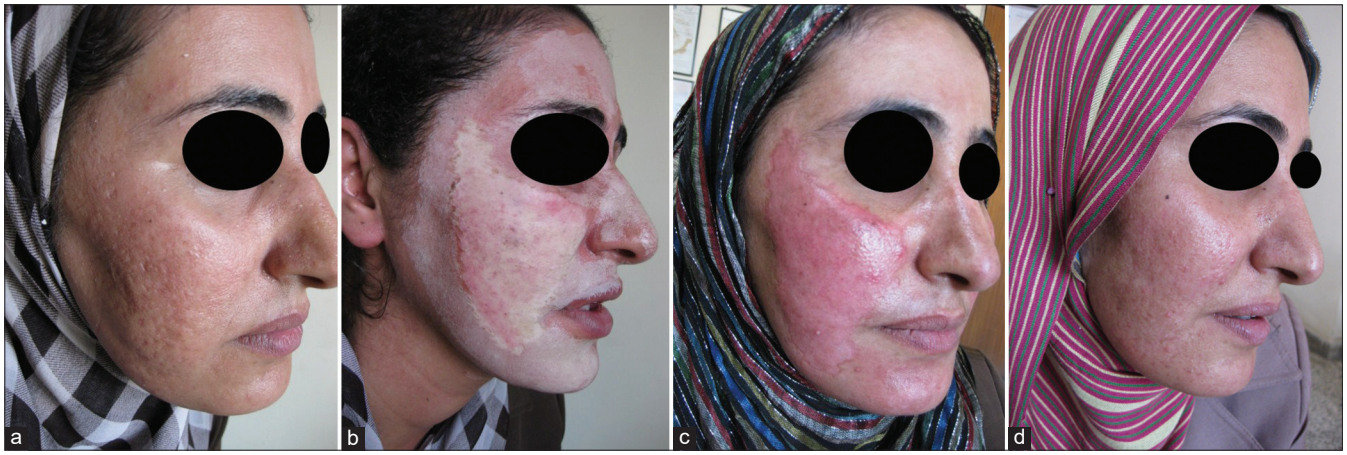

Figure 1: Twenty-nine-year-old female with boxcar acne scarring (a) before treatment, (b) at the end of the session, (c) after two weeks, and (d) after four months.

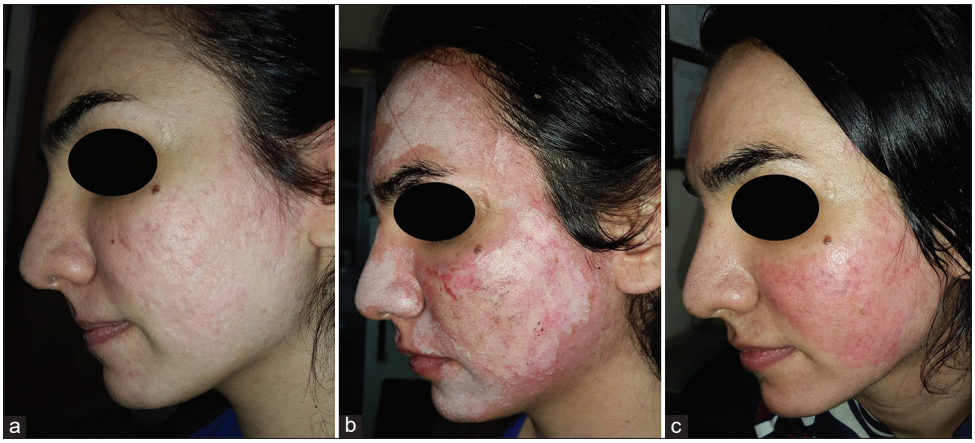

Figure 2: Twenty-two-year-old female with boxcar acne scarring (a) before treatment, (b) at the end of the session, and (c) after two weeks.

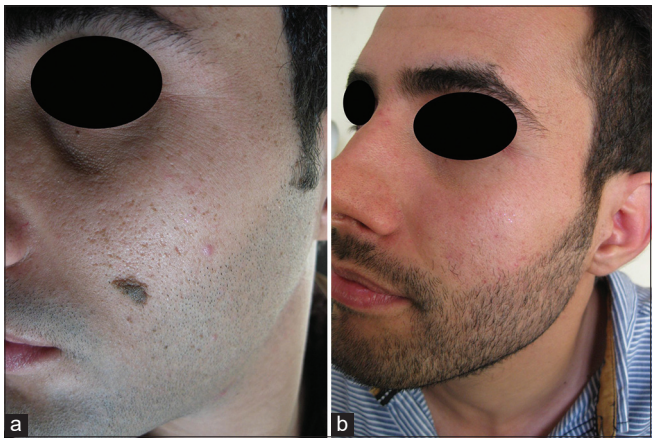

Figure 3: Twenty-one-year-old male with a combination of icepick and boxcar acne scarring (a) before treatment and (b) after twelve months.

and other normal skin flora and immunological reactions [2].

Inflammatory acne lesions may result in permanent scars, the severity of which may depend on the severity of the acne lesion and the delay in treating the acne. About 1% of people have had acne scars, although only 1 in 7 is considered to have "disfiguring scars" [32]. Severe scarring caused by acne is associated with substantial physical and psychological distress, particularly in adolescents [33].

Because acne vulgaris is a major health problem, in which scarring is the most common complication, early treatment is essential in order to prevent disfiguration. There exist numerous methods and techniques for treating and correcting acne scarring. The earliest and oldest technique is mechanical dermabrasion [14,15]. This technique may be effective but often needs general anesthesia. Also, this procedure is messy and bloody as using a brush causes blood contamination to the surroundings, even causing the transmission of infection from patients to the medical staff. Also, it is a costly procedure and may generate complications [34].

CO_2 and other lasers have also been used as methods of dermabrasion for acne scars. This is, however, a

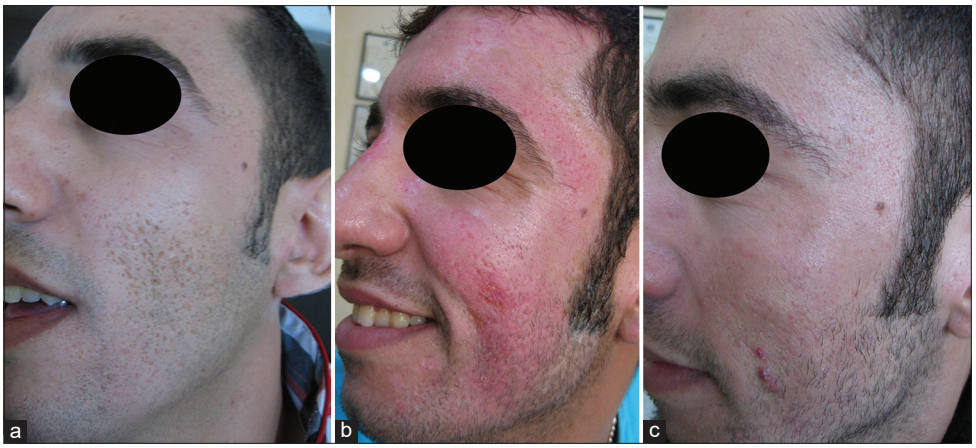

Figure 4: Twenty-five-year-old male with icepick acne scarring (a) before treatment, (b) after four weeks, and (c) after two years.

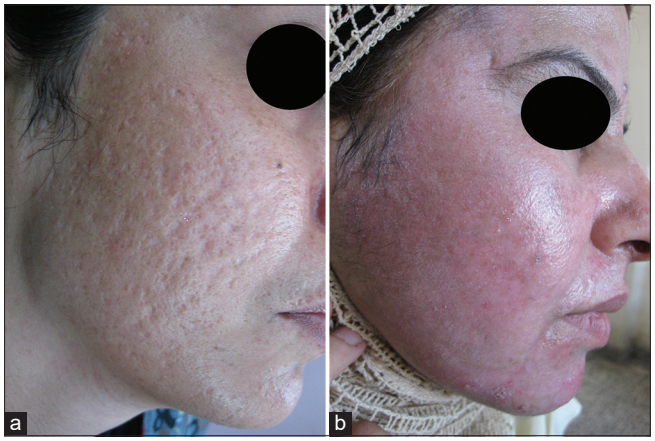

Figure 5: Thirty-three-year-old female with boxcar mixed up with icepick acne scarring (a) before treatment and (b) after two months.

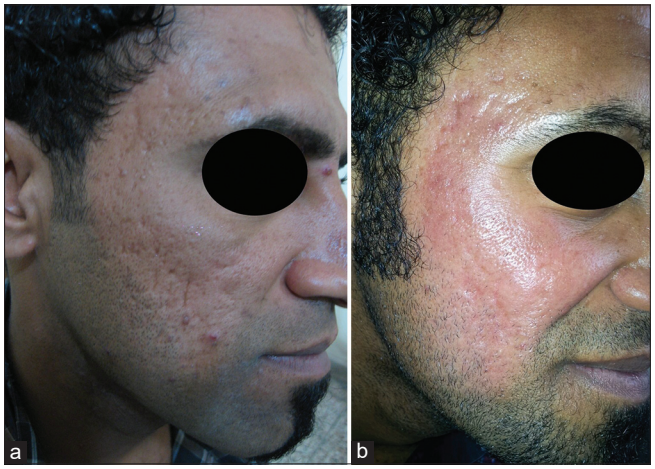

Figure 6: Twenty-seven-year-old male with a combination of boxcar and icepick acne scarring (a) before treatment and (b) after two months.

risky procedure, as lasers require protection for the doctor's and patient's eyes, are costly, require significant experience, and may require many sessions to achieve the final cosmetically acceptable outcome [26]. Deep peeling has also been used to correct acne scars, but although this is a simple and cheap procedure on an outpatient basis, it requires many sessions and is not as effective as mechanical or laser dermabrasion, hence it might be reserved for mild scarring [8].

The present work demonstrated a new innovative technique that involves heat dermabrasion with heated needle diathermy combined with 35% TCA peeling.

This is the largest study in the world, achieving marked (56%) to excellent (40%) results, and was done on an outpatient basis under local anesthesia with only one session was needed. It is effective for all types of acne scars, whether icepick, boxcar, or rolling, while, with other procedures, rolling scars are difficult to treat. In all other types of dermabrasion and peeling, the most important complication to be afraid of is long-standing hyperpigmentation [35]. Although, in the present work, there was no permanent hyperpigmentation, the patients usually experienced hypopigmentation of the dermabraded area; all our patients, however, had a dark complexion and were of Fitzpatrick's skin types III and IV [10-12].

In all techniques of dermabrasion, patients with active lesions of acne vulgaris should avoid this procedure, while 10% of the patients in our work had active acne vulgaris in addition to the scarring, and heat dermabrasion caused a long-term remission of the acne vulgaris in addition to the clearance of the scarring. This has recently been supported by Sharquie et al., who used 35% TCA and 88% lactic acid peeling in the treatment of active acne vulgaris, which induced a long-term remission without drug therapy for acne [11,12]. Some patients with active acne vulgaris express no wish to be treated because of the course of the therapy that was too long, the use of medications, the scarcity of

time to be spared for the treatment, or the fear of side effects or complications. In these situations, we may recommend other therapies, such as TCA or lactic acid peeling, laser, or even heat dermabrasion [11,12,22].

The mechanism of action of TCA and lactic acid peeling has not been well documented but is assumed to work by minimizing the size of sebaceous glands involved in acne pathogenesis, by changing the microflora of the skin, which involves reducing the size of the bacterial flora in the acne lesions, and by changing the immunological reactions involved in acne formation and scarring [9]. The same mechanism may also be used in heat dermabrasion with TCA peeling, as shown in the present work.

Propranolol was used in the present work to reduce post-inflammatory erythema and to decrease the probability of hemangioma formation, which might theoretically have occurred because heat dermabrasion may create thermal burns, and this concept was used in the treatment of patients with burn hemangioma [36].

CONCLUSION

This is an innovative technique for treating moderate-to-severe acne scars with the direct contact of a diathermy needle followed by TCA peeling, which gave marked (56%) and excellent (40%) results within only one session. It is an easy, clean, and cheap procedure that may be used on an outpatient basis and without significant complications such as hyperpigmentation. Also, it may be used in the treatment of active acne vulgaris, with acne scarring leading to a long-term remission without acne therapy.

Additionally, this method of dermabrasion may be recommended in the therapy of xeroderma pigmentosum of the face, facial acanthosis nigricans, adenoma sebaceum, and severe facial wrinkling.

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

Untoward effects on the skin by the use of personal protection equipment

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ABSTRACT

Background: COVID-19 (coronavirus disease 2019) is the global pandemic that emerged in Wuhan, China, and has rapidly spread throughout the world. Healthcare workers (HCWs) who care for patients suffering from COVID-19 are at greater risk of contracting the infection and, for this reason, PPE (personal protective equipment) is worn. As PPE covers the entire surface area of the body and is worn for long hours, HCWs are likely to suffer from untoward effects on the skin. **Methods:** To determine the occurrence of untoward effects on the skin from the use of PPE among HCWs, a questionnaire was prepared and circulated online among HCWs caring for COVID-19 patients. The questionnaire included questions regarding the grade and the duration of use of PPE and untoward effects on the skin. Univariate and multivariate analysis was employed to identify the potential factors for untoward effects on the skin from the use of PPE. **Results:** A total of 415 HCWs responded to the questionnaire. The survey found three types of untoward effects on the skin. Among all, 389 (93.7%) had mask-related effects on the skin, 318 (76.6%) had glove-related effects on the skin, and 89 (21.4%) had gown-related effects on the skin. There was a significant association between the gender, the occupation, the level of PPE, the duration of use of PPE, and the moisture received during the use of PPE and the untoward effects on the skin. **Conclusion:** Untoward effects on the skin from the use of PPE among HCWs are quite common Educating HCWs on these effects may help them to report early and receive proper care.

Key words: PPE (personal protective equipment); COVID-19 (coronavirus disease 2019); untoward skin effects

INTRODUCTION

COVID-19 (coronavirus disease 2019), which emerged in Wuhan, China, in December 2019, is caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). With no remedy to date, the virus has become a boundless pandemic, with 17 million cases and 600,000 mortalities across the world, with no differentiation between the poor and the rich [1]. SARS-CoV-2 is primarily transmitted through respiratory droplets (> 5–10 μm) and direct contact. Airborne transmission is possible during procedures and treatments that generate aerosols [2]. The fact that respiratory droplets and direct contact are the established routes of transmission of SARS-CoV-2 emphasizes the need for the use of appropriate PPE (personal protective equipment) by HCWs (healthcare workers) treating COVID-19 patients.

PPE is designed to provide protection against serious injuries or illnesses resulting from chemical, physical, mechanical, electrical, radiological, and other hazards [3]. PPE comprises equipment that protects the mouth, nose, eyes, ears, bare skin, and other vulnerable parts depending on one's working environment [4]. PPE includes items such as gloves, safety glasses and

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shoes, earplugs, hoods, respirators, coveralls, vests, and full-body suits [5]. Based on the degree of protection provided, PPE is classified into four categories. Level A comprises an encapsulated suit and a self-contained breathing apparatus that provides the highest level of protection available for both contact and inhaled threats. Level B comprises an encapsulating suit or junction seams sealed with a supplied air respirator or a self-contained breathing apparatus that provides a high level of protection adequate for unknown environmental entry and a supplied air ensemble with increased mobility and dexterity. Level C comprises a splash suit and an air-purifying respirator that provides significantly increased mobility and decreased physical stress with extended periods of time with no fit testing required for the hood. Level D comprises work clothes and standard precautions such as surgical masks, gloves, and splash protection, providing the lowest level of respiratory and skin protection [6].

The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend N95 masks for HCWs caring for patients suspected or confirmed to have highly transmissible respiratory infections. The N stands for NIOSH (National Institute for Occupational Safety and Health), and the 95 indicates filter efficiency. Thus, an N95 mask is 95% efficient at filtering particles 300 nm in size and larger [7]. An N95 mask is made from a fine mesh of synthetic polymer fibers, often a non-woven polypropylene fabric, produced by melt-blowing to form filtration layers against hazardous particles. Gloves for medical examination, which act as a barrier against possible transmission of infection, are made from latex or synthetic materials, such as nitrile or vinyl. Gowns used for isolation and protection are made from non-woven materials such as polypropylene, polyester, or polyethylene alone or in combination [8]. Because no single protective equipment is capable of protecting against all hazards, PPE should be used in conjunction with other protective methods, including exposure control procedures and equipment. The use of PPE causes significant discomfort and, thus, impairs the wearer's ability to perform work. Choosing well-fitting PPE based on the expected exposure provides the wearer with a comfortable environment to perform their work. However, the use of PPE may cause certain skin problems due to long-term sealing, friction, and pressure [4]. As reported by Foo et al. [9], the most common adverse reaction to an N95 mask is acne, followed by itch (caused by gloves) and rash (caused by gowns).

India reported its first COVID-19 case on January 30, 2020. Despite aggressive lockdown measures, confirmed cases continued to rise on a daily basis, reaching one million cases on July 17, 2020 [10]. In March 2020, some of our colleagues teleconsulted us for skin reactions after the use of PPE during the treatment of COVID-19 patients. For this reason, we began to suspect that the untoward effects on the skin from PPE were more common than expected and, thus, we decided to explore this issue in a study.

MATERIALS & METHODS

Study Design

A cross-sectional study was conducted from April to June 2020 at a tertiary care center in Bengaluru, a dedicated hospital for the treatment of COVID-19 cases.

Data Collection

A questionnaire was prepared to determine the untoward effects on the skin from the use of PPE among HCWs treating COVID-19 patients. The questionnaire was revised after reviewing articles and feedback from the medical and nursing staff. The questionnaire included demographic data (age, sex, occupation, place of work), information on the use of PPE (grade of PPE, duration of use of PPE, sweating during the use of PPE) and the untoward effects on the skin due to wearing masks, gloves, and gowns, as well as and the aftercare received. The questionnaire was distributed among HCWs as an online document by e-mail and social media such as WhatsApp. Participants who voluntarily filled the questionnaire and submitted it within a week were included in the study.

Statistical Analysis

Univariate analysis was performed first to identify the potential factors for the untoward effects on the skin from the use of PPE with a chi-squared test. A p value below 0.05 was considered significant and these variables were entered for multivariate analysis. All analysis was done with the SPSS software, version 20.0.

RESULTS

A total of 415 HCWs responded to our questionnaire. The mean age was 29.43 ± 3.8 years. 371 (89.4%) were

less than 35 years of age and 44 (10.6%) were 35 years of age or older.

191 (46%) were male and 224 (54%) were female. 314 (75.7%) were doctors and 101 (24.3%) were nursing staff. 77 (18.6%) were working in a screening OPD, 286 (68.9%) in a COVID ward, and 52 (12.5%) in both a screening OPD and a COVID ward. 399 (96.1%) and 16 (3.9%) wore level B and level C PPE, respectively. 33 (8%) wore PPE for 3 hours, 48 (11.5%) for 3–6 hours, and 334 (80.5%) for more than 6 hours a day. Two layers of gloves were worn by 132 (31.8%) and three layers of gloves were worn by 283 (68.2%). The frequency of handwashing during the day was more than ten times in 220 (53%) and less than or equal to ten times in 195 (47%).

The survey found three types of untoward effects on the skin. 389 (93.7%) had mask-related effects on the skin, 318 (76.6%) had glove-related effects on the skin, and 89 (21.4%) had gown-related effects on the skin (Table 1). 72.5% reported a pressure effect on the skin due to the use of a mask, 47.5% had vague itching on the face, 35.9% had dry skin, 26.7% had pigmentation on the nasal bridge, 26.5% had a flare of acne, and 10.6% had folliculitis. 1.2% reported herpes simplex on the nose and the perinasal area. Additionally, 5.8% reported having a runny nose, and 0.5% had a worsening of their asthma due to the regular and prolonged use of a mask.

Table 1: Prevalence of untoward effects on the skin after the use of PPE.

Type of ppe	Sign/symptom	Number of persons with sign/symptoms n (%)
1. Mask related effects [389 (93.7)]		
	Itch	197 (47.5)
	Dry Skin	149 (35.9)
	Redness	105 (25.3)
	Acne flare	110 (26.5)
	Folliculitis	44 (10.6)
	Herpes Simplex	05 (1.2)
	Pigmentation	111 (26.7)
	Peeling of skin	49 (11.8)
	Pressure Effect on skin	301 (72.5)
	Running Nose	24 (5.8)
	Worsening Asthma	02 (0.5)
	Other Symptoms	13 (3.1)
Gloves related effects [318 (76.6)]		
	Itch	244 (58.8)
	Dry Skin	198 (47.7)
	Redness	58 (14.0)
	Pressure Effects on skin	52 (12.5)
Gown related effects [89 (21.4)]		
	Itch	63 (15.2)
	Dry Skin	14 (3.4)
	Redness	10 (2.4)
	Pressure effects on skin	23 (5.5)

Glove-related effects on the hands were noted, such as itching in 58.8% of cases, dry skin in 47.7%, redness in 14%, and a pressure effect in 12.5%. Gown-related effects were noted on the trunk, axilla, and groin, such as itching in 15.2% of cases, dry skin in 3.4%, redness in 2.4%, and a pressure effect in 5.5%.

Table 2 shows the anatomical distribution of the untoward effects on the skin from the use of PPE, with the brunt on the hands 318 (76.6%), followed by the nose 291 (70%).

The data collected was subjected to univariate analysis, and a chi-squared test was employed to compare the categorical values (Table 3). There was a significant association between the gender, the occupation, the level of PPE, the duration of use of PPE, the moisture received during the use of PPE, and the untoward effects on the skin.

Characteristics with a p value less than 0.05 on univariate analysis were subjected to multivariate analysis with logistic regression (Table 4). Skin injuries were set as the dependent variable (0: absent; 1: present), and the single factors of a p value less than 0.05 (Table 3) were set as the independent variable.

An odds ratio (OR) above 1 suggested a positive association between the mask-related effects and the occupation, the moisture received during the use of PPE, the level of PPE, and the duration of use of PPE. Also, a positive association was seen between glove- and gown-related effects and the occupation, the moisture received during the use of PPE, and the level of PPE. In our study, 75.7% of participants were doctors and 24.3% were nursing staff, so the association between the occupation and the untoward effects needs to be further evaluated. The Hyperhidrosis Disease Severity Scale (HDSS) was employed to assess the severity of sweating. The mean score during the use of PPE was 1.95 while, otherwise, it was 1.19, with a significant p value of 0.001, which suggests that most HCWs tend

Table 2: Anatomical distribution of untoward effects on the skin.

Location	n (%)
Forehead	241 (58.1)
Nose	291 (70.0)
Cheeks	90 (21.6)
Ear	4 (0.96)
Hands	318 (76.6)
Trunk	26 (6.3)
Axilla	14 (3.4)
Groin	2 (0.48)

Table 3: Univariate analysis of untoward effects on the skin

Characteristics	Mask related skin effects n (%)	P	Gloves related skin effects n (%)	P	Gown related skin effects n (%)	P
Gender						
Male (191)	177(92.7)	0.408	141(73.8)	0.213	34(17.8)	0.095
Female(224)	212(94.6)		177(79.0)		55(24.6)	
Age						
<35 Years(371)	347(93.5)	0.619	288(77.6)	0.162	81(21.8)	0.577
≥35 Years(44)	042(95.5)		030(68.2)		08(18.2)	
Occupation						
Doctor(314)	296(94.3)	0.430	251(79.9)	0.005	79(25.2)	0.001
Nursing staff(101)	93(92.1)		67(66.3)		10(9.9)	
Level of PPE						
B(399)	376(94.2)	0.036	307(76.9)	0.448	86(21.6	0.789
C(16)	13(81.2)		11(68.8)		3(18.8)	
Duration of PPE use						
3 Hours(33)	31(93.9)	0.999	20(60.6)	0.065	8(24.2)	0.034
3 to 6 Hours(48)	45(93.8)		39(81.2)		17(35.4)	
6 Hours(334)	313(93.7)		259(77.5)		64(19.2)	
Soaky Wet during PPE use						
Yes(352)	336(95.5)	0.001	279(79.3)	0.003	82(23.3)	0.030
No(63)	53(84.1)		39(61.9)		7(11.1)	
Layers of gloves						
2(132)			105(79.5)	0.337		
3(282)			213(75.3)			
Frequency of hand wash per day						
>10 times (190)			173(78.6)	0.304		
≤10 times (225)			145(74.4)			

Table 4: Multivariate analysis of factors associated with untoward effects on the skin

Factors	Mask			Gloves			Gown		
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P
Gender	0.673	0.292-1.553	0.275	0.707	0.439-1.139	0.154	0.685	0.417-1.125	0.135
Occupation	1.664	0.393-7.036	0.489	1.932	0.969-3.855	0.062	3.134	1.259-7.803	0.014
Soaky wet	5.350	1.829-15.652	0.024	1.791	0.913-3.514	0.090	1.732	0.688-4.361	0.243
Level of PPE	1.901	0.444-8.130	0.386	1.076	0.326-3.552	0.905	1.042	0.258-4.201	0.954
Duration of use	1.029	0.205-5.164	0.972	0.350	0.159-0.773	0.009	0.991	0.411-2.390	0.985

to sweat profusely, contributing to the untoward effects on the skin.

As a method of aftercare for untoward effects on the skin, 346 (83.4%) used moisturizers, 93 (22.4%) used soothing lotions, 26 (6.3%) needed an antibiotic, either orally or topically, and 1 (0.2%) needed to dress the wound for a week.

Figures 1a – 1f show clinical pictures of untoward effects on the skin from the use of PPE observed in our study.

DISCUSSION

HCWs (healthcare workers) are at the frontline of treating COVID-19 patients, wearing PPE for long hours and, therefore, being susceptible to PPE-related untoward effects. In our study, the most prevalent untoward effect on the skin from the use of PPE were mask-related effects, followed by glove-related and gown-related. This predominance in mask-related effects might be due to the greater number of sebaceous glands and a moderate number of eccrine sweat glands on the face, which may trigger acne and increase sweating, respectively.

The pressure effect of the mask on the bridge of the nose—the most frequent untoward effect of a mask—is due to the anatomical structure of the face, in which the nose is the most protruding element. The forehead was the second most common site for untoward effects, such as acne and folliculitis, which were due to the distribution and occlusion of the pilosebaceous ducts and the pressure effect by goggles, face shields, or surgical caps pressing on the forehead. These were

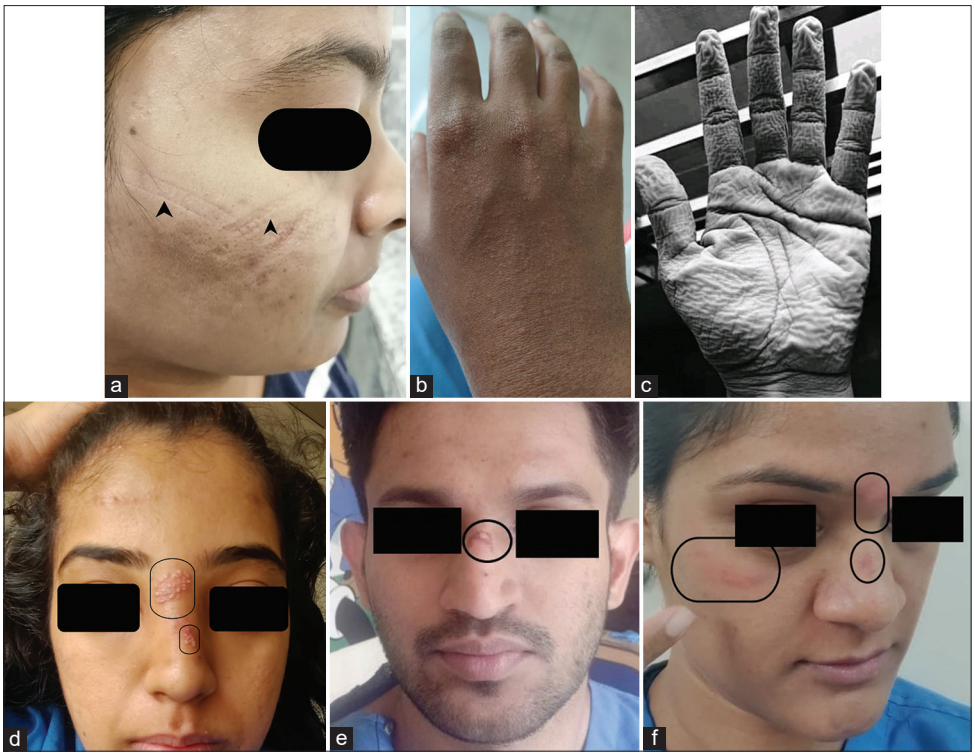

Fig 1: (a) Pressure effect from the mask. (b) Allergic contact dermatitis from the gloves. (c) Wrinkling of the skin due to excessive sweating. (d) Herpes simplex infection on the nose (black rectangle). (e) Postinflammatory hyper- and hypopigmentation secondary to the erosion on the bridge of the nose from the mask (black circle). (f) Erythema due to the pressure effect from the goggles (black circle and rectangle).

the contributing factors for the untoward effects on multiple parts of the face.

This was similar to the observation made by Jiang et al. [11] in a study among medical staff in China, noting that device-related pressure injuries were more common than moisture-associated effects. A similar observation was made by Foo et al. [9] and Lin et al. [12]. We found little pressure effect on the ear, as the type of N95 mask that was used had overhead straps, not ear straps. The herpes simplex cases may be attributed to the reactivation of the virus due to the stress and anxiety in treating COVID-19 patients. A homeostatic interaction model suggests that the hypothalamic–pituitary–adrenal axis, especially corticosteroids, is the primary driving force of stress-induced secondary immune deficiencies that impairs viral clearance and, hence, may predispose to the reactivation of the herpes virus [13].

Dry skin, itch, and redness were also reported frequently on the face, hand, and trunk, probably from the frequent handwashing and bathing and the use of soaps and sanitizers, as well as contact dermatitis from the components of the mask, such as the rubber straps or metal clips, the gloves, and the fabric of the gown. Additional factors responsible for untoward effects are heavy and airtight PPE that makes it difficult to volatilize perspiration, thus changing the microclimate of the skin and decreasing skin tolerance. Soaked skin due to sweat combined with pressure increases the friction coefficient between the PPE and skin, thus causing abrasions and peeling of the skin [14].

Hence, promoting education on the proper use of PPE and restricting the duration of wearing PPE to not more than six hours a day may, at the administrative level, help in reducing the untoward effects on the skin. At the personal level, HCWs should be encouraged to follow the standards of the use of gloves, hand hygiene, and skincare. In the case of severe dermatoses or sustained aggravation of existing dermatoses, a dermatological referral is recommended [12].

Limitations

The limitations of this study were subjective evaluation of skin changes (self-perceived skin changes) and a small sample size.

CONCLUSION

The study suggests that all HCWs should be educated on the possible skin effects from the use of PPE and on the protective measures available for reducing these

effects, such as prophylactic dressings and creams suitable for different parts of the body that would effectively keep the moisture balance and prevent fogging of the goggles.

According to the author's knowledge, this is one of the pioneer questionnaire-based studies conducted in India relating to untoward effects on the skin from the use of PPE among HCWs.

Ethical Approval

Ethical approval was obtained from the Institutional Ethics Committee.

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

Impact of prurigo nodularis on quality of life and psychiatric comorbidities among children and their parents in Yaoundé, Cameroon

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ABSTRACT

Background: Prurigo nodularis (PN) is a recurrent, itchy dermatosis in children secondary to arthropods bites. The objective of this study was to determine the impact of PN on the quality of life (QoL) of affected children and their parents and to investigate the presence of depression and anxiety. **Method:** We performed a cross-sectional study during the period from February through May 2017 at the dermatology departments of six hospitals in Yaoundé, Cameroon. Children suffering from PN and their parents were included. We collected sociodemographic data, assessed the QoL of the children and their parents (CDLQI, DLQI, FDLQI), and evaluated anxiety and depression among them (GAD-7 and PHQ-9). **Results:** A total of 112 children (median: 2 years; range: 5 months – 16 years), including 62 males and 50 females and their 112 parents (median age: 31 years; range: 20 – 65 years), were included in the study. As far as QoL was concerned, 29 children and 112 parents were selected. Most children (93.1%) and a large majority of the parents (99.1%) experienced negative impact on their QoL. We found no depression or anxiety among these two groups. **Conclusion:** Prurigo nodularis has a negative impact on QoL among affected children and their parents. However, we found no psychiatric comorbidities associated with this pathology in our study.

Key words: Prurigo nodularis; Quality of life; Parents; Children; Cameroon

INTRODUCTION

Prurigo nodularis (PN) is a recurrent, itchy dermatosis in children secondary to arthropods bites [1]. It is due to cellular hypersensitivity to environmental arthropods and is characterized by pruritus and papular or papulovesicular erythematous skin lesions on the exposed areas: the upper and lower limbs, the neck area, and the trunk [1,2]. Because PN is often chronic and recurrent despite adequate management [2], it may alter the psychological and social well-being of patients and have an impact on their quality of life (QoL) [3]. PN is a childhood condition and its management requires parents to accompany their children during consultation and to care for them; this may be a source of psychological stress for these parents [4]. To the best of our knowledge, the literature offers no data on PN, particularly the impact of PN on QoL among children in Cameroon. This is the reason why we decided to conduct this study, which aimed to assess the QoL of patients with PN and their parents and to investigate the existence or absence of psychiatric comorbidities.

MATERIALS AND METHODS

Method

This was a descriptive, cross-sectional study that took place for a period of four months, from February through

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May 2017, in six hospitals of Yaoundé, namely, Yaoundé Central Hospital (YCH), Biyem-Assi District Hospital (BADH), Gyneco-Obstetric and Pediatric Hospital of Yaoundé (GOPHY), University Teaching Hospital of Yaoundé (UTHY), Essos Hospital Center (EHC), and Subdivisional health Center of Elig-Essono. These hospitals were chosen by convenience, based on the availability of a dermatologist. Our sampling was non-probabilistic and consecutive. Our target population was children attending dermatological consultation for dermatosis during this period.

In the study, we included: 1) children aged 0 to 16 years attending dermatological consultation because of PN after clinical examination, whose parents gave their consent, and 2) parents or guardians of children suffering from PN, who gave their consent to participate in the study.

Furthermore, all children and parents who refused to participate or who decided to withdraw were excluded from the study without any constraint.

Ethical Approval

We requested and obtained the research authorizations from the administrative authorities of the hospitals included in this study.

Data Collection

Data collection took place during dermatological consultations. Thus, after informing patients about the study and obtaining their informed consent, patients fulfilling the inclusion criteria were retained after the consultation. A questionnaire containing sociodemographic data, the effect of PN on the QoL of patients and research on psychiatric comorbidities, was completed by all patients according to the periods adapted to each scale: one week for the CDLQI, two weeks for the PHQ9 and GAD7, and one month for the FDLQI.

MATERIAL

Data Collection Tools

The data was collected using:

- A technical sheet providing information on sociodemographic data (age, sex, place of residence, type of residence, profession of parents/guardians);
- **Assessment scales of QoL in children and parents/guardians:** 1) *The Children's Dermatology Life Quality Index (CDLQI)* assessed QoL in children aged 4 to 16 years [5]. Patients responded to questions about their illness over the last week prior to inclusion; this included 10 questions divided into six items: symptoms (question 1 and 2), sleep (question 9), social life and leisure (questions 4, 5, and 6), study (question 7), relationships (questions 3 and 8), and treatment (question 10). Each question was scored from 0 to 3, giving a possible score range from 0 (no impact of the skin disease on QoL) to 30 (maximum impact on QoL); 2) *The Family Dermatology Life Quality Index (FDLQI)* [6] assessed the QoL of parents/guardians of these children. Parents or guardians responded to questions about the impact that their child's illness had had on them over the last four weeks prior to inclusion; this consisted of ten items: emotional distress, physical well-being, personal relationships, reactions with others, social life, hobbies/leisure, time, extra housework, job/study, and household expenditure. Each of these items was scored from 0 to 3. The total score varied from 0 to 30 points and was calculated by adding the score obtained from each of the different questions;
- **Anxiety and depression screening scales:** 1) *The 9-Item Patient Health Questionnaire (PHQ-9)* is a nine-point, self-assessment scale employed to diagnose mental depression according to nine criteria for major depression in the Diagnostic and Statistical Manual of Mental Disorders, Version 4 (DSM-IV) [7]; each item was scored from 0 to 3; 2) *Generalized Anxiety Disorder 7-Item (GAD-7)* is a 7-item anxiety rating scale, a useful screening tool for diagnosing generalized anxiety disorder [8]; each item was scored from 0 to 3. The total score varied from 0 to 21. This was used to screen the presence of mental depression and anxiety in children aged ≥ eight years as well as in their parents.

Interpretation of QoL Scores

The CDLQI made it possible to assess the children's QoL and the parents' FDLQI. Responses to these two scales were interpreted as follows: 1) extremely (3 points); 2) a lot (2 points); 3) a little (1 point); and 4) not at all (0 points). The total score was calculated by adding the scores obtained from each question. The interpretation of the scores was as follows: 1) 0–1: no effect at all on the patient's life; 2) 2–6: small effect on the patient's life; 3) 7–12: moderate effect on the patient's life; 4) 13–18: large effect on the patient's life; and 5) 19–30: extremely large effect on the patient's life.

Interpretation of Depression and Anxiety Scores

The PHQ-9 and GAD-7 questionnaires were used to screen the presence of mental depression and anxiety, respectively, in children aged ≥ eight years. The same questionnaire was taken by their parents. Responses to each item in these two scales were rated as follows: 1) nearly every day (3 points); 2) - more than half the days (2 points); 3) several days (1 point); and 4) not at all (0 points).

The total score was calculated by adding the score obtained from each question, thus varying from 0 to 27 in the PHQ-9 and from 0 to 21 in the GAD-7. A PHQ-9 score of ≥10 had a sensitivity and specificity of 88% for depression [7], while a GAD-7 score of ≥10 had a sensitivity of 89% and a specificity of 82% for anxiety [8]. Therefore, the results were interpreted as follows: 1) a score of ≤10: no depression or anxiety; and 2) a score of ≥10: depression or anxiety.

Correlation Study

We looked for the existence of a correlation between the age and the QoL score, between the age and the anxiety and mental depression scores, and between the duration of PN and the QoL score, respectively in children and adults. We also looked for a correlation between the child's age and the parents' QoL and anxiety and depression scores.

Statistical Analysis

The data collected was encoded by the CSPRO 6.3 software, then exported to SPSS 23.0 for statistical analysis. Qualitative variables were described by their numbers and percentages and quantitative variables by their means associated with their standard deviation. The Mann–Whitney test was employed to compare medians. Pearson and Spearman linear correlation tests were used to determine the correlation between the patient's age and the QoL scores and the depression and anxiety scores on one hand and between the child's age and the child's scores, the parents' QoL and the depression and anxiety scores on the other hand. The threshold of significance was set at 5%.

Ethics Statement

Before beginning the study, ethical clearance was obtained from the institutional ethics committee of the Faculty of Medicine and Biomedical Sciences of Yaoundé and authorizations from the directors of hospitals included in the study were obtained. The patients were informed about the different aspects of the study and their agreement was only obtained after the parents gave their consent to participate in the study and obtaining an agreement for children aged >7 years. We ensured the anonymity of the patients and the confidentiality of the information collected.

RESULTS

Sociodemographic Characteristics of Children

We included a total of 112 predominantly male children (62/112; 55.4%), with a sex ratio of 1.2. The most represented age group was 0 to 5 years (78.6%). The median age was 2 (18 months – 4 years), varying from 5 months to 16 years. In these children, the median duration of PN was 8 (2–18) months, varying from 1 to 108 months.

Sociodemographic Characteristics of Parents

Our study included 112 predominantly female parents (109/112; 97.3%). The mean age among the parents was 33 ± 8.2 years, varying from 20 to 65 years. Among these parents, 56.2% were married and most of them had high school education (50.9%).

QoL Assessment and Screening for Mental Depression and Anxiety in Children

Children's QoL Assessment (CDLQI)

In our sample, 29/112 children were aged from 4 to 16 years old and we assessed their QoL over the last week prior to inclusion with the CDLQI. Table 1 shows the distribution of these children according to responses to the CDLQI's questions.

The most affected QoL items were *symptoms* and *study* (Table 1). As far as the *symptoms* items are concerned, the questions relating to the sensation of itching and/or soreness (28/29; 96.6%) and discomfort related to the skin problem (25/29; 86.2%) were mostly involved (Table 1). As for the *study* item, only 3 children (10.3%) felt no impact of their condition on their schoolwork (Table 1).

The mean QoL score in the 29 affected children was 8.6 ± 2.8, ranging from 0 to 15. QoL was impaired in almost all children (27/29; 93.1%). It was slightly, moderately, and severely altered in 5/29 (17.2%), 17/29 (58.6%), and 5/29 (17.2%), respectively (Table 2).

We found moderate QoL impairment in 7 boys (41.2%) and 10 girls (83.3%). The median QoL score in boys was 9, with extremes of 0 and 15, while in girls it was 10, with extremes of 4 and 12. Furthermore, this difference was not statistically significant ($p = 0.91$).

Comparison of QoL between Boys and Girls by CDLQI

There was no statistically significant difference between the median score of different QoL items (symptoms, activities, leisure, personal relationships, study, and treatment) between boys and girls ($p > 0.05$) (Table 3).

Table 1: Distribution of the children according to the CDLQI.

Variable		Number ($n = 29$)	Percentage (%)
How itchy, "scratchy", sore, or painful has your skin been?	Not at all	1	3.4
	Only a little	10	34.5
	Quite a lot	18	**62.1**
How embarrassed, self-conscious, upset, or sad have you been because of your skin?	Not at all	4	13.8
	Only a little	16	**55.2**
	Quite a lot	9	31
How much has your skin affected your friendships?	Not at all	12	41.4
	Only a little	14	**48.3**
	Quite a lot	3	10.3
How much have you changed or worn different or special clothes/ shoes because of your skin?	Not at all	11	**38**
	Only a little	9	31
	Quite a lot	9	31
How much has your skin trouble affected going out, playing, or doing hobbies?	Not at all	17	**58.6**
	Only a little	11	38
	Quite a lot	1	3.4
How much have you avoided swimming or other sports because of your skin trouble?	Not at all	13	**44.8**
	Only a little	12	41.4
	Quite a lot	4	13.8
How much has your skin problem affected your schoolwork?	Not at all	3	10.3
	Only a little	14	**48.3**
	Quite a lot	12	41.4
How much trouble have you had because of your skin with other people calling you names, teasing, bullying, asking questions, or avoiding you?	Not at all	18	**62.1**
	Only a little	6	20.7
	Quite a lot	5	17.2
How much has your sleep been affected by your skin problem?	Not at all	12	**41.4**
	Only a little	6	20.7
	Quite a lot	11	37.9
How much of a problem has the treatment for your skin been?	Not at all	20	**69**
	Only a little	8	27.6
	Quite a lot	1	3.4

Table 2: Distribution of the children according to the level of deterioration in quality of life (CDLQI)

Quality of Life	Boys *n* (%)	Girls *n* (%)	Total *n* (%)
no effect at all on the patient's life	2 (11.8)	0 (0)	2 (6.9)
small effect on the patient's life	3 (17.6)	2 (16.5)	5 (17.2)
moderate effect on the patient's life	7 (41.2)	10 (83.3)	17 (58.6)
large effect on the patient's life	5 (29.4)	0 (0)	5 (17.2)
extremely large effect on the patient's life	0 (0)	0 (0)	0 (0)
Total	**17 (100)**	**12 (100)**	**29 (100)**

Assessment of Anxiety and Depression in Children

Among our 112 children, 19 were ≥8 years old; we administered the PHQ-9 and GAD-7 questionnaires to them. After rating each question from the PHQ-9 and GAD-7, we obtained scores that ranged from 0 to 4 and from 0 to 6, respectively. We found no cases of mental depression or anxiety in our sample.

Assessment of QoL and Searching for Anxiety and Depression in Parents

We assessed the QoL of the 112 parents accompanying our children. Table 4 shows the distribution of the parents according to responses to the FDLQI over the last four weeks preceding their inclusion in the study. Emotional distress and expenditure were the most intruding factor for the parents (Table 4).

We found a moderate change in QoL in more than half of the parents (76/112; 67.9%). Furthermore, this alteration in QoL was mild in 20/112 (17.9%) and severe in 15/112 (13.4%). Only one parent seemed to be unaffected by his child's illness. The mean QoL score for parents was 9.4 ± 2.1, ranging from 0 to 17.

Researching Anxiety and Depression in Parents

We looked for the presence of anxiety or mental depression in the 112 parents in our sample. After rating each question from the PHQ-9 and GAD-7, we obtained scores that ranged from 0 to 8 and from 0 to 9, respectively. No cases of anxiety or mental depression were found among the parents. We found no statistically significant difference between the median score for depression and anxiety of the parents

Table 3: Comparison of the QoL score by the CDLQI according to the sex of child

Quality of Life Items	Median (IQR)	*p* Value
Symptoms		
Boys	3 [2 – 4]	0.56
Girls	2 [2 – 4]	
Activities		
Boys	2 [1 – 2]	0.78
Girls	2 [1 – 3]	
Leisure		
Boys	1 [0 – 2]	0.18
Girls	2 [0 – 2]	
Personal relationships		
Boys	2 [0 – 2]	0.68
Girls	2 [1 – 2]	
Study		
Boys	1 [1 – 1]	0.70
Girls	1 [1 – 1]	
Treatment		
Boys	2 [1 – 2]	0.26
Girls	1.5 [1 – 2]	

accompanying girls compared to the score of the parents accompanying boys ($p > 0.05$) (Table 5).

Correlation Study

Association between Age and QoL Score

We found no linear correlation between the age of a child and the child's QoL score ($r = 0.05$; $p = 0.79$) on one hand and between the age of a parent and the parent's QoL score ($r = 0.15$; $p = 0.12$) on the other hand.

Association between Duration of Evolution of PN and QoL Score

We found no linear correlation between the duration of evolution of PN and the QoL score in children ($r = 0.15$; $p = 0.44$) on one hand and between the duration of development of PN and the QoL score in parents ($r = 0.04$; $p = 0.65$) on the other hand.

Table 4: Distribution of the parents according to responses to the FDLQI.

Items		Number ($n = 112$)	Percentage (%)
How much emotional distress have you experienced due to your child's skin disease?	Not at all	1	0.9
	A little	20	17.8
	Quite a lot	88	**78.6**
	Very much	3	2.7
How much has your child's skin disease affected your physical well-being?	Not at all	30	26.8
	A little	51	**45.5**
	Quite a lot	31	27.7
How much has your child's skin disease affected your personal relationships with him/her or with other people?	Not at all	98	**87.5**
	A little	13	11.6
	Quite a lot	1	0.9
How much have you been having problems with other peoples' reactions due to your child's skin disease?	Not at all	33	29.5
	A little	31	27.7
	Quite a lot	47	**41.9**
	Very much	1	0.9
How much has your child's skin disease affected your social life?	Not at all	98	**87.5**
	A little	9	8
	Quite a lot	5	4.5
How much has your child's skin disease affected your recreation/ leisure activities?	Not at all	63	**56.3**
	A little	36	32.1
	Quite a lot	13	11.6
How much time have you spent on looking after your relative/partner?	Not at all	10	9
	A little	79	**70.5**
	Quite a lot	23	20.5
How much extra housework have you had to do because of your child's skin disease?	Not at all	12	10.7
	A little	56	**50**
	Quite a lot	44	39.3
How much has your child's skin disease affected your job/study?	Not at all	55	**49.1**
	A little	43	38.4
	Quite a lot	13	11.6
	Very much	1	0.9
How much has your child's skin disease increased your routine household expenditure?	Not at all	8	7.1
	A little	42	37.5
	Quite a lot	62	**55.4**

Association between age and mental depression and anxiety score

We found no linear correlation between the age of a child and the score for mental depression ($r = 0.25$; $p = 0.29$) or anxiety ($r = 0.22$; $p = 0.35$). In contrast, among parents, there was a weak positive linear correlation between the age and mental depression ($r = 0.22$; $p = 0.02$). In fact, this score increased with the age of the parent (Figure 1).

Association between Child's Age and QoL Score and Parental Anxiety and Depression Score

There was a weak negative linear correlation between the child's age and the parent's QoL ($r = -0.31$; $p = 0.001$). Indeed, the younger the child, the more the parent's QoL was altered. There was also a weak positive linear correlation between the child's age and parental anxiety ($r = 0.25$; $p = 0.007$). In fact, the parent's anxiety score increased with the child's age. There was a weak positive linear correlation between the child's age and parental mental depression ($r = 0.21$; $p = 0.03$); the parent's mental depression score increased with the child's age (Table 6).

DISCUSSION

To our knowledge, this work is one of the few African studies assessing QoL and psychiatric comorbidities in children with PN as well as in their parents.

Overall, QoL was impaired in 93.1% of children and 99.1% of parents. In our series, there was a weak

Table 5: Comparison of mental depression and anxiety scores of parents accompanying boys compared to those accompanying girls

Score	Child's Sex	Median (IQR)	*p* Value
Depression	Boys	2.0 (0 – 3)	0.11
	Girls	1.0 (0 – 2)	
Anxiety	Boys	0 (0 – 2)	0.08
	Girls	0 (0 – 1)	

Table 6: Correlation studies.

	r	*p* Value
Correlation between the child's age and the parent's QoL		
QoL among parents	-0.31	0.001
Child's age		
Correlation between the child's age and the parent's anxiety		
Anxiety among parents	0.25	0.007
Child's age		
Correlation between the child's age and the parent's depression		
Depression among parents	0.21	0.03
Child's age		

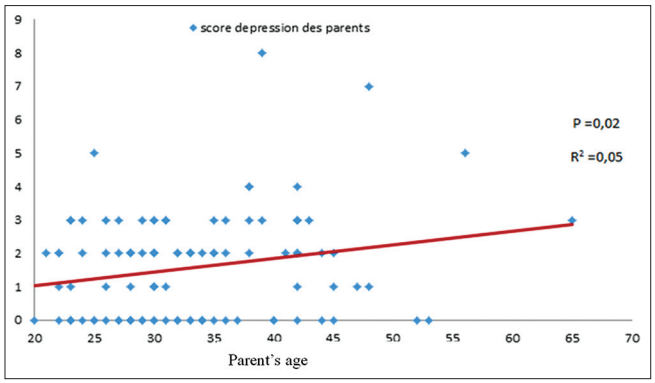

Figure 1: Linear correlation of the depression score among parents and their ages.

negative linear correlation between the child's age and the parent's QoL (r = -0.31; p = 0.001). In children and parents, we found no psychiatric comorbidities.

Quality of Life in Children and Parents

The mean QoL score in children was 8.6 ± 2.8; overall, the child's QoL was moderately impaired. This mean score was close to that of Monti et al. from Italy (7.0 ± 5.2), who also found a moderate alteration in QoL in a cohort of children suffering from atopic dermatitis [4]. In contrast, Maridet et al. from France found an average CDLQI score of 6.1, which means an overall slight deterioration in QoL in children suffering from chronic prurigo [9]. The higher level of QoL alteration during PN compared to chronic prurigo might be explained by the periodic occurrence of more inflammatory acute flare-ups during PN compared to chronic prurigo. Chronic prurigo is also said to be somewhat accepted in children. Items of QoL that posed the biggest problem in children were *symptoms*, with a negative impact of pruritus and/or discomfort in almost all children (28/29; 86.2%), and *study* (26/29; 89.7%). In 2009, Kouassi et al. from Ivory Coast also noted a highly significant effect of pruritus on QoL among children with atopic dermatitis in their series (65%) [10]. The itchy, displaying, and recurrent nature of these dermatoses would explain these children's feelings. Over half of our children had trouble with sleeping (58.6%) and felt sadness (96.2%) because of their skin problem. Several series in the literature corroborate our results [10]. Prurigo and itchy dermatoses generally affect QoL in both adults and children. Brenaut et al., reported in their multicenter cohort in Europe, an alteration in QoL ranging from *very significant* to *extreme* in 63.0% of adult patients with PN [11]. The Ivorian study on the QoL of children with atopic dermatitis also found a similar profile; indeed, the impact of the condition on QoL ranged from *no effect* to *very strong effect* [10]. Among our participants, only 2 (6.9%) children had no altered QoL. Overall, itchy dermatoses affect patients' QoL, are a source of expense for families, and may even lead to psychiatric comorbidities, such as depression, anxiety, and suicidal ideation [11,12].

Among the parents, the mean QoL score was 9.4 ± 2.1, with a moderate impact of their child's affection on their QoL. This QoL score was higher than that of the children (8.6 ± 2.8), which reflects a greater alteration in QoL in the parents than in the sick child. This finding might be explained by the importance of the cost of long-term care; most parents admit that their child's illness leads to increased expenses (21/29; 72%). Overall, the QoL of the parents is at least as impaired as that of the sick child.

In addition, parental QoL is negatively correlated with the child's age (r = -0.31; p = 0.001). Although this correlation is weak, the QoL of parents is mostly altered when the child is much younger. Our work is corroborated by one of Monti et al., who found a weak inverse correlation between the age of the child with atopic dermatitis and the parent's QoL (r = -0.26; p = 0.046) [4]. Parents seem more worried about their children's illness when they are young.

Anxiety and Mental Depression

We found no cases of anxiety (GAD-7) or mental depression (PHQ-9) in either children or parents in our sample. All scores were below 10. This result suggests that, in our context, although unaesthetic, PN does not affect the child's QoL to the point of causing mental depression and anxiety in both the child and the parent. However, the tendency seems different when prurigo affects adults. Indeed, Brenault et al., in their cohort of 27 patients with prurigo, found a proportion of 30.4% of cases of mental depression, 39.1% of anxiety, and 21.8% of suicidal ideation [11].

Correlation Study

We found a weak positive correlation between the parental age and the parental mental depression score (r = 0.22; p = 0.02). The older the parents are, the higher this score. Indeed, parents become less and less inclined to endure stress from their child's illness with age. We also found a weak positive linear correlation

between the child's age and the parent's anxiety score ($r = 0.25$; $p = 0.007$) on one hand and a weak positive linear correlation between the child's age and the parent's mental depression score on the other hand ($r = 0.21$; $p = 0.03$). Conversely, there was a weak negative linear correlation between the age of the child and the QoL of the parents ($r = -0.31$; $p = 0.001$) in our series; the parent's QoL was mostly altered if the child was younger. In 2011, Monti et al. found similar results in their cohort. Their work revealed that QoL among the parents of children with atopic dermatitis was also negatively correlated with the age of the children ($r = -0.26$; $p = 0.046$) [4]. Concerning itchy skin diseases in children, parents are more affected by the condition of their child if the child is younger.

Limitations of our Study

Our study might have had some limitations due to the fact that: 1) Our study population was a hospital-based study and, therefore, was not representative of the general population. 2) We made a choice of convenience for the different hospitals in which patient recruitment took place. 3) All the QoL scales that we employed had been tested on Caucasian populations. Research should be done to find better ways to measure mental depression and anxiety in young children—less than four years old—and in Africans in general.

CONCLUSION

The QoL of children with PN and of their parents is mostly moderately impaired. Parental QoL impairment is inversely correlated with the child's age. However, PN, although with an impact on the QoL of children and their parents in our environment, is not associated with psychiatric comorbidities, including mental depression and anxiety. The clinician should consider the QoL aspect of the sick child and parent in order to improve their overall management.

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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

Hospital prevalence and causes of non-adherence to acne treatment: A report from Nepal

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ABSTRACT

Background: With acne being a chronic and relapsing condition, patients may not be compliant with its treatment, especially because of the various reasons leading to treatment failure. This study aimed to determine the hospital prevalence and causes of non-adherence to acne treatment among patients attending the dermatology outpatient department of a tertiary care hospital in eastern Nepal. **Materials and Methods:** This was a cross-sectional study conducted from April 22 through May 20, 2017, and was based on a preset proforma distributed among the attendees at the dermatology OPD of BPKIHS, Dharan, Nepal. A validated questionnaire was used to ascertain the patient's non-adherence to acne treatment. If non-adherence was confirmed, sociodemographic details, along with a detailed history of the illness, including the duration of the illness, the age of onset, and the examination findings, were noted in the proforma. **Results:** The study found the hospital prevalence of non-adherence to acne treatment to be 61.76%. The majority of the non-adherent patients were females 10–20 years old. In 76.8% of the cases, both oral and topical treatment was prescribed, and both modes of treatment were abandoned by a majority of the participants (56.5%). Failing to remember to take the medications at the right time (45.7%), being unaware of the necessity of their continuation (34.8%), and the appearance of their side effects (28.3%) were the three most prevalent reasons for abandoning the prescribed treatment. **Conclusion:** Greater non-compliance was observed in patients taking both oral and topical medications. Among the different reasons for non-compliance, failing to remember to take the medications and being unaware of the necessity of their continuation were the two most prevalent answers. Hence, educating patients on the importance of treatment adherence seems to be of great value in minimizing non-compliance.

Key words: Acne vulgaris; Adverse effect; Education; Medication adherence; Nepal; Treatment

INTRODUCTION

Acne is a very common non-infectious skin condition frequently encountered in dermatological practice [1]. The Global Burden of Disease (GBD) project estimates the prevalence of acne at 9.4%, ranking it as the eighth most prevalent disease in the world [2]. In a study conducted in rural Nepal, the point prevalence of acne was found to be 7.7% [3]. Likewise, in a report from western Nepal, the prevalence among the pediatric age group was found to be 10.1% [4].

Different treatment modalities may be employed for acne, such as topical retinoids, antibiotics, benzoyl peroxide, alpha hydroxy acid, azelaic acid, niacinamide, hydrogen peroxide, anti-seborrheic medications. Some commonly prescribed systemic treatments are antibiotics, retinoids, and hormonal treatments [5]. Additionally, estrogen levels tend to be found low in females with acne, thus further supporting the role of hormonal therapy in the treatment of acne [6].

Adherence is the extent to which a patient follows agreed-on treatment recommendations. Non-adherence may be classified into primary non-adherence – failure to obtain and initiate the treatment – and secondary non-adherence – failure to abide by the procedure of the treatment or discontinuing the

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treatment too early. Non-adherence is a pervasive problem in all fields of medicine, particularly in treating chronic conditions. Chronic conditions, including acne, show low secondary adherence rates because patients often miss doses and discontinue treatments [7]. Due to non-compliance, the treatment outcome will be less than optimum. Hence, the patient may experience frustration, resignation, and a lower quality of life. It is, therefore, becoming increasingly imperative that the factors associated with non-adherence to acne treatment must be assessed to devise alternatives and strategies to improve the patient's compliance toward the advised medical treatment.

MATERIALS AND METHODS

This was a cross-sectional study that aimed to determine the hospital prevalence of non-adherence to acne treatment and the reasons behind the non-adherence in acne patients attending the dermatology outpatient department of B.P. Koirala Institute of Health Sciences. The study was carried out from April 22 through May 20, 2017. All subjects with the diagnosis of acne vulgaris with non-adherence to treatment were included in the study after informed consent. A validated ECOB questionnaire was employed to ascertain the patient's non-adherence to acne treatment [8]. Excluded were patients seeking acne treatment for the first time, those compliant with the prescribed treatment, and those unwilling to participate in the study. The study was conducted according to the declaration of Helsinki. Sociodemographic details, along with a detailed history of the illness, including the duration of the illness, the age of onset, and the examination findings, were noted in the proforma. Acne was classified into four grades (grade I, II, III, and IV) according to the pleomorphic grading system [9]. The study employed purposive sampling. Data entry was performed with Microsoft Excel. Analysis was performed with SPSS, version 11.5. Descriptive statistics was employed to explore the characteristics of the collected data by calculating percentages, means, ranges, and standard deviations. Ethical clearance was obtained from the Departmental Research Unit.

LIMITATIONS

In the ECOB questionnaire, the color of the medication packaging is accepted as a correct answer to the question: "Do you remember the name of the last drugs you took?" However, since there may be more than one manufacturer of the same drug, this answer could not be accepted. Since the details of the adherent patients have not been taken, bivariate and multivariate analysis could not be performed. Since the study was cross-sectional, causal inferences could not be made. A study with a longer duration, a follow-up period, and bigger sample sizes may generate more details. Inclusion of other widely recognized adherence scales, such as the Morisky Medical Adherence Scale or the Medication Event Monitoring System may help to better determine the extent of adherence.

RESULTS

During the study, a total of 68 acne patients visited the dermatology OPD. Among them, 42 fulfilled the criteria for non-adherence to acne treatment, hence giving a hospital prevalence of 61.76%. More than half of them (52.2%) were 10–20 years old, with a mean age of 21.3 ± 5.8 years. The majority (87.0%) of the participants were females (Table 1). Non-adherence was the highest (82.6%) among participants suffering from acne for more than a year. The face was the most commonly (97.8%) affected site. More than half of the participants (54.3%) had grade III acne. Comedones were found unanimously in all 46 participants, while pustules were predominant among 84.8% of the participants. In 91.3% of cases, medications were prescribed by a dermatologist. More than half (56.5%) had a family member as their companion during the consultation (Table 2). For 76.8%, both oral and topical treatments were prescribed, and both modes of treatment were abandoned by a majority of the participants (56.5%) (Table 3). Among the numerous reasons enumerated in the proforma, failing to remember to take the medications at the right time (45.7%), being unaware of the necessity of their continuation (34.8%), and the appearance of their side effects (28.3%) were the three most prevalent reasons for abandoning the prescribed treatment (Table 4). Itching (17.3%) was the most frequently encountered side effect among the participants who claimed to have abandoned the prescribed treatment because of the side effects of the medications. Half (50.0%) claimed there was no difference in their condition when the treatment was withdrawn. A majority (71.7%) used no alternative treatments after abandoning the prescribed treatment for acne, while the rest (28.3%) resorted to beauty products such as moisturizers and cleansers (Table 5).

Table 1: Sociodemographic profile of the patients

Characteristic	Category	No. of patients	Percentage
Age (yrs.)	10–20	24	52.2
	21–30	17	37.0
	31–40	5	10.9
Gender	Male	6	13.0
	Female	40	87.0
Occupation	Self-employed	3	6.6
	Business	2	4.3
	Doctor	1	2.2
	Homemaker	5	10.9
	Student	35	76.1
Literacy	Literate	45	97.8
	Illiterate	1	2.2

Table 2: History and general information about the patients' illness

Characteristic	Category	No. of patients	Percentage
Duration of the illness (yrs.)	< 1	8	17.4
	1–2	14	30.4
	3–5	14	30.4
	> 5	10	21.8
Body parts affected	Face	45	97.8
	Chest	9	19.6
	Back	20	43.5
	Shoulders	4	8.7
Severity (acne grade)	I	4	8.7
	II	10	21.7
	III	25	54.3
	IV	7	15.2
Type of lesions	Papules	35	76.1
	Pustules	39	84.8
	Nodules	7	15.2
	Cysts	6	13.0
	Comedones	46	100.0
Medication prescribed by	Dermatologist	42	91.3
	OTC medication	2	4.3
	Beauty parlor	2	4.3
Companion during the consultation	None	18	39.1
	Family member	26	56.5
	Friend	2	4.3

DISCUSSION

Acne affects prepubescents and teenagers as well as adults, and may have devastating impact on one's mental and social well-being. Those who seek help for their acne not only do so because of the severity of the disease but also because of the sociocultural factors and the disease's impact on other people's attitude toward and perception of them. This is also determined by their coping capacity. Compliance with the prescribed treatment regimen is an essential element in the overall effectiveness of the therapy [10]. According to our study, the rate of non-adherence to acne treatment was found to be 62.16%, which is quite similar to a cross-sectional study done on 500 patients with acne vulgaris, in whom poor adherence was found in 64.4%

Table 3: Details on the prescribed treatment and its discontinuation

Characteristics	Category	No. of patients	Percentage
Prescribed treatment	Topical	9	19.1
	Oral	2	4.1
	Both	35	76.8
Treatment discontinued	Topical	12	26.1
	Oral	8	17.4
	Both	26	56.5
No. of medications taken altogether	1	4	8.7
	2	12	26.1
	3	15	32.6
	4	11	23.9
	5	3	6.5
	6	1	2.2

Table 4: Reasons for discontinuing the prescribed treatment

Category	No. of patients	Percentage
Being unaware of the necessity of continuation	16	34.8
Good improvement with the medications taken	9	19.6
No improvement with the medications taken	12	26.1
Dissatisfaction with the doctor	4	8.7
Side effects from the medications taken	13	28.3
Unable to dedicate enough time for a follow-up	11	23.9
Failing to remember to take the medications at the right time	21	45.7
Laziness	2	4.3

Table 5: Side effects of the previously prescribed treatment and the use of alternative treatment

Category		No. of patients	Percentage
Itching		8	17.3
Swelling		1	2.2
Pigmentation		1	2.2
Dryness of the hair and skin		4	8.7
Diarrhea		2	4.3
Drowsiness		1	2.2
Abdominal pain		2	4.3
Difference in the acne after discontinuing the treatment	Better than before	3	6.5
	Worse than before	20	43.5
	No difference	23	50.0
Use of an alternative treatment to manage the acne	Yes	13	28.3
	No	33	71.7

of cases [11]. In a similar fashion, an international observational study on acne treatment found the overall risk of poor adherence to be 50%, with regional variations of 43% in the Americas, 48% in Asia, and 58% in Europe. Unlike this report, the higher rate of non-adherence in our study might be correlated with the ease of directly contacting a dermatologist in Nepal, so that, in case of a disease flare, they are able to immediately visit the specialist again. Likewise, the considerable availability of over-the-counter medications in Nepal

might be another reason for the higher non-adherence. Hence, the patients might not have been taking the treatment seriously enough. Yentzer et al. highlighted that acne treatment compliance is only about 50% in a non-clinical trial setup, but may increase in clinical trials. They found maximum compliance among the frequently followed-up group. However, a daily electronic reminder and a parental reminder did not improve compliance [12]. This suggests that frequent visits to the doctor may influence and encourage the patient to adhere to the treatment.

Most of the studies assessed adherence with a validated ECOB questionnaire. Its advantages are as follows: may be employed easily in routine clinical practice; may readily be adapted to other languages; and may even be taken by children younger than 15 years [8,13]. In a study conducted in Japan, there was an overall rate of poor adherence in 76% of the participants [14].

In our study, 52.2% of the participants were 10–20 years old, with a mean age of 21.3 ± 5.8 years. The majority (87.0%) were females. Almost all were literate (97.8%), with more than half of all participants having attended higher secondary education (60.9%). This finding is comparable with a study by Dréno et al., who have also shown that poor adherence was independently correlated with a young age, most visibly in patients less than 15 years old as well as 15–25 years old [13].

What our study shows is that both modes of treatment (oral and topical) were abandoned by a majority of the participants (56.5%). This is in contrast with a study conducted in France, which showed an 81% adherence rate to one or both modes of acne treatment [8]. According to a past review, adherence was higher for oral treatments than topical. The authors concluded that frequent office visits and web-based educational tools may significantly improve adherence to acne treatment [15]. In a study conducted in the U.S., the adherence rates with topical antibiotics were determined at 4.04%, retinoids at 57.28%, contraceptives at 48.99%, glucocorticoids at 1.64%, while the adherence rates with oral antibiotics were determined at 3.89%, retinoids at 2.29%, and glucocorticoids at 1.98% [16]. In a more recent study on adherence to topical acne treatments, discontinuation occurred mostly with the use of retinoids (40%), benzoyl peroxide combinations (44.1%), and retinoid combinations (60%). Furthermore, the discontinuation of these treatments was reported to have been due to side effects, with rates of 50%, 33.3%, and 65.7%, respectively [17]. Likewise, a previous report showed that a complex treatment regimen, lack of a response, side effects, lack of time, forgetfulness, inconvenience, and others were common reasons for secondary non-adherence to acne therapy [10]

In our study, failing to remember to take the medications at the right time (45.7%), being unaware of the necessity of their continuation (34.5%), the appearance of their side effects (28.3%), and no improvement with the medications taken (26.1%) were the most prevalent reasons for abandoning the prescribed treatment. Likewise, 91.3% of the participants were prescribed the treatment by a dermatologist, more than half (56.5%) had a family member as a companion, and almost all (97.8%) were literate. Therefore, we feel that if the patient is counseled properly about the possible side effects of the medications and about the need for long-term treatment, which is due to the chronic and relapsing nature of the disease, the chance of non-adherence may be minimized to a great extent. A recent study on adherence rates in five chronic skin diseases, including acne, showed that unresponsiveness was the most common reason for treatment discontinuation, with the highest significance in patients with severe acne. Forgetfulness, fear of side effects, and a longer duration of treatment were other common factors [18]. This also supports our suggestion that these factors may be minimized to a great extent with adequate counseling by the doctor prescribing the treatment. However, among the five dermatological diseases (acne vulgaris, psoriasis, atopic dermatitis, hair growth disorders), patients with acne vulgaris were more adherent to treatment and more motivated, probably due to the appearance of lesions in exposed areas [18]. Other factors linked to non-adherence, according to another study, included treatment dissatisfaction, the use of an over-the-counter topical medication or previous systemic therapy, lack of improvement in symptoms, lack of knowledge on the treatment, being male, poor education, living alone or being single, unemployment, insufficient time resources, feelings of frustration, and other comorbidities [19]. A pilot randomized controlled trial found that, even after demonstrating the product and sampling the fixed combination of adapalene or benzoyl peroxide gel, adherence rates decreased from 86% after one week of treatment to 36% within six weeks of treatment [20].

Good adherence correlated with patients who had a better understanding of acne and its treatment. The best adherers used cosmetics, experienced good

clinical improvement, had more severe acne, used either isotretinoin or topical therapy alone, and were both knowledgeable about and satisfied with their treatment. An increase in acne disability and a decrease in the duration of treatment or alcohol intake showed a direct correlation with high compliance. Adherence with topical therapy was positively associated with the negative impact of acne on quality of life [21].

It may be assumed that non-adherence rates are higher than recorded, jeopardizing the reported treatment efficacy rates. This implies that much larger sample sizes are required in trials to achieve statistical significance [22].

Simplification serves as one solution to non-adherence, allowing treatment to better fit into the patient's lifestyle. Among patients who were prescribed one, two, or three acne treatments, primary adherence was significantly higher in those who were prescribed one medication [7]. Education, specifically dynamic education, which involves more informative patient–physician interaction, may also increase adherence. Patients with acne who had greater adherence expressed a positive effect of their education and interaction with the dermatologist on their behavior, while those dissatisfied with their interaction with the dermatologist reported feeling unsure as to why they needed continuous treatment, what the expected results were, or how to prevent acne in general [14]. Scheduling follow-up visits is an effective method of intervention to increase adherence [23].

CONCLUSION

In this study, the hospital prevalence of non-adherence to acne treatment was found to be 62.16%. Greater non-compliance was observed in patients taking both oral and topical medications. Among the different reasons for non-compliance, failing to remember to take the medications at the right time was the most prevalent answer, followed by being unaware of the necessity of their continuation, the appearance of their side effects, no improvement with the medications taken, an inability to dedicate enough time for a follow-up, and others. It seems, thus, that we may be able to minimize non-adherence to acne treatment to a great extent with adequate counseling.

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

Dermoscopy of mycosis fungoides: A study on 31 patients

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ABSTRACT

Background: Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. Its clinical presentation is highly variable, ranging from erythematous patches to plaques and nodules. **Objectives:** The aim of this study was to describe the dermoscopic features of MF depending on its clinical and histological subtype. **Materials and Methods:** This was a retrospective, observational study held at the Department of Dermatology and Venerology in Fez, Morocco, over a period of four years. Included were cases in which the diagnosis of mycosis fungoides was established by histopathological and immunohistochemical examination. **Results:** Our results were overall in line with previous evidence. Dermoscopy of the classical form of MF is made of short linear vessels, dotted vessels, and orangish-yellow, patchy areas. In poikiloderma MF, we found mainly multiple pigmented polygonal structures, as reported in the literature. **Conclusion:** We found no significant relationship between dermoscopy and histology, which might be explained by the small size of our sample. To our knowledge, this has not been described before in the literature and others studies with larger samples are necessary to determine the validity of ours results.

Key words: Mycosis fungoides; Dermoscopy; Anatomopathology; Variants of mycosis fungoides

INTRODUCTION

The clinical diagnosis of cutaneous lymphoproliferative disorders (CLD) is one of the most difficult challenges in dermatology due to their heterogeneous and protean clinical presentation [1]. Since 2009, when Moura et al. described the dermoscopic features of lymphomatoid papulosis, interest toward dermoscopy of CLD has increasingly grown, and plenty of papers have been published on the topic [2-5].

Dermoscopy is a non-invasive technique aiding in the diagnosis of both pigmented and non-pigmented skin lesions. It allows the visualization of features invisible to the naked eye. By the assessment of characteristic vascular structures, colors, and patterns, dermoscopy may improve diagnostic accuracy for several dermatologic conditions [6]. Thus, it may be regarded as an intermediate step between clinical examination and dermatopathology [7]. The aim of our study was to describe the dermoscopic features of mycosis fungoides depending on its clinical and histological subtype.

MATERIALS AND METHODS

This was a retrospective, observational study held at the Department of Dermatology and Venerology in Fez, Morocco, over a period of four years—from January 2017 through December 2020. Included were cases in which the diagnosis of mycosis fungoides was established by histopathological and immunohistochemical examination.

Clinical and dermoscopic photographs were collected from each patient, and findings were reviewed, as well

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as the histopathologic features from previous biopsies. The capture of the dermoscopic images was performed with a DermLite dermoscope with polarized and non-polarized light.

The variables included in the dermoscopic evaluation were the following: dotted vessels; glomerular vessels; purpuric vessels; comma vessels; fine, short, linear vessels; spermatozoa-like structures; patchy, orangish-yellow areas; white scales; multiple pigmented polygonal structures; yellow scales; and rosettes.

All variables were summarized by descriptive statistics. Qualitative variables were described in terms of proportions. Statistical analysis of the data was performed with the Epi software, version 3.4 (2007).

Ethics Statement

Ethical approval was obtained from the ethics committees at the faculty of Medicine, University Sidi Mohammed Ben Abdellah in Fez, Morocco. All patients were informed of the conditions pertaining to the study and gave their written informed consent for the study and publication.

RESULTS

A total of 31 patients with MF were included. The median age was 54 years, with extremes ranging from 28 to 80 years. The male-to-female ratio was of 0.93.

The clinical presentation was dominated by macules (74%), followed by plaques (67%), papules (29%), nodules (22%), poikiloderma (22%), and tumors (9%). The classical form was the most frequent clinical form (54%). Other clinical forms included the pilotropic (19.4%) and poikilodermal form (19.4 %), hypopigmented MF (3.2%), and palmoplantar MF (3.2%).

Histological examination identified the classical MF in the majority of the patients (80.6 %), followed by pilotropic (19.4%) MF. The lymphocytic infiltrate was mainly located in the dermis (48%), followed by the epidermis (32%), and finally both the epidermis and dermis in 19.4%.

Biopsies revealed band-like lymphoid infiltrates in 64.5% of the cases, followed by Pautrier's microabscesses (22.6%) and nodular infiltrates (12.9%).

Dermoscopic analysis of all cases found the following signs: white scales (90%), orangish-yellow areas (58%), dotted vessels (54%), short, linear vessels (42%), purpuric vessels (35%), rosettes (35%), spermatozoa-like vessels (19%), comma vessels (19%), and multiple pigmented polygonal structures (19%).

Dermoscopy signs according to the clinical presentation are shown in Table 1. Dermoscopy of the classical clinical subtype revealed the following: a vascular pattern made of dotted vessels (51%) (Fig. 1), glomerular vessels (50%), short, linear vessels (Fig. 2) (50%), purpuric vessels (28.6%), and spermatozoa-like vessels (28.6%). Other findings included orangish-yellow areas (57%) (Fig.1), white scales (78%), and rosettes (28.6%).

Dotted vessels, rosettes, and orangish-yellow areas were the most frequently found signs in pilotropic MF. As

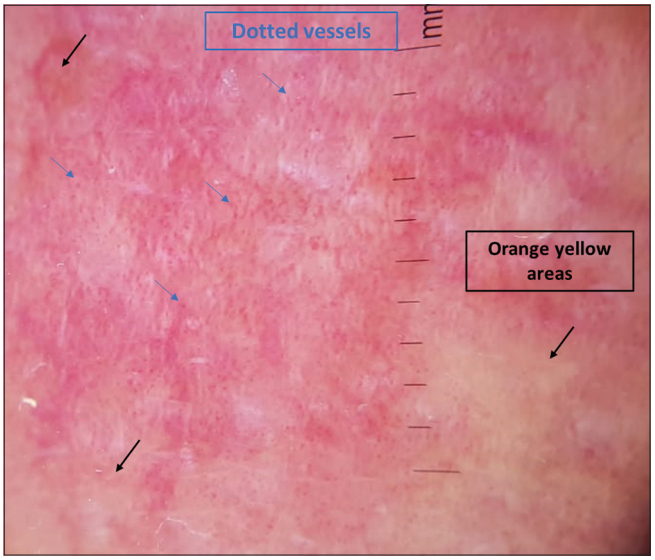

Figure 1: Dermoscopy of classic plaque-stage MF showing dotted vessels (blue arrows) and orangish-yellow areas (black arrows).

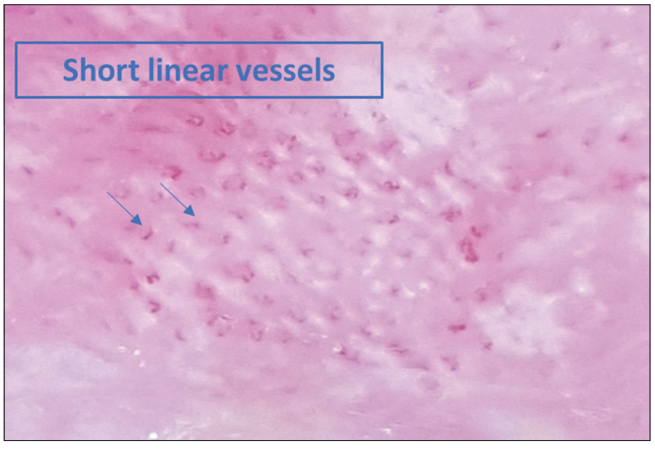

Figure 2: Dermoscopy of classic patch MF showing short, linear vessels.

Table 1: Dermoscopic findings according to the clinical presentation

	Comma vessels N(%)	Irregular linear vessels N(%)	Dotted vessels N(%)	Short linear vessels N(%)	Spermatozoa like vessels N(%)	Glomerular vessels N(%)	Purpuric vessels N(%)	Orangish--yellow patchy areas N(%)	White scales N(%)	Rosette N(%)	Multiple polygonal pigmented structures N(%)	Zones jaunes orange
Patch n 23	4(17,4)	4(17,4)	13(56.5)	9(39.1)	4(17,4)	6(26.1)	9(39.1)	12(52.2)	21(91.3)	7(30.4)	5(21.7)	12(52.2%)
Plaque n 21	3(14.3)	3(14.3)	14(66.7)	9(42.9)	5(23.8)	8(38)	8(38)	15(71)	18(85.7)	1(4.8)	1(4.8)	
Papule n 9	2(22.2)	1(11.1)	5(55.6)	4(44.4)	3(33.3)	5(55.6)	3(33.3)	7(77.8)	8(88.9)	4(44.4)	0	
Tumor n 7	3(42.9)	1(14.3)	6(85.7)	5(71.4)	4(57.1)	4(57.1)	3(42.9)	6(85.7)	6(85.7)	4(57.1)	0	
Poikiloderma n 7	1(14.3)	1(14.3)	1(14.3)	2(28.6)	0	0	1(14.3)	2(28.6)	7(100)	2(28.6)	6(85.7)	
Nodule n 3	2(66.7)	1(33.3)	2(66.7)	1(33.3)	2(66.7)	1(33.3)	2(66.7)	3(100)	3(100)	2(66.7)	0	

for poikilodermal MF, multiple pigmented polygonal structures (Fig. 3) and white scales were found in all cases (Fig. 4).

Regarding the topography of the lymphoid infiltrate, patients with dermal infiltrate presented mostly with orangish-yellow areas (64%), dotted vessels (56%), short, linear vessels (40%), and rosettes (36%). On the other hand, those with epidermal infiltrate exhibited the following signs: white scales (81%), dotted vessels (62.5%), purpuric vessels, and short linear vessels (31%).

When the lymphoid infiltrate was band-like, dermoscopy showed: white scales (95%), orangish-yellow areas (60%), dotted vessels (60%), and short, linear, and glomerular vessels (40%).

As for nodular infiltrate, we found: white scales (75%), orangish-yellow areas (75%), dotted vessels (50%), and short, linear vessels (50%).

Dermoscopic findings according to the histology are shown in Table 2.

DISCUSSION

The prognosis of MF is generally favorable at an early stage because of the availability of skin-directed therapies, such as topical glucocorticosteroids, nitrogen mustard lotion, and phototherapy. By contrast, for patients with an advanced disease, the prognosis is unfavorable, owing to the unavailability of effective treatment [8,9]. Therefore, early diagnosis is the safest strategy to reduce disease-related mortality. However, early diagnosis of MF may be extremely difficult, owing to its non-specific clinical manifestations [10].

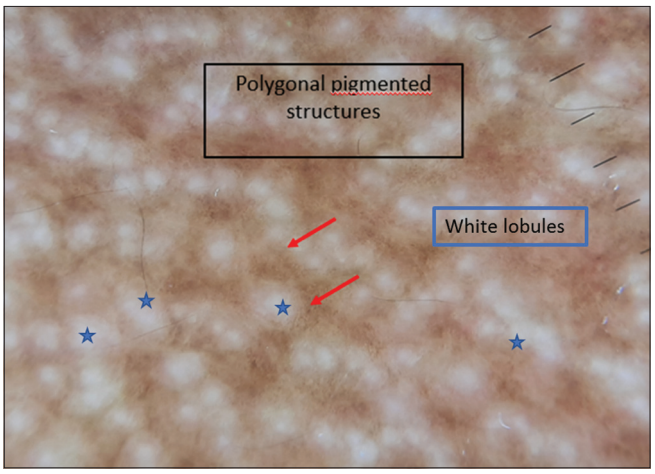

Figure 3: Dermoscopy of poikilodermal MF showing multiple pigmented polygonal structures with white lobules.

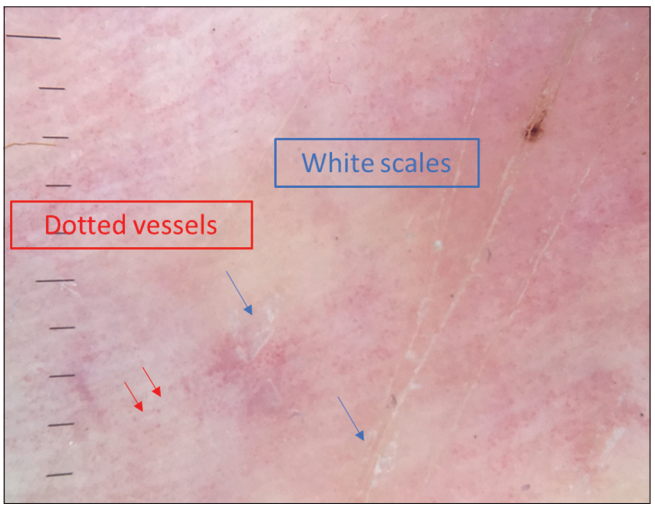

Figure 4: Dermoscopy of keratodermal MF showing dotted vessels on a pink background with white scales.

The dermoscopic patterns of MF were described in a series of 32 cases with early-stage MF by Lallas et al., who suggested that fine, short, linear vessels (sensitivity:

Table 2: Dermoscopic findings according to the histology

	Comma vessels N(%)	Irregular linear vessels N(%)	Dotted vessels N(%)	Short linear vessels N(%)	Spermatozoa-like vessels N(%)	Glomerular vessels N(%)	Purpuric vessels N(%)	Orangish-yellow patchy areas N(%)	White scales N(%)	Rosette N(%)	Multiple pigmented polygonal structures N(%)	Zones jaunes orange
Classic MF n19	3(15.8%)	2(16%)	11(58%)	9 (47.4)	4(21.1%)	9(47.4%)	8(42.1%)	12(63.2%)	16(84.2%)	7(36.8%)	0	12(52.2%)
Pilotropic MF n6	2(33.3%)	1(16.7%)	6(100%)	2(33.3%)	2(33.3%)	1(16.7%)	2(33.3%)	5(83.3%)	6(100%)	3(50%)	0	
Poikilodermal MF n 6	1(16.7%)	1(16.7%)	0	2(33.3%)	0	0	1(16.7%)	1(16.7%)	6(100%)	1(16.7%)	6(100%)	
Nodular infitrate n 4	1(25%)	1(25%)	2(50%)	2(50%)	1(25%)	0	1(25%)	3(75%)	3(75%)	2(50%)	0	
Band-like infiltrate n 20	4(20%)	2(10%)	12(60%)	8(40%)	5(25%)	8(40%)	6(30%)	12(60%)	19(95%)	4(20%)	7(35%)	
Isolated lymphocytes n3	1(33%)	1(33%)	1(33%)	1(33%)	0	0	1(33%)	1(33%)	3(100%)	2(66.7%)	1(33%)	
Thecae of lymphocytes n 7	2(28.6%)	0	4(57%)	3(42%)	3(42%)	3(42%)	2(28.6%)	3(42%)	5(71%)	1(14%)	1(14%)	

93.7%; specificity: 97.1%), together with orangish-yellow patchy areas (sensitivity: 90.6%; specificity 99.7%), represents specific criteria for the diagnosis of early MF [11]. The characteristic spermatozoa-like structures—composed of a dotted and a short, curved, linear vessel—were less common but also highly specific for the diagnosis of early MF. Bosseila et al., in a series of 25 patients with MF, confirmed the dotted pattern as the most frequently encountered vascular pattern in MF lesions, followed by the linear pattern [12]. We reached the same conclusion in our study, in which the most common vascular patterns—dotted vessels (54%), short, linear vessels (42%), and orangish-yellow areas —were found in 58% of all cases. As for the spermatozoa-like structures, they were found only in 19.4% of the cases.

Concerning poikilodermal MF, Xu et al. have described dermoscopy of this unusual variant, revealing as key dermoscopic features multiple polygonal structures consisting of lobules of white storiform streaks characterized by dotted and hairpin vessels, with septa of pigmented dots. In addition, red and yellowish smudges are detectable in poikilodermal MF [13-15]. These brown, mottled, reticular pigmentation with fine, gray dots may reflect basal pigmentation, liquefaction, and melanophages in the superficial dermis. Our study revealed the presence of these multiple polygonal pigmented structures in all patients presenting with poikilodermal MF, along with white scales and short, linear (28.6%) vessels. We also found rosettes (25%) as a new dermoscopic sign of poikilodermal mycosis fungoides, which has not been reported before in any study.

The most characteristic dermoscopic findings of keratoderma due to mycosis fungoides are relatively large amber scales on a white-to-pinkish background, sparse, whitish scales, and several non-specific reddish fissures [16]. There was only one case of keratoderma in our study, in which dermoscopy revealed dotted vessels with scales on a pink background (Fig. 4).

Regarding the correlation between dermoscopy and histology, in band-like infiltrate, we found mainly white scales, orangish-yellow patchy areas, and dotted vessels. In nodular infiltrate, we found white scales and orangish-yellow patchy areas. In isolated lymphocyte rosettes with white scales and in thecae of lymphocytes, we found whites scales and dotted vessels. Classical MF was characterized by glomerular and dotted vessels with orangish-yellow patchy areas; poikilodermal MF by multiple pigmented polygonal structures with rosettes; and pilotropic MF by dotted vessels, rosettes, and white scales.

We found no significant relationship between dermoscopy and histology (topography and morphology of the lymphoid infiltrate), which might be explained by the small size of our sample. To our knowledge, this has not been described before in the literature and others studies with larger samples are necessary to determine the validity of our results.

CONCLUSION

Our results are overall in line with previous evidence. Dermoscopy of the classical form of MF involves short linear vessels, dotted vessels, and orangish-yellow patchy areas. In poikiloderma MF, we found mainly multiple pigmented polygonal structures, as reported in the literature.

More studies should be conducted to determine the correlation of these dermoscopic structures with histological changes (morphology and topography of the lymphoid infiltrate).

Statement of Human and Animal Rights

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

Statement of Informed Consent

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

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Our Dermatology Online

Brief Report

Heat dermabrasion of congenital nevi as a simple, innovative technique

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ABSTRACT

Background: Congenital nevi are a relatively common dermatological problem that carries a risk of malignant transformation. **Patients and Methods:** The following is an interventional study in which five patients with congenital melanocytic nevi were enrolled, 3 (60%) females and 2 (40%) males. After local anesthesia, heat dermabrasion was performed with a diathermal needle until complete debulking was achieved and bleeding points appeared. Follow-up was done every two months for four months. **Results:** The location of the nevi in all cases was the face, while the size was variable, ranging from 1 to 17 cm. Erythema was observed on the sites of the removed nevi after two weeks and then gradually went to normal during the follow-up period, leaving minimal scarring. Complications were absent and no relapses were observed during the follow-up period. **Conclusion:** This is a simple, easy, and innovative technique that employs heat dermabrasion and, thus, avoids excision and suturing with or without grafting or flaps.

Key words: Congenital melanocytic nevus; Heat dermabrasion; Malignant melanoma

INTRODUCTION

Congenital melanocytic nevi (CMN) are either present at birth or appear in the first several weeks of life, with an incidence of 1% to 2% in newborns [1]. They consist of benign proliferations of neural-crest cell-derived melanocytes [2], and no significant gender predilection has been demonstrated. CMNs occur most commonly on the trunk and extremities, although scalp and facial involvement is seen as well. For practical purposes, small congenital nevi are at most 1.5 cm in diameter, medium-sized congenital nevi are 1.5 to 20 cm in diameter, large congenital nevi are 20 to 40 cm in diameter, and giant congenital nevi are more than 40 cm in diameter [2].

Small and medium-sized CMNs are usually round or oval. These lesions are usually slightly elevated at birth and may be brown. They may or may not be associated with hypertrichosis [3].

CMNs may be a great burden and reduce the patient's quality of life due to their cosmetic appearance [4]. Moreover, there is an increased risk of developing malignant melanoma (MM) in patients with CMN, especially with larger CMNs [5]. Large and giant lesions have a high risk of developing MM, but small and medium-sized lesions have a lower risk. Previously, the lifetime risk of MM in patients with CMN was estimated to be up to 40% in giant CMNs [1], but more recent studies indicate an overall lower incidence with CMN, at about 0.7% to 2.9% [6,7].

The treatment of CMNs is primarily based on two factors: their cosmetically disfiguring appearance and the increased risk of progression to melanoma. The decision to remove a CMN is on an individual basis and depends on the age of the patient, the risk of melanoma, the anatomic location, the anticipated cosmetic outcome, the presence or absence of neurocutaneous melanosis, and the complexity of removal [3].

In the last century, complete nevus excision had been the first choice of management to reduce the risk of malignant transformation [8]. However, excision has not

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been proven to reduce the risk of melanoma [9]. In the past, dermabrasion was sometimes performed, resulting in a less elevated and more lightly pigmented CMN [3].

Lasers such as Q-switched ruby, Q-switched alexandrite, carbon dioxide (CO_2) have also been used to treat CMNs, but the recurrence of pigmentation is an issue because of the persistence of the nevus cells [10].

Laser devices are utilized for epidermal and dermal pigmented skin diseases [11,12], and these devices may be categorized into ablative and pigment-specific [13]. The management of CMNs with lasers, however, remains controversial, mainly because of the absence of evidence on their efficacy and safety concerns. Some state that lasers may decrease the risk of malignancy by reducing the melanocytic mass, while others are concerned about the potential carcinogenic risk of sublethal laser damage [9,14].

A novel and safe technique known as heat dermabrasion with a diathermal needle was introduced by Sharquie for the treatment of different types of acne scarring and nose volumeplasty for a bulky nose under local anesthesia in one session with minimal or no adverse effects, and proved its safety [15-19].

The aim of the present study was to find a new and easy technique for the removal of congenital nevi, which thus avoids excision and possible grafting or flaps.

PATIENTS AND METHODS

The following was a prospective, interventional, surgical procedure in which five patients with a CMN were treated during the period from January 2013 through October 2018—3 (60%) females and 2 (40%) males. Their age ranged from 5 to 16 years with a mean of 12 years.

A proper history was taken, including the sex and age, the duration of disease and the age of onset, the associated symptoms, and the past medical and drug history.

A full clinical examination was performed to identify the site, size, color, and associated signs.

The study followed the principles of the Declaration of Helsinki and a formal written consent was obtained from each patient's parents before the surgical procedure, after explaining in full the method of intervention, possible complications, follow-up, prognosis, and need for before-and-after treatment photographs at the same place, at a constant distance, and in the same lighting.

The patients were prepared by cleaning the site of the nevus and the adjacent area with 70% alcohol, waiting several minutes until it dried, then moving an impregnated gauze with normal saline repeatedly over the same area in different directions for further cleaning and sterilization. After local anesthesia, heat dermabrasion was performed with a diathermal needle until complete debulking was achieved and bleeding points appeared. Topical povidone was applied twice daily with oral antibiotics to be seen after two weeks. Then, follow-up visits were scheduled for every two months for four months.

The patient's satisfaction with the response after the treatment was assessed as follows: 1) full satisfaction, 2) partial satisfaction, 3) no satisfaction.

Data was described statistically in terms of range, mean, frequency (no. of cases), percentage (%), and male-to-female ratio.

RESULTS

The location of the nevi in all cases was the face and the size was variable, ranging from 1 to 17 cm. (Table 1).

In 4 (80%) cases, there was a complete clearance of hyperpigmentation after heat diathermy, while, in one patient, there was a marked reduction in hyperpigmentation, but not a complete clearance of the largest. Nonetheless, the hair density in the treated nevus was reduced.

No important side effects apart from mild pain, transient edema, and crust formation were observed at the end of two weeks of the treatment session.

Erythema was observed at the sites of nevi after two weeks and then gradually went to normal during four months of follow-up, leaving minimal scarring. No relapses were observed during the follow-up period and

Table 1: The age of the patient and the site and size of the CMN

Case No.	Age (yrs.)	Site	Size (cm)
1	13	Right side of the face	3
2	12	Left side of the face	7.5
3	16	Forehead combined with an adjacent epidermal nevus	17
4	5	Nose/right side	1
5	14	Lower left eyelid/upper part of the left cheek	2.5

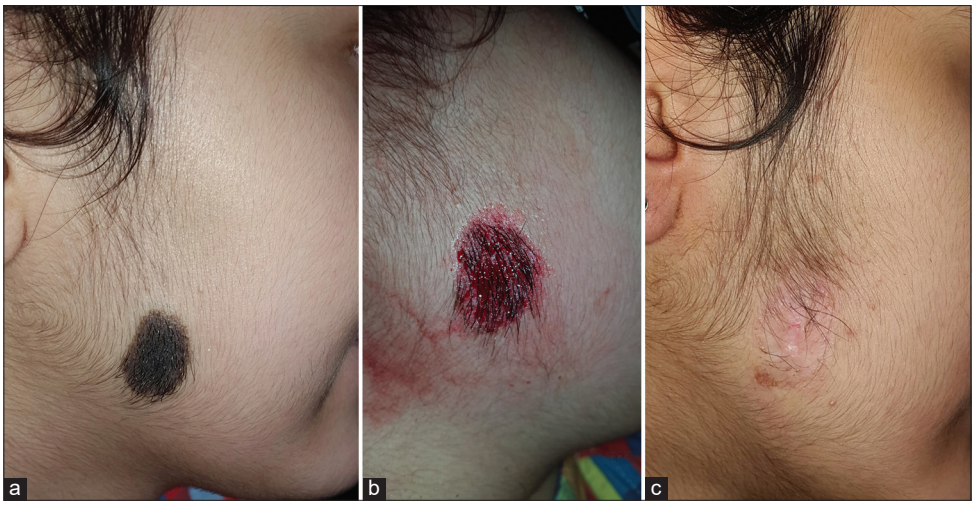

Figure 1: Thirteen-year-old female with a medium-sized CMN on the right side of the face (a) before treatment, (b) at the end of treatment, and (c) two months after treatment.

no further patient visits to the treating doctor to record any complications or relapses. Repigmentation was not noted during the follow-up period. In one patient, who was a relative to the treating doctor, the follow-up period was around five years with no relapses or complications. In all patients, there were marked cosmetic results and full satisfaction was achieved in all patients.

Figs. 1 –2 show photos of the patients prior to the session, at the end of the session, and during the follow-up period. While one patient showed CMN on the forehead superimposed and neighboring epidermal nevus (Fig.3).

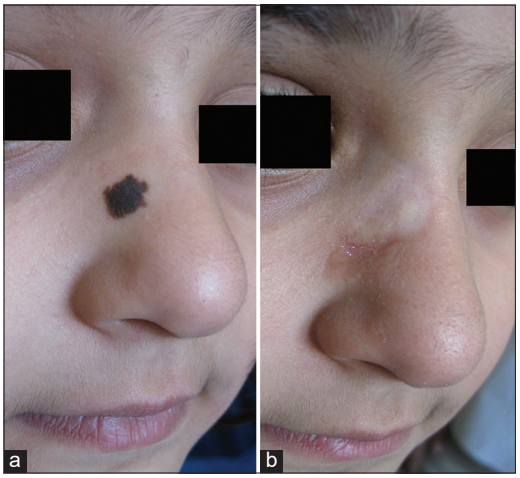

Figure 2: Five-year-old female with a small CMN on the right side of the nose (a) before treatment and (b) four months after treatment.

DISCUSSION

Numerous methods and techniques to treat CMNs exist. One early is surgical excision. Complete nevus excision has been used to reduce the risk of malignancy [8]. However, surgical excision has not been proven to decrease the risk of MM [9]. Furthermore, CMNs may be too large to be completely removed with surgery, and excision may lead to unwanted cosmetic results, such as scarring and restrictions in joint mobility [9]. Besides, surgical excision is costly and requires experience in nevus excision, grafting may be needed, especially in large and giant CMNs, and general anesthesia may sometimes be required. As with any surgical intervention, the possible complications involved with surgical excision need to be considered, such as bleeding, infection, and the risks entailed by general anesthesia.

Mechanical dermabrasion has sometimes been performed in the treatment of CMNs [3]. This technique might be effective but often requires general anesthesia, especially with large nevi. Also, the procedure is bloody and messy, as using a brush causes blood contamination to the surroundings, possibly leading to the transmission of infection from the patient to medical staff. The post-dermabrasion area is usually tender, thinner, and more fragile, and repigmentation may occur [20,21].

Although Q-switched, CO_2, and other lasers have also been used in the treatment of CMNs, they are also risky. A laser is costly and requires protection for the doctor's and the patient's eyes, considerable experience, numerous sessions to achieve the final, cosmetically acceptable outcome. The use of lasers for the management of CMNs remains controversial, mainly because of the absence of evidence on their efficacy and safety concerns [9,14]. Pigment lasers have been shown

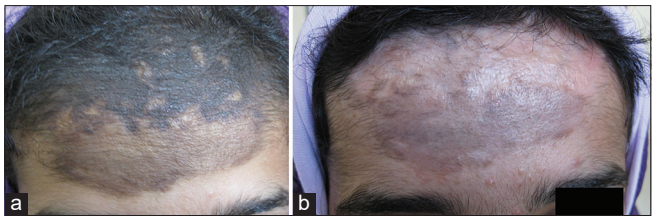

Figure 3: Sixteen-year-old female with a medium-sized CMN on the forehead combined and superimposed with an epidermal nevus (a) before treatment and (b) four months after treatment.

to bear a high rate of repigmentation, in up to 54% of patients. Also, ablative lasers are associated with a high incidence of complications, such as hypopigmentation and hypertrophic scarring [22]. Even then, the use of heat dermabrasion as an innovative technique in the present work produced only mild scarring during the follow-up period and gave a satisfactory cosmetic appearance, with full patient satisfaction during one session.

Heat dermabrasion is a safe technique, as it was used in the treatment of facial acne scarring in 250 patients with 35% TCA peeling, and no complications such as hypertrophic scars or keloids as the face skin is rich in skin appendages such as hair follicles and sebaceous glands. Nevertheless, one should be cautious of the chin and mandibular areas as these show a more marked tendency for scarring [23]. Still, to achieve minimal scarring after congenital nevi, heat dermabrasion would be more acceptable than excision and suturing or excision and grafting. This new technique is also safer and less costly than an ablative laser or mechanical dermabrasion [9,14,20-22].

No patient had a nevus recurring or complications such as hypertrophic scars or keloids after the follow-up period.

The limitations of this study were a small number of cases and a limited follow-up period. Therefore, more clinical data and lengthened follow-up periods are required to prove the safety of this novel treatment and record any possible relapses.

CONCLUSION

This is a simple, easy, non-costly, innovative technique that uses heat dermabrasion to treat small and medium-sized CMNs, avoiding excision and suturing with or without grafting or flaps. The heat of diathermy removes most or all residual melanocytes that could not be cleared by dermabrasion. Neither complications nor relapses were observed during our follow up-period.

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

Effect of platelet-rich plasma on diffuse effluvium in post-COVID-19 infection

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ABSTRACT

Since the beginning of the COVID-19 pandemic, dermatologists are increasingly often seeing cutaneous changes in patients who are positive or who have already recovered from the disease. What is particularly striking is the increasing number of patients who suffer from increased hair loss sometime after recovery from COVID-19. We present twenty cases of a post-COVID-19 infection with anagen effluvium treated with platelet-rich plasma (PRP). A total of three treatments were performed, one each month. After the second treatment, the patients noticed reduced hair loss and, after the third treatment, the condition had almost returned to normal. Due to the increasing number of cases of hair loss after COVID-19 infection, we have ascertained a connection between the two diseases. The treatment of our choice is safe and produces minimal side effects.

Key words: COVID-19; Anagen effluvium; Platelet-rich plasma

INTRODUCTION

Since the beginning of the COVID 19 pandemic, we have witnessed major changes in our daily lives. The world has faced a challenge that necessitated strict measures and changes in the daily activities of every kind. Dermatologists are increasingly often seeing cutaneous changes in patients who are positive for COVID-19 or who have already recovered from the disease. Those who were infected with the virus experienced immense psychosocial and physiologic stress [1]. What is particularly striking is the increasing number of patients consulting dermatological clinics due to increased hair loss sometime after recovery from COVID-19. Some studies suggest the possibility of COVID-19 infection being a significant trigger for effluvium, but the use of ivermectin, hydroxychloroquine, azithromycin, or other medications for COVID-19 cannot be ruled out, and the global pandemic itself is a source of psychosocial stress [1].

The hair growth cycle follows three phases. At any given moment, around 85% of hair follicles are in the growing phase, 5% are resting, and 10% are shed. In a situation of acute stress or other triggering factor, more than 50% of hair follicles may enter the telogen phase. A clinical presentation and the evidence of a well-defined trigger are almost always diagnostic of effluvium and do not require a biopsy [2].

Anagen effluvium occurs after an injury to the hair follicle, impairing its mitotic or metabolic activity. Chemotherapy, toxic chemicals, radiation, and some inflammatory diseases are also capable of diminishing the metabolic activity of hair follicles, resulting in anagen hair loss [3]. In the treatment of effluvium, it is essential to identify and remove the causative factors as well as to administer medications such as corticosteroids, minoxidil, and novel treatments such as CNPDA (caffeine, niacinamide, panthenol, dimethicone, and an acrylate polymer) [4].

Due to the frequent issues with hair loss in patients after COVID-19 and effluvium persistent for longer than normal, we chose treatment with platelet-rich plasma (PRP). PRP has been used for some time for hair

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diseases with great efficiency and its use is becoming an increasingly acceptable solution for dermatologists.

PRP therapy is an excellent treatment for impaired hair growth as it affects almost all essential components required for the survival of hair follicles: keratinocytes, stem cells, arrector pili muscles, blood vessels, and neural cells [5].

CASE REPORT

Herein, we present twenty cases of a post-COVID-19 infection with anagen effluvium. All were previously confirmed with a COVID-19 infection by PCR and were in a mild-to-moderate clinical state. They were examined by a dermatologist for diffuse effluvium two months after being diagnosed with the coronavirus. Serological examination was performed on all of them and only seventeen showed elevated levels of IgG for SARS-CoV-2. In all patients, dermatological examination revealed a diffuse loss of hair volume without defined alopecic patches. In all patients, the diagnosis was made on the basis of a clinical examination, a trichogram, and trichoscopy. A trichogram revealed a large proportion of dystrophic anagen hair.

We treated 16 females and 4 males with PRP. A total of three treatments were performed, one each month. Before treatment, the patients were advised not to take medications that might prolong bleeding, such as aspirin or nonsteroidal anti-inflammatory drugs. It was also necessary for each patient to wash their hair well at home before treatment. We used the local anesthetic lidocaine and then carefully injected PRP. The entire treatment took around 25–30 minutes. After the treatment, the patients were not allowed to wash their hair for 48 hours. For pain, they were advised to use acetaminophen. No patient complained of more serious side effects other than mild scalp numbness. After the second treatment, the patients noticed reduced hair loss and, after the third treatment, the condition had almost returned to normal. After the final administration of PRP injection, the patients graded their level of satisfaction from 1 to 5 (1: unsatisfied; 2: poorly satisfied; 3: sort of satisfied; 4: satisfied; 5: very satisfied).

DISCUSSION

Anagen effluvium is most commonly caused by chemotherapy, but may also be caused by bleomycin, dactinomycin, daunorubicin, fluorouracil, methotrexate, azathioprine, bismuth, levodopa, colchicine, albendazole, cyclosporine, and possibly strontium ranelate and pegylated interferon alfa-2a/ribavirin therapy [6,7]. The causes of anagen arrest also include radiation therapy, endocrine diseases, alopecia areata, cicatrizing disease, trauma, and pressure [8].

Anagen effluvium is usually self-limiting and normalizes within several weeks, although in some cases hair loss is prolonged and presents a considerable problem for the patient. However, we are witnessing a number of patients experiencing issues with hair loss after a COVID-19 infection and six months after healing.

PRP is a simple and effective method of treating all types of non-scarring alopecia and may be considered an option in the treatment of these patients. PRP is derived from the centrifugation of the patient's own blood and contains growth factors working on different target cells that influence wound healing, thereby playing an important role in tissue repair mechanisms, enhancing soft tissue healing and regeneration at various levels [9].

CONCLUSION

Due to the increasing number of cases of hair loss after COVID-19 infection, we have ascertained a definite connection between these two diseases. Hair loss may be due to the toxic effect of the infection on the hair follicle, but the drugs used to resolve the condition and the stress that the pandemic brings may play a role in the pathogenesis.

The treatment with PRP that we chose is safe and produces minimal side effects. In all our twenty patients, we achieved satisfactory results, with reduced hair loss after the second treatment and complete normalization after the third treatment. Patient satisfaction was 4.15 on average (graded from 1 to 5).

The role of stress in hair loss during the COVID-19 pandemic is also discussed by many patients with this problem but without a history of COVID-19.

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

BAP1 mutation in a patient with oculocutaneous albinism

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ABSTRACT

Dermatologists and dermatopathologists are uniquely positioned to identify BRCA1-associated protein (BAP1)-related cutaneous diseases. Recognition of BAP1 mutations is critical to patients and their families to assure they are appropriately counseled and screened for malignancy. A twenty-year-old male with a history of oculocutaneous albinism type 2 (OCA2) and basal cell carcinoma (BCC) presented to the dermatologist for a full-body skin examination. A 7 mm erythematous papule on the left upper back was biopsied and found to be a BAP1-inactivated melanocytic tumor (BIMT). To our knowledge, this is the first case of oculocutaneous albinism of any type and a BAP1 germline mutation presenting in the same patient.

Key words: Albinism; BAP1; BAPoma; OCA2; Oculocutaneous

INTRODUCTION

The term *albinism* refers to a number of diseases unified by the genetic inheritance of reduced melanin production. Oculocutaneous albinism (OCA) encompasses a number of autosomal recessive inherited diseases in which melanin production is absent or reduced in various ectodermally derived tissues, including the eyes, skin, and hair [1]. OCA2 is the most prevalent type of OCA worldwide [2]. The reduction in melanin manifests itself in increased actinic damage and, subsequently, increased incidence of squamous cell carcinomas (SCCs), BCCs, and melanomas in these patients [3-5].

Mutations in the BAP1 tumor-suppressor gene are inherited in an autosomal dominant pattern and predispose families to the development of various cutaneous neoplasms, including BCC, BAP1-inactivated melanocytic tumor (BIMT), and cutaneous melanoma. Beyond cutaneous diseases, this mutation also puts patients at higher risk for internal malignancies, including uveal melanoma, renal cell carcinoma, and malignant mesothelioma [6,7]. Dermatologists and dermatopathologists are uniquely positioned to identify BAP1-associated cutaneous diseases. Recognition of BAP1 mutations is critical to patients and their families to assure they are appropriately counseled and screened early for malignancy. Herein, we present a case of oculocutaneous albinism type 2 and a BAP1 germline mutation in the same patient.

CASE REPORT

A twenty-year-old male with a history of oculocutaneous albinism type 2 and basal cell carcinoma (BCC) presented to the dermatologist for a full-body skin examination. The examination was notable for a depressed and elongated 4 mm papule on the left nasal bridge as well as a 7 mm erythematous papule on the upper left back (Fig. 1). The lesions were anesthetized and two shave biopsies were performed in the typical fashion.

Histopathology of the lesion on the left nasal bridge revealed BCC. Histopathology of the lesion on the upper left back revealed a predominantly intradermal, compound, melanocytic proliferation with nuclear pleomorphism, multinucleated cells, and rare mitoses

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(Fig. 2a). BAP1 immunostaining revealed no staining of the involved melanocytes (Fig. 2b). A diagnosis of a BAP1-inactivated melanocytic tumor (BIMT) was confirmed.

Subsequent immunostaining of the patient's BCC on the left nasal sidewall (Fig. 3a) revealed diminished staining for BAP1 (Fig. 3b), further supporting an inherited BAP1 germline mutation. Mohs surgery and a simple excision were performed for the BCC and BIMT, respectively. The patient was referred to an ophthalmologist and for a clinical genetics program at our institution.

DISCUSSION

Oculocutaneous albinism type 2 (OCA2) is an autosomal dominant disease caused by mutations in the OCA2 gene (formerly known as the P gene) on chromosome 15q11. The function of the P protein is yet to be outlined in detail but research suggests a likely role in regulating the pH of various organelles as well as facilitating glutathione accumulation within vacuoles [1]. Hypopigmentation seen in a small subset of patients with Prader–Willi syndrome (PWS) and Angelman syndrome (AS) represents a form of OCA2 as a result of contiguous imprinting deletions of chromosome 15q, which includes the OCA2 gene [8].

In the U.S., the overall prevalence of OCA2 is estimated at around 1:36,000, but is much higher in individuals of African descent [2]. The clinical spectrum of OCA2 is broad. Young patients show some pigmentary dilution of the hair, skin, and iris. Although pigmented melanocytic nevi and lentigines commonly develop in sun-exposed areas, patients have little to no ability to tan and, thus, tend to sustain a large burden of actinic damage over their lifetimes [1,3]. This actinic damage, and the subsequent cutaneous mutation burden, manifests itself in an increased incidence of skin cancers, including SCC, BCC, and melanoma in these patients [3-5].

BRCA1-associated protein (BAP1) is a gene on chromosome 3p encoding a deubiquitinating enzyme. This enzyme has been shown to play a role in multiple cellular processes, including cellular differentiation, transcription, regulation of the cell cycle, and DNA repair [9]. Mutations and deletions in BAP1 were first reported in association with breast and lung cancers. Wiesner and colleagues described a tumor predisposition syndrome involving BAP1 mutations

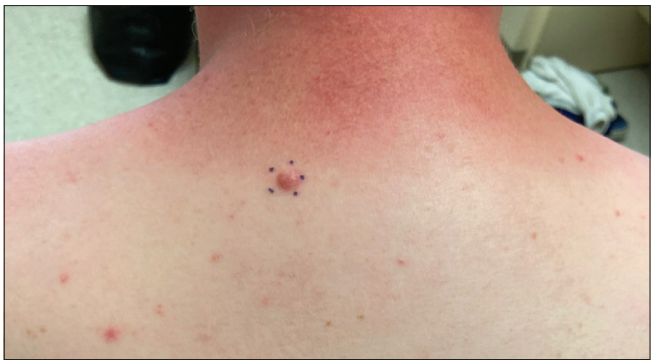

Figure 1: A 7 mm erythematous papule on the left upper back.

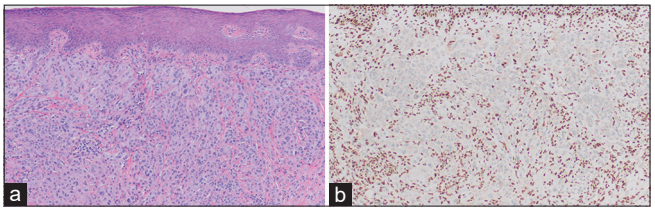

Figure 2: (a) Closely apposed nests of large, oval melanocytes with eccentric nuclei and admixed lymphocytes in the lesion on the upper back (H&E; 10×). (b) A notable lack of staining of spitzoid melanocytes comprising the bulk of the tumor on the upper back; positive staining of keratinocyte nuclei in the overlying epidermis, lymphocytes, as well as smaller adjacent melanocytes (BAP-1 immunostaining; 10×).

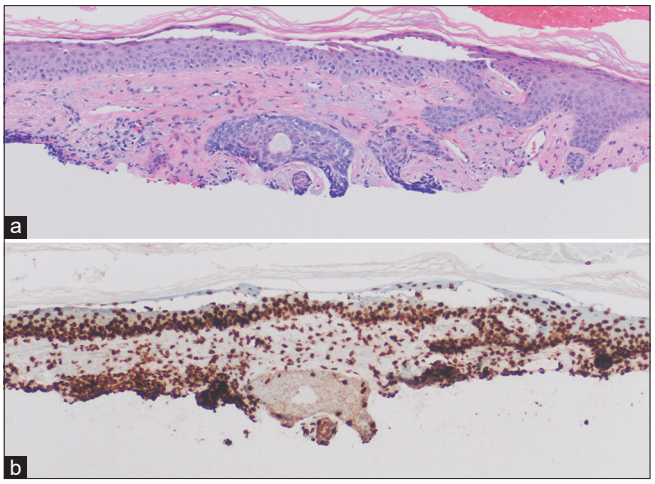

Figure 3: (a) Basal cell carcinoma on the nasal sidewall (H&E; 20×). (b) Diminished BAP-1 staining of the lesion on the nasal sidewall (BAP-1 immunostaining; 20×).

inherited in an autosomal dominant pattern. Most notably, this syndrome includes the development of 5-50 skin-colored, red, and brown dome-shaped papules during the second decade of life [10].

The nomenclature of this neoplasm is still debated and terms to describe it include BAP1-inactivated melanocytic tumor (BIMT), melanocytic BAP1-mutated atypical intradermal tumor (MBAIT), atypical Spitz tumor (AST), a cutaneous atypical and epithelioid

melanocytic lesion, BAPoma, a melanocytic nevus/tumor with a BAP1 mutation, and a Wiesner nevus.

Histopathology of the tumor is partially reminiscent of the Spitz nevus, but the characteristic features of Spitz nevi, including epidermal hyperplasia, Kamino bodies, clefting adjacent to nested melanocytes, hypergranulosis, and spindled melanocytes, are normally absent in BIMT [11]. It is challenging to reliably distinguish a BIMT from a spitzoid melanoma and research has demonstrated a significant lack of interobserver agreement, even among experts [12].

Continued studies on families with germline BAP1 mutations have further described this tumor predisposition syndrome. In addition to BIMTs, these patients have increased risk of uveal and cutaneous melanomas, mesothelioma, lung adenocarcinoma, clear cell renal cell carcinoma, and BCC [6,7].

Although commonly following a benign course, there is still insufficient data to predict the clinical behavior of BIMTs, and a simple lesion excision is usually recommended. More importantly, early recognition and diagnosis of BIMTs aids in establishing an underlying germline mutation in BAP1 and facilitates early screening and detection of malignant neoplasms in the patient and their family. An awareness of this clinical entity and the underlying BAP1 tumor predisposition syndrome uniquely positions dermatologists and dermatopathologists to identify this high-risk cohort of patients [13].

CONCLUSION

To our knowledge, this is the first case of oculocutaneous albinism of any type and a BAP1 germline mutation appearing in the same patient. This unfortunate coincidence of an increased UV-induced mutation burden (secondary to OCA2) and a tumor predisposition syndrome (germline mutation in BAP1) theoretically put our patient at an even greater risk of developing malignant cutaneous and ocular disease throughout his life. We are planning to continue with aggressive screening and close monitoring by both dermatology and ophthalmology. Our patient was adopted and, thus, family counseling was not necessary. Further studies are needed to determine if mutations in both the OCA2 and BAP1 genes are purely coincidental or if there are other factors increasing the probability for the co-occurrence of these mutations.

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

Pathomimia among children provoked by deodorant spray: 2 new cases

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ABSTRACT

Pathomimia is defined as a fictitious disease caused consciously by the patient themself and for which they deny responsibility. We report two new cases of children with atypical clinical pathomimia. Two girls of 11 and 14 years of age with no particular medical history, but with family conflicts, presented a similar clinical appearance: painful erythemato-bullous lesions on the left upper limb and the abdomen. Lesions appeared one after another leaving rounded hypochromic scars. All lesions were in accessible areas. The results of the questionnaires answered by the mothers show that the two girls had been using spray deodorant frequently. The diagnosis of pathomimia by cold burn due to misuse of deodorant spray was suspected. A dermatological and child psychiatry support was set up. There have been few cases of pathomimia by cold burn caused by misuse of deodorant spray. It, therefore, seems necessary to report these cases.

Key words: Pathomimia; Pathomimia among children; Cold burn; Misuse of deodorant spray

INTRODUCTION

Factitious disorders are reported in approximately 1% of patients seen in psychiatry [1]. Pathomimia is a type of fictitious disorder caused consciously by the patient themself and for which they deny all responsibility [2]. Pathomimia is rare among children. We report two new cases of children with atypical clinical pathomimia caused by deodorant spray.

CASE REPORT

Case 1: A 11-year-old female with no history of illness, including psychiatric diseases, consulted for erythematous bullous lesions of the flexion face of the left upper limb, which appeared one after another from the distal area of the forearm to the shoulder over a period of 4 days. A dermatological examination found lesions in a layered arrangement along the limb resulting in crusty lesions, then rounded and linear hypochromic scars (Fig. 1).

Case 2: A 14-year-old girl, with no particular pathological history, consulted for a sudden appearance, in an interval of 15 days, of multiple lesions of different age, erythematous and erythematous bullous painful center on the left upper limb and abdomen and some lesions on the leg. The lesions quickly gave way to crusty lesions, then rounded hypochromic scars. All these lesions were located in accessible areas and at the contralateral level of the dominant hand (Figs. 2 and 3). The patient had benefited, before consulting us, from a skin biopsy objectifying epidermal necrolysis evoking a bullous fixed pigmented erythema but there was no medication taken reported by the patient herself or her family.

For the two patients, we noted the presence of recent school-associated difficulties with significant family

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conflicts. An interview with the two mothers revealed that the two girls had frequently been using deodorant sprays. Faced with this important detail, which adds to emotional vulnerability and to the family conflicts reported by the family, the typical aspect of burn injury and the arrangement of the lesions only in accessible areas made us suspect the diagnosis of pathomimia by cold burn due to misuse of deodorant spray. Dermatological and child psychiatric care was implemented for the two patients. Dermatological care involving occlusive dressings based on petrolatum and healing creams was prescribed (Fig. 4). This had led to the appearance of new lesions on the right forearm in the second case. The dressings were maintained even after the lesions had healed in order to avoid any manipulation or recurrence. On the psychological level, collaboration with child psychiatrists was established. The 14-year-old patient had to be hospitalized in a child psychiatry unit for 5 days, revealing deep psychological damage. During this period, the patient presented no new lesions. The two patients were lost to follow-up; case 1 after two consultations and case 2 after leaving the child psychiatry service.

DISCUSSION

This paper reports two cases for their didactic value, the diagnosis of which was mistaken leading to abusive assessments. Cutaneous pathomimies involve the creation of skin self-lesions: the pathomime intervenes on the body. These lesions, secondary to external actions, are maintained and repeated, while the patient denies any participation in their creation and maintenance. Once the lesions are installed, the patient asks to be cured. The dominant motivation for taking action is repeatedly wanting to be recognized as sick [2]. The clinical

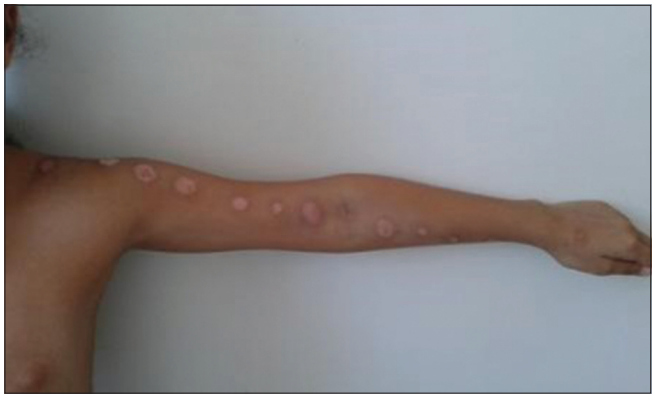

Figure 1: Rounded and linear hypochromic lesions arranged on the left upper limb.

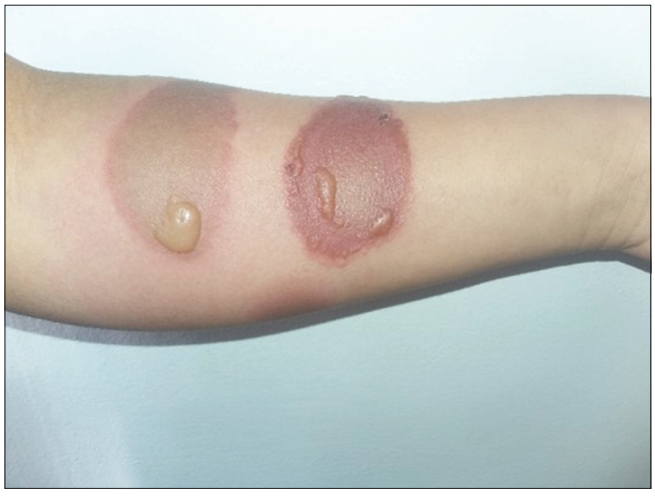

Figure 2: Erythematous bullous lesions on the left upper limb.

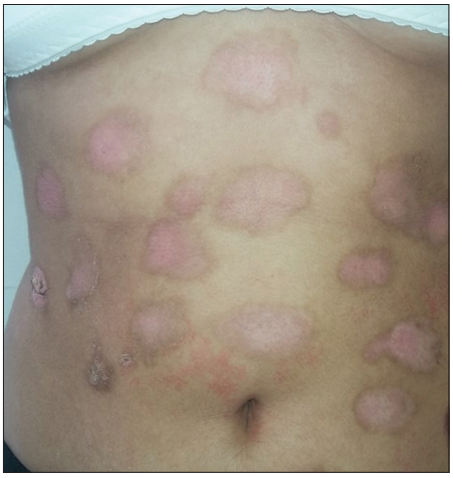

Figure 3: Lesions on the abdomen quickly giving way to crusty lesions, then rounded hypochromic scars.

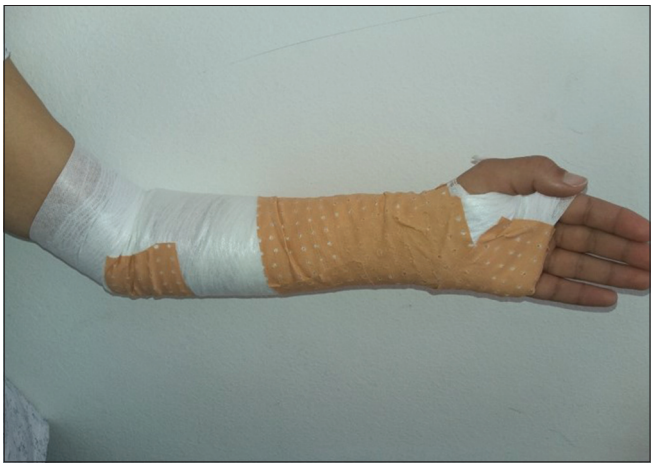

Figure 4: Dressing treating and covering of the lesions.

picture is often stereotyped with bizarre linear or geometric lesions on accessible areas—the face, neck, hands, forearms—and a fuzzy clinical history [3]. Defontaine-Catteau specifies three attitudes: beautiful indifference, demonstration, and the maintenance and aggravation of lesions [4]. On the psychopathological level, we find elements in favor of relatively poor mentalization, search for love or rejection of the regressive type, indifference to the symptom, emotional dependence, impulsivity, mystification, aggressive sadomasochistic impulses, fragile narcissism, and mechanisms of denial defenses [2]. In the literature, there are few cases of infantile pathomimia, in these children as in ours; we often observe academic difficulties and a family life in crisis [3]. Cutaneous pathomimia in children represents around 1 in 23,000 consultations and nearly 1 in 785 consultations in pediatric dermatology, according to a Mexican study. Childhood pathomimia mainly affects prepubescent girls with an average age of 12 years (2–18 years). The history with the family and the child is often fuzzy, and there are no symptoms or associated prodrome. Diagnosis is often late, delayed by the absence of consultation or by an incorrect diagnosis. In addition, almost half of the patients do not attend a second consultation [5]. The clinical spectrum extends from surface erosion most frequently, to hyper- or hypopigmented lesions, excoriations, ulcerated lesions created by physical or chemical agents; infectious skin lesions such as abscesses or cellulitis by injection of contaminated material, nail granulomas, lymphedema by chronic restriction of a limb, contusion, necrotic, purpuric eczematiform lesions, to a more advanced stage of scabs and scars [5-6]. A cohort published in 2018 was able to report only 56 cases of pathomimia by use of spray, including children and adults. The team demonstrated that the median age of this type of patient was 13 years, that 70.5% were females, and that the median time before consulting was 6 days. Two subgroups were identified: a group that inflicted injuries on themselves in a group known as the *courage test* and a group that inflicted injuries on their own indicating psychological distress [7]. It should be noted that the use of a spray from a distance of 5 cm for a period of 30 seconds lowers the temperature by 15°C, which causes cold burns responsible for lesions similar to those in our two patients [8]. Anxiety and depression are the most frequently noted conditions, followed by personality disorders in patients with pathomimia [9]. Treatment of such children is special. Forced disappearance of lesions is possible by occlusive dressing, with the possible consequence of the appearance of similar lesions elsewhere on the body [10], an attitude that we adopted in our patients and that led to the appearance of new lesions on the right forearm in the second case. The main difficulty lies in psychological care. It is not advisable to confront the child directly. The best attitude remains to hide from the child that one has understood [6]. Indeed, the immediate proposal for a psychiatric consultation can be perceived as a rejection on the part of the doctor with a risk of worsening the lesions especially when the child is confronted [5] or can scare the patient away. Nevertheless, the need for a psychiatric consultation is obvious [6].

CONCLUSION

Skin pathomimia among children is a rare diagnosis and one of elimination. The diagnosis should be suspected if skin lesions are not consistent with any dermatosis and if the lesions are located in areas accessible to the dominant hand. It is a psychopathological manifestation that is difficult to manage and requires cooperation between a dermatologist and a child psychiatrist.

Consent

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

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Our Dermatology Online

Case Report

Collision tumor: Merkel cell carcinoma and sebaceous carcinoma overlying Bowen's disease

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ABSTRACT

Collision tumors are the rare lesions in which two or more histopathologically distinct tumors coexist with distinct morphological features. Herein, we present the case of an 89-year-old male under clinical surveillance for multiple previous head and neck lesions. The patient presented himself with a forearm lesion, which was excised and proven by histopathology to be a collision tumor: Merkel cell carcinoma and sebaceous carcinoma were overlying Bowen's disease. Although the patient was treated with a further wide local excision, the lesion reappeared and, despite his treatment with radiotherapy, the patient died from complications. Most combinations of collision tumors involve a basal cell carcinoma (BCC) and a melanocytic nevus. A similar case has not yet been described in the literature. The etiology of collision tumors remains unknown.

Key words: Collision tumor; Sebaceous carcinoma; Merkel cell carcinoma; Bowen's disease

INTRODUCTION

Collision tumors are rare in the dermatology literature and refer to lesions in which two or more histopathologically distinct tumors coexist with distinct morphological features [1], including Merkel cell carcinoma and sebaceous carcinoma overlying Bowen's disease.

Merkel cell carcinoma represents a rare neuroendocrine tumor with an incidence rate of 0.7 cases per 100,000 in the U.S. [2]. These carcinomas are associated with a high rate of local recurrence, around 21% [3], and often develop metastatic disease. On the first presentation, 26% and 8% show nodal and distant disease, respectively [4].

Sebaceous carcinomas are likewise rare tumors, with a predominance toward males (0.32 per 100,000) when compared to females (0.16 per 100, 000) [5]. These most commonly occur in the upper eyelid [6] and are tumors are associated with a 16% recurrence rate and a 20% metastatic rate [7].

Bowen's disease, also known as carcinoma *in situ*, is slow-growing and responds favorably to local treatment modalities. If untreated, the lesions have the potential to transform into invasive squamous cell carcinoma, in approx. 3–5% of cases [8].

CASE REPORT

An 89-year-old male had been under clinical surveillance for six years for multiple head and neck lesions—squamous cell carcinoma (SCC) and actinic keratoses—which were fully excised. Comorbidities included osteoarthritis, glaucoma, Klinefelter syndrome, previous DVT, and paroxysmal atrial fibrillation.

During treatment for another facial SCC, the patient had a rapidly growing lesion on the right forearm, which was simultaneously excised under local anesthetic.

Histology of the lesion on the forearm revealed a collision tumor, involving a Merkel cell carcinoma and a

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sebaceous carcinoma overlying Bowen's disease, which was completely excised.

The overlying epidermis showed proliferative squamous cell carcinoma *in situ* (Bowen's disease), which was fully excised (Figs. 1 and 2).

The case was discussed in a skin multidisciplinary team (MDT) meeting after the excision. The collision tumor on the forearm had to undergo a further wide local excision with 20 mm margins of the collision tumor on the forearm and five-year clinical follow-up were recommended. CT staging was organized.

Two weeks later, the lesion was widely excised with a 2 cm margin. Histology from this wide excision revealed residual islands of Merkel cell carcinoma with no evidence of sebaceous carcinoma or Bowen's disease. A small nodule of Merkel cell carcinoma was still abutting the peripheral resection margin. The deep resection margin was clear and another local resection was advised.

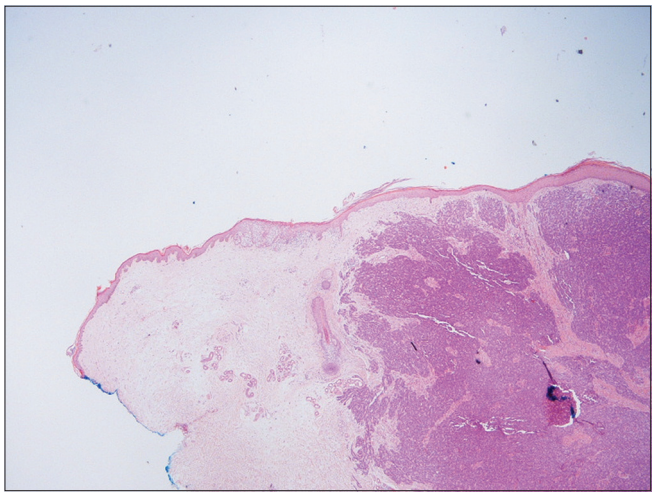

Figure 1: Merkel cell carcinoma on the left consisting of expansile nodules and sheets of round cells occupying the dermis and extending deep into the reticular dermis and squamous cell carcinoma *in situ* (Bowen's disease) in the overlying epidermis on the right (H&E).

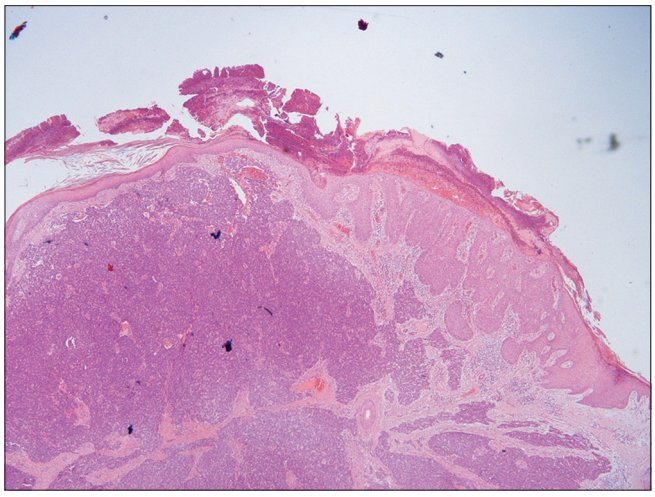

Figure 2: Merkel cell carcinoma on the right and sebaceous carcinoma on the left within the epidermis.

Following the re-excision, a further MDT discussion recommended radiotherapy of the local region. On the next treatment appointment, the patient had a local recurrence of the tumor, 4 × 3 cm in size at the distal end of the forearm wound.

A CT scan revealed that the tumor had spread locally to the axilla with extensive lymphadenopathy in the right subpectoral, right axillary, and right lateral chest wall lesions, but also extending up into the lower right neck. No definite lung, liver, or adrenal metastases were evident on imaging.

The patient underwent a ten-day course of palliative radiotherapy, which finished prematurely due to the COVID-19 pandemic. Then, the patient felt increasingly unwell and passed away with complications of the disease and sepsis 43 days later.

DISCUSSION

Cutaneous collision tumors are rare. A PubMed search reveals approx. 38 references of case series and reports describing 40 cutaneous collision tumors and 3 retrospective studies describing a total of 234 lesions [9,10]. Most combinations involve basal cell carcinomas (BCCs) and melanocytic nevi or melanocytic nevi and seborrheic keratoses [11]. Among the case reports and case series, only three describe collision tumors with more than two tumors within the same lesion.

Merkel cell carcinoma has previously been described with squamous cell carcinoma [12], lentigo maligna [13], and basal cell carcinoma [14]. A collision tumor involving Merkel cell carcinoma and sebaceous carcinoma has only been described in one other report: a report from 2009 on a 61-year-old Japanese male with a lesion on the eyelid [15].

As per the diagnosis and treatment of Merkel cell carcinoma, the European consensus-based interdisciplinary guidelines claim that "there is no formal evaluation of excision margins in the literature." However, the European Association of Dermato-Oncology (EADO) and the European Organization

for Research and Treatment of Cancer (EORTC) recommend a 1-to-2 cm excision margin [16]. Additionally, only in patients with clinical evidence of regional lymph node involvement should a lymph node biopsy be conducted. The report recommends a follow-up every four months during the first three years, then every six months for up to five years. However, this article describes the management of patients with metastasis as well as local disease. Merkel cell carcinoma is thought to be caused by UV light and Merkel cell polyomavirus is also implicated [17].

In the case of sebaceous carcinoma without orbital involvement, the recommended surgical therapy typically involves the excision of the visible tumor plus 5–6 mm of the surrounding healthy tissue in all directions [18]. Follow-up is recommended for at least five years [19].

A sebaceous carcinoma may be associated with Muir–Torre syndrome (MTS) in cases with mutations in DNA mismatch repair genes, resulting in microsatellite instability [20] and visceral cancers, most commonly breast and colorectal.

The etiology of collision tumors remains unknown, potentially sharing a common carcinogen (UV light). Immunodeficiency has also been suggested to play a part, as well as embryology and common derivatives of cells.

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

Cutaneous squamous cell carcinoma (cSCC) arising from a chronic skin fistula: A case report

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ABSTRACT

Squamous cell carcinoma (SCC) of the skin is the second most common form of skin cancer, characterized by abnormal, accelerated growth of squamous cells. We describe an unusual case of cSCC developing in a 38-year-old patient with a chronic skin fistula of the knee after a trauma in childhood. Multiple surgical biopsies were taken from the tumor site, which revealed the development of cutaneous squamous cell carcinoma. MRI revealed a tumor located on the skin. The patient was treated with a large surgical resection of the tumor with safety margins. A histological examination revealed a well-differentiated cSCC. After three years of follow-up, no recurrence was observed. The development of cSCC in a chronic skin fistula of the knee is rare. The diagnosis is often made by histological examination of biopsies. Malignant transformation should be suspected in a chronic skin fistula with recurrent episodes of inflammation, repeated purulent discharge, poor healing, and a chronic fistula.

Key words: Cutaneous squamous cell carcinoma; Chronic knee fistula; Chronic inflammation of the skin

INTRODUCTION

Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) are the first and second most common types of skin cancer, respectively. Other significant skin lesions are actinic keratosis and melanoma.

Actinic keratosis and basal cell carcinoma are easily excised and have a very good prognosis, whereas cSCC has a poor prognosis, especially if it invades the lymph nodes and adjacent structures.

It may also appear in any area of the skin, especially in areas exposed to the sun. It may develop on healthy skin as well, but is, still, more likely to develop on damaged skin.

The literature has proposed ultraviolet-light exposure, genetics, carcinogens, immunosuppression, and trauma as etiologies [1].

Squamous cell carcinoma (SCC) occurs when DNA damage from exposure to ultraviolet radiation or other damaging agents trigger abnormal changes in squamous cells.

The clinical suspicion of cSCC in a chronic skin fistula of the knee is low, leading to a delayed diagnosis and treatment.

We report an extremely rare case of cSCC developing in a 38-year-old male with a chronic knee fistula after a childhood knee trauma.

CASE RREPORT

A 38-year-old male presented himself with a traumatic history of the right knee without fracture at 6 years of age. The right knee had developed a secondary infection with a chronic fistula showing discontinuous purulent discharge. The patient had received discontinuous

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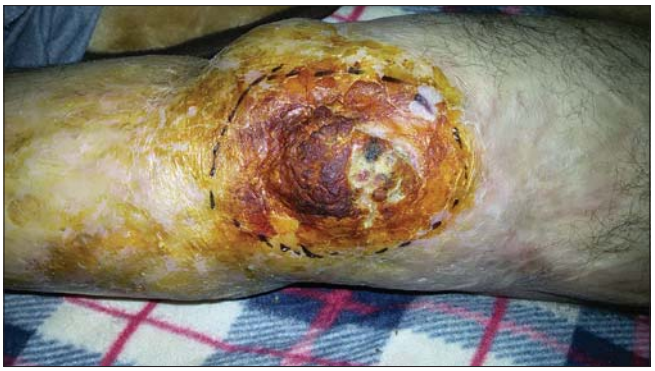

Figure 1: An image showing a cutaneous squamous cell carcinoma of the knee with excision limits.

antibiotic treatments for thirty years. The past medical history was unremarkable.

A physical examination revealed a budding crusty ulcerative lesion 3 × 3 cm in size and a skin fistula with purulent discharge on the right knee formed by chronic inflammation (Fig. 1).

An examination of the lymph nodes showed no inguinal lymphadenopathy or other lymphadenopathy.

The patient underwent a surgical biopsy of the skin at 38 years of age.

The pathological diagnosis was cutaneous squamous cell carcinoma (cSCC) of the knee.

MRI revealed a skin lesion of the right knee located on the skin below the patella without locoregional invasion (Figs. 2 and 3).

The clinical diagnosis based on the imaging findings and the pathological diagnosis was SCC arising from a chronic skin fistula after childhood trauma of the knee. Staging for nodal disease was negative.

The patient underwent wide surgical excision of the tumor with safety margins.

On a four-year follow-up, the patient was doing well and revealed no local recurrence or distant metastasis.

DISCUSSION

The skin is a unique epithelial tissue covering the body and providing physical and biological surface protection. It is composed of three layers: the epidermis, the dermis, and the subcutaneous layer.

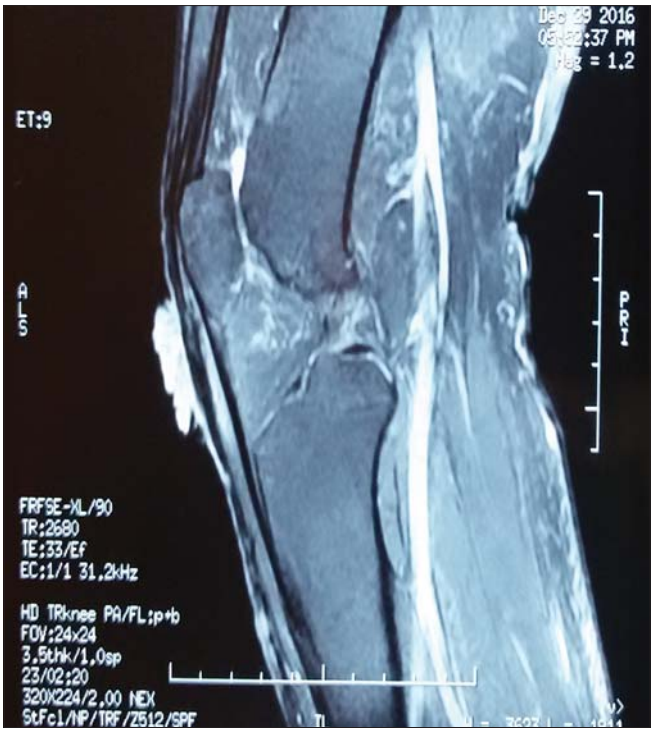

Figure 2: MRI of the knee showing a localized tumor in the skin.

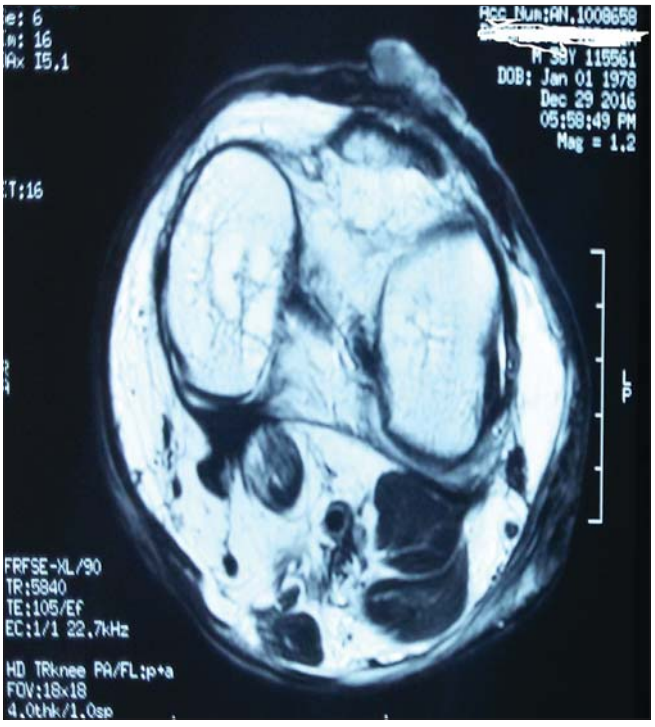

Figure 3: Cross-sectional MRI of the knee showing a localized tumor in the skin.

There are four major types of skin malignancies: basal cell carcinoma, squamous cell carcinoma, melanoma, and non-epithelial skin cancers [2].

Cutaneous squamous cell carcinoma (cSCC) arises from malignant proliferation of epidermal

keratinocytes. cSCC is the second most common skin cancer in the U.S., representing around 20% of all skin cancers [3-5].

The risk factors of skin carcinogenesis include chronic cutaneous inflammation, viral infection, ultraviolet radiation (UVR), and other inflammation-inducing agents and traumas [6,7].

Squamous cell carcinoma most commonly appears after the age of 50 in areas of past sun exposure and typically occurs in males with light skin and light eyes and with a history of UV solar radiation exposure. However, anyone with a history of significant UV exposure, whether from past medical treatment or the sun, is at an increased risk. Squamous cell carcinoma is also considerably prevalent in patients who are immunosuppressed and, in these patients, may develop into aggressive subtypes [8-10].

UV radiation is accepted as the major risk factor for squamous cell carcinoma of the skin.

Tanning lamps, therapeutic UV exposure, and ionizing radiation are all well-known risk factors for the development of squamous cell carcinoma.

Extrinsic factors, such as ultraviolet light from sun exposure, are linked to cSCC, while intrinsic factors, such as the use of antioxidants, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) [11], are reported to reduce the risk of developing the disease [12].

It is now clear that pro-inflammatory immune cells play an important role in skin cancer development.

Chronic inflammation is linked to the development and progression of multiple cancers, including those of the lung, stomach, liver, colon, breast, and skin. Inflammation not only drives the oncogenic transformation of epithelial cells under the stress of chronic infection and autoimmune diseases, but also promotes the growth, progression, and metastatic spread of cancers.

Inflammation is characterized by the infiltration of plasma and leukocytes to tissues, which undergo disrupted homeostasis. The causes of inflammation range from pathogenic infection and tissue injury to tissue stress and malfunction, but the process of inflammation may bring detriment to the host, depending on the nature, duration, and magnitude of the inflammatory response elicited during infection or disease.

The pathophysiology of malignant degeneration of chronic wounds and irritation has been elucidated [13]. Chronic irritation and injury of the skin cause constant epithelial regeneration and ulceration, leading to dysplasia and eventual carcinoma.

The sites of chronic inflammation at risk of cSCC development are diverse and include scars, burns, chronic ulcers, sinus tracts, and inflammatory dermatoses, such as lichen sclerosus and atrophicus [14], but cSCC after a knee trauma and a chronic skin fistula in the knee are rare.

SCCs may appear as scaly red patches, open sores, rough, thickened or wart-like skin, or raised growths with a central depression. At times, SCCs may crust over, itch, or bleed. The lesions most commonly arise in sun-exposed areas of the body, but may also occur in other areas of the body, including the genitals.

A biopsy should be performed on any lesion suspected of being a cutaneous neoplasm.

All patients suspected of or diagnosed with a cSCC should undergo a regional LN examination. Any enlarged nodes should be examined histologically either by fine-needle aspiration or an excisional biopsy.

Common therapies for invasive cSCC include surgical excision, electrodesiccation and curettage (ED&C), Mohs surgery, cryotherapy, and radiation therapy [15].

Surgical excision is the primary treatment option [16,17]. The current mainstay treatment is complete surgical clearance of the lesion with histologically clear margins. Knowing that the majority of SCCs may easily and successfully be treated, if allowed to grow, these lesions may become disfiguring, dangerous, and even deadly, or may become invasive and grow into the deeper layers of the skin and spread to other parts of the body. On the other hand, because of the rate of metastasis from locally recurrent tumors arising from sun-damaged skin, the selection of the right treatment for each primary tumor is crucial to avoid unnecessary critical outcomes.

The optimal treatment may be determined by a multidisciplinary team involving input from a dermatologist, Mohs surgeon, surgical oncologist, vascular surgeon, and radiation oncologist, especially for complicated cases. A multidisciplinary evaluation may guide treatment decisions in order to minimize risk without compromising efficacy.

Tumor-positive nodes should be managed by aggressive surgical resection of all local and regional disease.

The addition of adjuvant radiation to lymphadenectomy may result in higher healing rates, which Veness reported to be 73% five-year disease-free survival (DFS) [18]. Thus, early detection of nodal metastasis may improve the outcome of a high-risk cSCC.

The use of chemotherapy in the management of a high-risk cutaneous cSCC remains relatively unexplored.

Regular follow-up after treatment is necessary, including physical examination and palpation of lymph node areas. The appearance of a cSCC should be documented histologically and treatment determined by a multidisciplinary team.

CONCLUSION

The cSCC is less common than basal cell carcinoma (BCC), but the number of reported SCC cases has been steadily increasing.

Cutaneous squamous cell carcinoma (cSCC) may develop on sites of chronic inflammation, including chronic skin fistulas.

The development of a cSCC in a chronic skin fistula of the knee is rare. Symptoms are usually attributed to chronic inflammation and diagnosis is often reached late by a histological examination of biopsies. Therefore, malignant transformation should be suspected in a chronic skin fistula of the knee, with recurrent episodes of inflammation, repeated purulent discharge, and poor healing. A histopathological study of multiple biopsies allows making an accurate diagnosis of cSCC and initiate surgical excision, with or without adjuvant radiotherapy as the appropriate 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.

Statement of Informed Consent

Informed consent for participation in this study was obtained from the patient.

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Our Dermatology Online

Case Report

Submandibular tumor mass revealing a primary basaloid squamous cell carcinoma of the parotid gland

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ABSTRACT

Primary squamous cell carcinoma of the parotid gland is a rare neoplasm characterized by a rapid growth and an aggressive clinical course. Basaloid squamous cell carcinoma is yet much rarer and has a dark prognosis. Through a new case report we'll discuss anatomo-clinical features and differential diagnoses of this entity. An 83-year-old man presented with recent neck swelling. He had parotidectomy. Microscopic examination showed a malignant proliferation invading glandular parenchyma. Tumor cells were arranged in nests with peripheral palisading. They were polygonal and cohesive with abundant eosinophilic dyskeratotic cytoplasm. Perineural neoplastic invasion was observed. On different samples there were neither mucoid component nor intermediate cells. Immunohistochemical staining showed positivity of tumor cells for Cytokeratin 5/6 and P63 antibodies. The diagnosis can be retained only if a metastatic squamous cell carcinoma of upper aerodigestive tract is ruled out. To the best of our knowledge this is the second case reported in literature so far.

Key words: Salivary gland; Squamous cell carcinoma, Basaloid type; Case report

INTRODUCTION

Primary squamous cell carcinoma of salivary glands is a rare tumor. These tumors represent about 0.1 to 1.6% of all parotid gland tumors [1,2]. Basaloid squamous cell carcinoma (BSCC) is a high grade aggressive variant composed of two types of atypical cells; basaloid and mature squamous cells. This variant occurs mostly in the base of the tongue, hypopharynx and supra-epiglottic area of the larynx [3]. BSCC of the parotid gland is exceptional and to the best of our knowledge the present case is the second one reported in literature so far [4]. Through a new case report we will discuss clinical and pathological characteristics and differential diagnoses of this extremely rare tumor.

CASE REPORT

An 83-year-old male patient, without particular medical history outside a 30-pack-year smoking history, presented with left latero-cervical tumor mass. The patient reported general state alteration and rapid growth of the tumor. On physical examination the mass measured 5 cm in diameter. It was firm and seemed to be developed in the left parotid gland. At this level, skin was slightly glossy without bonding or ulcerations. No facial palsy was noted. Otherwise physical examination was normal. Sonography showed a hypoechogenic poorly circumscribed mass measuring 43 mm in diameter developed in the left parotid gland.

During surgery the tumor was tough infiltrating the sternocleidomastoid muscle (SCMM) and "sheathing" ipsilateral internal jugular vein and external carotid artery. Left total parotidectomy extended to the SCMM was made. Facial nerve was preserved.

Gross examination found expanded parotid gland measuring 7 cm in largest diameter with a pendant

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muscle flap. Cut surface showed a poorly circumscribed white grayish tumor measuring 45 mm in diameter. The tumor outcropped surgical margins.

Microscopic examination revealed a carcinomatous proliferation invading glandular parenchyma made of nests and cribriform clusters with comedonecrosis (Fig. 1). Tumor cells were large, polygonal and cohesive with abundant eosinophilic cytoplasm occasionally dyskeratotic. Tumor cells had peripheral palisading (Fig. 2). Perineural neoplastic invasion was observed (Fig. 2; insert). On different samples there were neither mucoid component nor intermediate cells.

Fat and muscular tissues around the parotid gland and surgical margins were invaded indicating incomplete surgical resection. Immunostaining showed positivity of tumor cells for: Cytokeratin 5/6 and P63 antibodies. Tumor cells stained negatively for Her2neu. Therefore, the diagnosis of BSCC was retained.

The patient had adjuvant radiation therapy with positive evolution retrospectively.

DISCUSSION:

Primary squamous cell carcinoma of the parotid gland is a rare tumor. Usually it's the metastasis of a squamous cell carcinoma of upper aerodigestive tract or a local extension of a cutaneous squamous cell carcinoma of head and neck. The presence of a glandular and/or intermediate component of a high grade mucoepidermoid carcinoma, not interested in sampling, is not rare. This should be kept in mind by pathologists since it's the most frequent parotid gland carcinoma [5].

BSCC is defined by the World Health Organization classification of head and neck tumors as an aggressive variant of high grade carcinoma that grows quickly with dark prognosis and both local and distant metastases. However, evolution depends on the tumor site (oral cavity, sinuses, hypo-pharynx) according to some cases reported in literature [6].

Medical history of radiation therapy in the area of head and neck is likely to be the main risk factor. Alterations in metaplastic cells of salivary gland ducts due to radiation therapy seem to have a key role in the pathogenesis of BSCC [5,7,8]. This is not the case of our patient who had no radiation therapy before. Smoking is not a proven risk factor of parotid gland

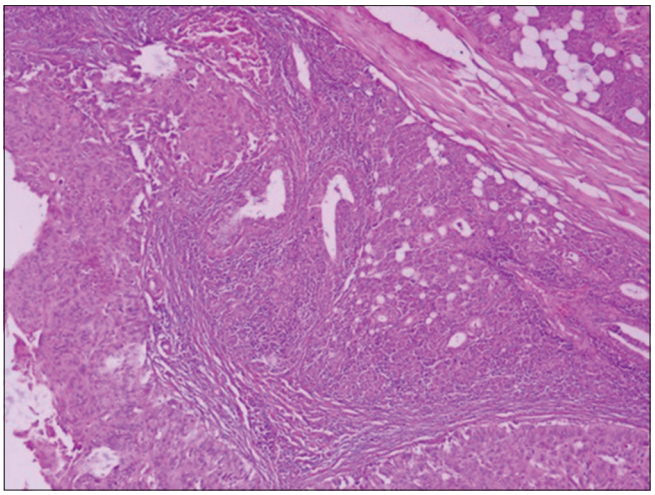

Figure 1: Atypical cells arranged in nests and cribriform clusters with comedonecrosis invading glandular parenchyma.

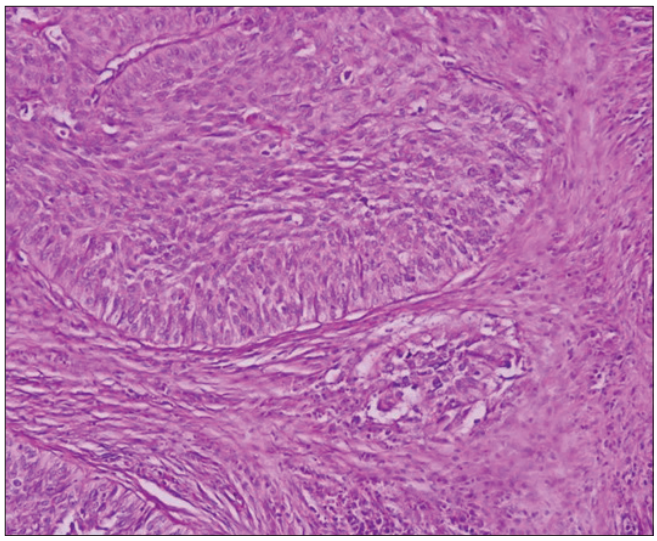

Figure 2: Large and cohesive malignant cells with abundant eosinophilic cytoplasm showing peripheral palisading (insert: Perineural neoplastic invasion).

squamous cell carcinoma in opposite to squamous cell carcinoma of upper aerodigestive tract [9]. BSCC is oftentimes positive for Human Papilloma Virus (HPV). HPV seems to be associated with a particular type of carcinoma seen usually in males in the fourth decade of life and is commonly of better prognosis with positive clinical course after radiation therapy [4,9].

The diagnosis of BSCC could be only made by pathologists. The tumor is made of basaloid-type cells with regular elongated oval nuclei. Tumor cells are arranged in lobules with peripheral palisading [4]. A cribriform pattern with comedonecrosis is commonly seen. Intracellular hyaline deposit is usually seen which mimics other salivary gland tumors. Less frequently

spindle-shaped cells and pseudo-rosettes might be observed. In situ or infiltrative conventional squamous cell carcinoma may be associated [6]. Basaloid tumor cells are commonly positive for Pan-Cytokeratin (AE1/AE3, CAM5.2), heavy molecular weight cytokeratin (34BétaE12) and EMA staining. The major part of basaloid carcinoma is positive for P63 staining [3].

Main differential diagnosis is mucoepidermoid carcinoma with squamous predominant component. Broad sampling is necessary to perceive the presence of Periodic Acid-Schiff stain positive mucoid component or intermediate cells in order to rule out a high grade mucoepidermoid carcinoma. Seeking cytoplasmic intermediate filaments (tono-filaments) and intracytoplasmic desmosome-like structures on ultrastructural studies permit to make the right diagnosis. Peripheral palisading may lead to think of basal cell carcinoma which is rare in salivary glands. In fact, the presence of keratinization usually straightens the diagnosis [6]. BSCC should be distinguished from other rare tumors such as hybrid tumors, undifferentiated carcinoma and metaplastic carcinoma of the salivary gland [7,8]. Once metastatic squamous cell carcinoma of upper aerodigestive tract is ruled out the diagnosis of primary BSCC of the parotid gland may be retained. BSCC requires complete surgical excision and lymph node dissection with or without adjuvant radiation therapy [4].

In conclusion, primary squamous cell carcinoma of the parotid gland is a rare malignant neoplasm of rapid growth and aggressive clinical course. BSCC is yet much rarer and has a dark prognosis. The diagnosis of BSCC can be retained only if a metastatic squamous cell carcinoma of upper aerodigestive tract, which is more frequent, is ruled out. Despite the development of imaging and radical surgical excision techniques, the prognosis of BSCC remains dark.

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

Mucous membrane pemphigoid (cicatricial pemphigoid) with autoreactivity to salivary gland neurovascular bundles

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ABSTRACT

Mucous membrane pemphigoid (MMP) (historically called cicatricial pemphigoid), is a rare, chronic autoimmune disease with subepithelial blisters. The blisters predominantly involve the mucous membranes, but also may affect the skin; the primary autoantigens are directed against the basement membrane zone (BMZ). A 75-year-old female presented to her dermatologist for the presence of blisters in her mouth and severe orodynia. Lesional skin biopsies were taken for hematoxylin and eosin (H&E), direct immunofluorescence (DIF) and immunohistochemistry (IHC) staining. The H&E review revealed a subepidermal blister with predominantly lymphocytes in the blister lumen, and also surrounding dermal neurovascular bundles and salivary glands. Splitting of the salivary ducts was observed. The DIF and IHC revealed the presence of polyclonal deposits at the BMZ of both the dermal/epidermal junction and salivary glands. HLA DP, DQ, DR antigen was positive in the vessels feeding the salivary glands. We further demonstrate simultaneous reactivity to other oral structures. The overall autoreactivity observed may explain the clinical scarring and compromise of salivary gland function often seen in MMP.

Key words: Mucous membrane pemphigoid; Salivary glands; Neurovascular bundles; Mesenchymal-endothelial cell junctions

Abbreviations: Mucous membrane pemphigoid (MMP); Hematoxylin and eosin (H&E); immunohistochemistry (IHC); Direct immunofluorescence (DIF); Basement membrane zone (BMZ); fluorescein isothiocyanate(FITC); 4',6-diamidino-2-phenylindole(DAPI); Human leucocyte antigen (HLA)

INTRODUCTION

Mucous membrane pemphigoid (MMP) represents a group of autoimmune blistering diseases affecting primarily the mucous membranes, and occasionally the skin [1-4]. For decades, the disease was titled cicatricial pemphigoid, including membranous lesions with or without skin lesions. MMP usually occurs after the fifth decade of life and produces scars due to involvement of the basement membrane zone (BMZ). The oral mucosa is affected in more than 90% of cases, but other mucosal areas can be affected. Ocular lesions may result in blindness and oral lesions may cause severe airway obstruction. Though oral and ocular mucosae can both be affected in one patient, patients with only oral involvement tend to have a benign outcome [1-4]. A diagnosis requires clinical history, an H&E lesional biopsy and direct immunofluorescence (DIF) and/or immunoblotting studies to demonstrate a linear deposition of immunoglobulins (IgG and/or IgA, and or complement component 3c (C3c), at the BMZ. The target antigens vary; subsets of patients affected exclusively by oral and ocular mucosal disease have autoantibodies against α-6 and β-4 integrins, respectively [1-4].

CASE REPORT

A 75-year-old female presented to her dermatologist for the presence of blisters in her mouth and severe

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orodynia. The physical exam revealed eroded blisters in the mouth with erythema and edema (Fig. 1a). Skin biopsies for hematoxylin and eosin (H&E) staining, for IHC and DIF were obtained. Our IHC and DIF processing were performed as previously described [5]. A diagnosis of MMP was reached, and the patient received systemic treatment with corticosteroids and mycophenolate, resulting in lesional improvement. The patient was later sent for a multidisciplinary consultation with a dentist, ophthalmologist, otolaryngologist, gynecologist, and gastroenterologist. For our DIF, we classified the findings as negative (-), weakly positive (+), positive (+++) and strongly positive (++++). IHC double staining was performed using a Leica Bond Max platform autostainer. Specifically, for red staining we utilized a bond polymer refined red detection DS9390, an alkaline phosphatase linker polymer and fast red chromogen. For brown staining, we utilized bond polymer refined detection DS9800, a horseradish peroxidase linker polymer and DAB chromogen, all from Leica (Buffalo Grove, Illinois, USA). Positive and negative controls were consistently run. We utilized antibodies against HLA-DP, DQ, DR antigen, clone CR3/43, and CD45 clones 2B11 + PD7/26, both from Dako-Agilent (Carpinteria, California, USA).

The H&E tissue sections revealed a subepithelial blister (Fig. 1b). Within the blister lumen predominantly lymphocytes were present, with occasional neutrophils and eosinophils. Within the dermis, a mild, superficial, perivascular infiltrate of lymphocytes, plasmacytoid cells, histiocytes, and a few eosinophils and neutrophils were identified near neurovascular bundles (Fig. 1b). Of interest, salivary duct lumina were filled with lymphocytes and some histiocytes. When cutting the biopsies with the microtome, the tissue easily separated at salivary gland lumina. Dermal scarring was not appreciated.

The DIF showed separation of the salivary ducts, creating a cavity. We noted IgG, IgM, IgD, anti-human fibrinogen, anti-human albumin, anti-kappa, and anti-lambda all positive (++++) with a linear distribution at the basement membrane zone (BMZ) of the dermal-epidermal junction, and also at the salivary gland BMZs (Figs. 1c and d). Deposits were also noted around upper dermal neurovascular bundles, and in mesenchymal/endothelial cell junctions throughout the dermis. Interestingly, multiple dendritic-like cells in the dermis were positive with C1q (++++). The neurovascular bundles in the dermis were also positive for FITC conjugated IgA (+++), and Complement/C3 was noted in a linear distribution at the BMZ (+++).

HLA-DP, DQ, DR antigen was positive via IHC in the salivary gland ducts and neurovascular bundles (Fig. 1e). IHC also demonstrated CD45 positive clusters as part of the inflammatory infiltrate under the blister, and around the salivary glands and neurovascular bundles (Fig. 1f).

DISCUSSION

MMP is a chronic autoimmune disease of unknown etiology, frequently involving the oral cavity and

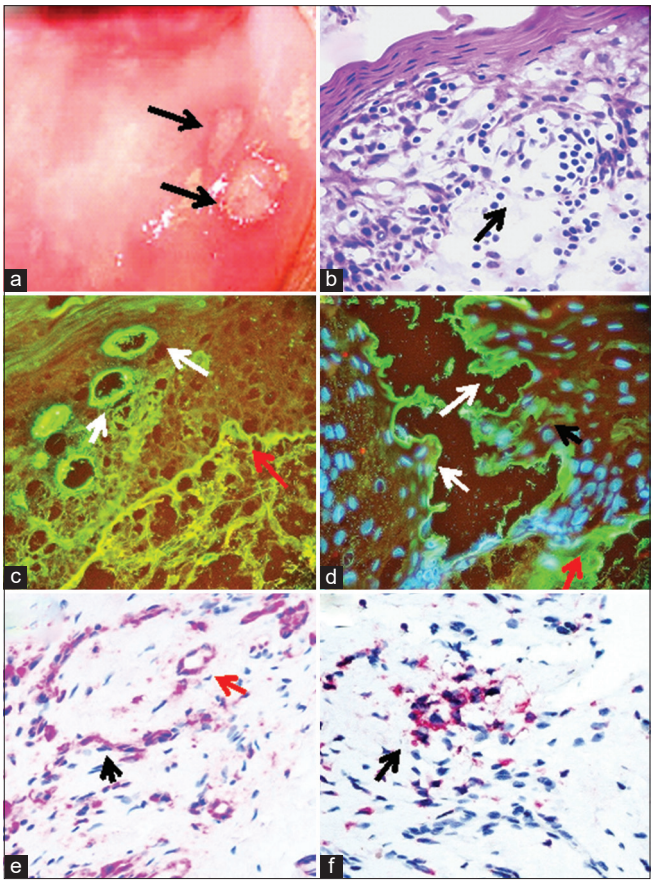

Figure 1: (a) Shows two superficial ulcers from sphacelated blisters on an erythematous oral mucosa. (b) H&E stain showing the subepidermal blister (black arrow) (400X). (c) DIF showing positive staining of a salivary gland duct in green using FITC conjugated fibrinogen (white arrows), as well as simultaneous staining at the BMZ (green staining; red arrow) (400X) (d) DIF showing positive staining of a split salivary duct with anti-human FITC conjugated antibody (green staining) (white arrows), and also shows a positive stain at the BMZ of the dermal-epidermal junction (green staining, black arrow) (400X). The nuclei of the cells were counterstained with DAPI (blue). (e) IHC using HLA DP, DQ, DR antigen shows positive staining in the vessels (fuchsia staining, black arrow) and the salivary glands (red arrow) (400X). (f) IHC using CD45 showing positive staining in the salivary glands (red staining, black arrow) (1000X).

sometimes the pharynx, larynx, esophagus, glottis, eyes (causing symblepharon) and genital mucosa [1-4]. Women are often more affected than men (ratio 2:1). The most common autoantigens described for MMP are bullous pemphigoid antigen 2 (BPAG2; BP180), bullous pemphigoid antigen 1 (BPAG1; BP230), integrins α6 and β4, laminin 5(laminin 332/epiligrin, α3β3, δ2 chain laminin), laminin 6 and type VII collagen [1-4]. It is characterized histologically by subepithelial blistering and by DIF featuring linear binding of IgG, IgA and C3 to the BMZ [1-4]. The predominance of mucosal involvement clinically distinguishes MMP from bullous pemphigoid. Consistent with our findings, other authors described three patients with cicatricial pemphigoid and positive immunofluorescence findings in the basement membrane zones of mucous glands in the pharynx, mouth, and nose [6,7]. The authors suggested that their findings were unique to cicatricial pemphigoid. In our case, the autoantibodies were present along the BMZ of the mucosal junctional zone, and the BMZs of the salivary glands and their ducts [6,7].

Here, we clearly demonstrate MMP autoantibodies to the basement membranes of salivary glands and their ducts, as well as to dermal neurovascular structures and the mesenchymal/endothelial cell junctions. These autoantibodies are present to multiple antibodies, complement, albumin and fibrinogen. Given our salivary gland findings, we suggest that their involvement could contribute to the scarring process.

Like ocular tears, saliva has a complex composition including electrolytes, immunoglobulins, proteins, enzymes, and mucins. Enzymes from the salivary glands begin to digest carbohydrates, enzymes from the stomach digest proteins, and enzymes from the exocrine glands of the pancreas digest carbohydrates, proteins, lipids, RNA, and DNA. Muscarinic acetylcholine receptors (mAChRs), including M1-M5 subtypes, are classic receptors in regulating water, ion, and solute transport in salivary glands [8].

MMP autoantibodies including IgG (97%), C3 (78%) IgA (27%), and IgM (12%) are directed against multiple antigens including bullous antigens 1 and 2, laminins 332 and 311, type VII collagen, α6 β4-integrin, and unidentified basal membrane zone antigens, highlighting a diverse molecular etiology including part of the cell junctions [9]. Elderly females are commonly affected, with a mean onset age of 50–80 years. The predominant mucosal sites involved are the oral mucosa, ocular mucosa, oropharynx, larynx, and genital region. Skin involvement is usually restricted to the regions of head, neck, and upper torso. A distinguishing feature of MMP is the scarring of the mucosa after the erosions and blisters heal.

CONCLUSION

Integrins are present in the salivary glands, particularly subunits beta 1, beta 3 and beta 4; this feature may explain our observed reactivity to the salivary glands [10]. The observed reactivity to the salivary glands may account for the frequent clinical scarring in MMP. Regarding the observed reactivity of the dermal neurovascular bundles, our experience when investigating multiple autoimmune skin diseases is that neurovascular bundles often demonstrate autoimmunity. In the current case we do not know the molecular etiology of this finding, warranting further studies.

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Our Dermatology Online

Case Report

Unexpected discovery of asymptomatic polycythemia vera in a patient with papulopustular rosacea caused by Demodex: A fortuitous association?

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ABSTRACT

Herein, we follow the case of a patient suffering from papulopustular rosacea caused by *Demodex* associated with polycythemia vera (PV), which was fortuitously diagnosed. Facial erythrosis must spark a suspicion of PV even if the case appears to be papulopustular rosacea caused by *Demodex*. This observation underlines the distinctive physiopathological processes of papulopustular rosacea caused by *Demodex* and that of PV; however, the dermatological clinical signs are similar. A skin biopsy does not allow us to differentiate the two pathological processes since only a blood sample analysis may exclude a diagnosis of PV. This case stresses the potential advantage of conducting systematic blood analyses for every patient presenting with clinical signs of rosacea, even of erythrodermic rosacea that does not respond to the classical therapeutics, to exclude the possibility of underlying asymptomatic PV. Dermatologists must be aware of the nonspecific dermal manifestations of this potentially fatal hematologic disorder.

Key words: Vaquez disease; polycythemia vera; papulopustular rosacea; erythrosis; *Demodex*

INTRODUCTION

Vaquez disease, or polycythemia vera (PV), is a chronic myeloproliferative neoplasm (NMP) with a prevalence of 1–3/100,000 persons. The median age of onset is sixty years, with a male-to-female ratio of 1:2 [1]. PV is a type of BCR-ABL-negative myeloproliferative syndrome similar to essential thrombocythemia, chronic myeloid leukemia, and myelofibrosis, which often originate from a genetic mutation affecting the normal activity of hematopoietic stem cells, resulting in clonal proliferation of mature yet abnormal cells [2].

PV is linked to the hyperproduction of erythrocytes through a mechanism independent of the rate of erythropoietin [3]. PV may remain asymptomatic for a long time, and a diagnosis may occur after a fortuitous discovery of polycythemia or after the manifestation of the nonspecific symptoms, such as fatigue, itching, and/or aquagenic pruritus and splenic enlargement [3,4]. The diagnosis is based on the WHO criteria [5]. Erythrosis is not a standard diagnostic criterion but may reveal the disease, as in our case.

CASE REPORT

A 59-year-old male consulted for persistent erythematous macules of the nose and cheeks with some erythrodermic papules (Fig. 1). The erythrosis had been present for two years but had been progressively worsening over the past several months. The patient had no remarkable medical history and did not express any specific complaints, except for moderated concomitant fatigue.

Clinical examination findings were normal. A biopsy was performed and favored granulomatous rosacea. Some follicular ostia were enlarged and keratotic, and contained *Demodex*. The upper dermis showed dilated vessels and a mostly lymphocytic infiltrate with periadnexal topography, infiltration of the epithelium,

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and sometimes small granulomas slightly separated from the follicles and made of epithelioid cells with some giant multinucleated cells (Figs. 2 and 3). Due to the complaint of fatigue, a routine blood test was performed. The results revealed hemoglobin at 23.6 g/dL (nle: 13–17), hematocrit at 75.9% (nle: 40–50), VGM at 78.7 μm^3 (nle: 80–99.8), MCH at 24.5 pg (nle: 27.5-34), a red blood cell count of 6,350,000/µL (nle: 4.30–6.1 million), hyperleukocytosis at 10300/µL (nle: 2100-7500), a platelet count of 485.10^3/µL (nle: 150–400), and a subnormal erythropoietin level.

A subsequent bone marrow biopsy showed hypercellularity, including prominent erythroid, granulocytic, and megakaryocytic proliferation. PCR molecular biology highlighted a mutation of exon 14 of V617F (71% of mutated alleles) and the absence of a mutation of exon 12 of the JAK2 gene. Abdominal echography revealed discrete splenomegaly without hepatomegaly. These results confirmed the diagnosis of a myeloproliferative syndrome with a PV type.

The treatment consisted of hydroxyurea 20 mg/kg/day and acetylsalicylic acid 80 mg, as well as bloodletting with the aim of obtaining a hematocrit under 45%. The demodicosis was treated locally with a cream containing 2% of benzyl benzoate with quick positive clinical results. One year later, the patient's erythrosis became more moderate.

DISCUSSION

PV is rarely mentioned in the differential diagnosis of papulopustular facial rosacea because of its low incidence and its atypical presentation. Rosacea is often mentioned as the first diagnostic hypothesis but has to be differentiated from other causes with vasomotor origin, related to medications or carcinoid tumors or mastocytosis. More frequently, rosacea has been differentiated from erythema pudicitae and menopausal hot flushes. Diabetes may also lead to the occurrence of facial erythema.

The clinical difference between PV erythrosis and rosacea is not always clear. If erythrosis is accompanied by pustules, a diagnosis of rosacea or lupus is most likely. Rosacea is physiologically characterized by vasodilation of blood and lymphatic vessels, by the induction of angiogenesis, and by local inflammation, in which colonization by *Demodex* is more likely than in the general population [6]. Local immunosuppressive factors may enable the proliferation of *Demodex*. These processes contribute to maintaining and amplifying clinical symptoms by positive feedback, as *Demodex* participates in inflammation by maintaining vasodilation and hence erythrosis, and secrete local

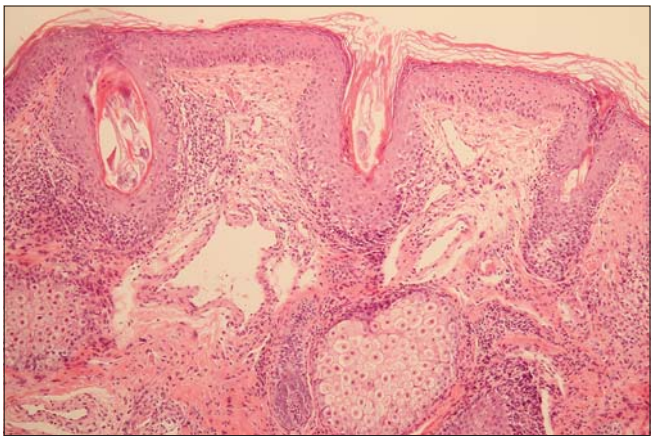

Figure 2: Superficial dermis with dilated vessels and periadnexal lymphoid cells (H&E, 50×).

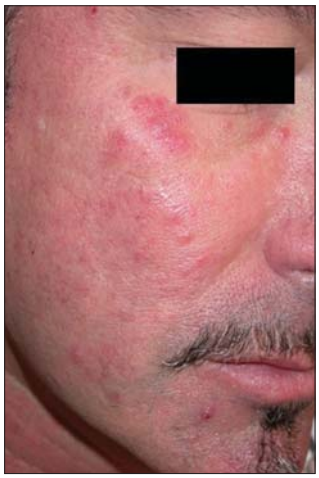

Figure 1: Persistent erythematous macules with erythrodermic papules of the cheek.

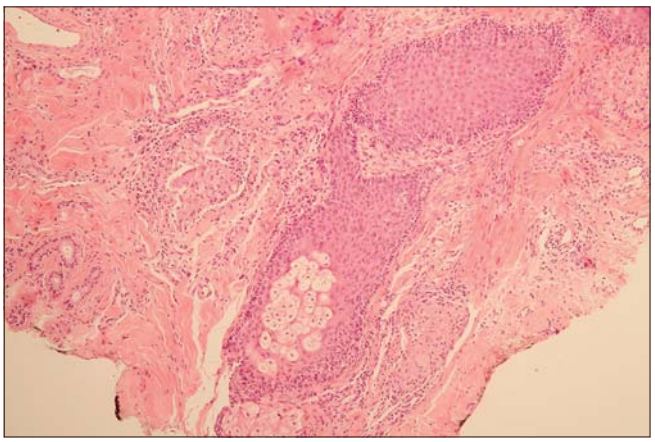

Figure 3: Lymphocytic infiltrate with mostly periadnexal topography, sometimes small granulomas constituted by epithelioid cells, with some giant multinucleated cells of the upper epidermis (H&E, 50×).

immunosuppressive factors favoring skin invasion by more *Demodex*, thus sustaining the inflammatory process [7].

The skin manifestations of PV, which may be clinically similar to those of rosacea, are secondary to polycythemia in the vascular flow. Because the blood vessels distend after reaching the large blood vessels of the internal organs, once the thickened blood reaches the skin capillaries, it may create a visible skin rash, which may be severe and deep, with or without telangiectasia. Some cases have been reported to have purpuric rashes, petechia, hemangioma, and an enlarged, thickened, red and cracked geographic tongue, cutaneous sarcoidosis, or granulomatous dermatitis [8-10].

Physiopathological parallelism may be drawn between these two entities: In both cases, erythema and telangiectasia may favor *Demodex* settlement in the skin, which contributes to the clinical symptomatology of rosacea [11]. It is impossible to differentiate these two pathologies only on the basis of a clinical examination and a skin biopsy. A hematological evaluation allows for a specific diagnosis of PV. The diagnosis of PV is important as, without adequate treatment, the survival period is estimated at merely 18 months, due to the high prevalence of thrombotic events. Venous or arterial thrombosis, hemorrhage, and transformation into myelofibrosis or myeloid leukemia are common complications of NMPs, such as PV.

CONCLUSION

In cases of suspected papulopustular rosacea or erythrosis rosacea, there is a need for differentiation from erythrosis linked to PV. A blood test allows for a specific diagnosis of PV. We postulate that vasodilation due to PV may promote the development of papulopustular rosacea in a sensitive patient. This case highlights the need for systematic blood testing in every patient presenting with clinical signs of rosacea, even of the erythrodermic kind, to exclude any underlying asymptomatic PV.

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

Dupilumab-induced facial erythema: Superior effect of a topical antifungal over oral

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ABSTRACT

Atopic dermatitis (AD) is a common disease that affects different age groups, ranging from mild to severe. For a patient with severe atopic dermatitis, systemic treatment options are limited and only one biological treatment is available: dupilumab. Dupilumab was initially approved by FDA for the treatment of adults with AD and recently approved for the treatment of adolescents with AD. As with approving other medications, some side effects are not reported before phase III trials. Thereby, we present a case of dupilumab-induced facial erythema treated with an oral and topical antifungal.

Key words: Dupilumab; Facial erythema; Redness; Atopic dermatitis

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory disease with an incidence of 10–30% in the pediatric population and 2–10% in adults [1]. Treatment is usually aimed to reduce the frequency and duration of flares in addition to symptomatic treatment. Most treatments are topical, treating mild to moderate AD and, until recently, systemic options treating severe AD have been limited. Dupilumab is considered a revolutionary medication in the treatment of AD, approved by the FDA (Food and Drug Administration) in March 2017 for the treatment of AD in adults. Furthermore, it was the first biological treatment approved for the treatment of AD [2,3]. In March 2019, it was approved by the FDA for the treatment of AD in adolescents [2]. Dupilumab is a fully-humanized monoclonal antibody that works by blocking a shared alpha receptor in interleukin 4 (IL-4) and interleukin 13 (IL-3), leading to an inhibitory effect, thus suppressing T-helper 2 (T_h2) inflammatory mediators, which are strongly involved in the pathogenesis of AD [4]. Dupilumab is considered a safe medication, with reported side effects that include local site reaction, antibody development, conjunctivitis, oral herpes simplex, arthralgia, and eosinophilia in order. Nevertheless, as with any other medication, some side effects are reported after phase III trials. Facial erythema was reported in several articles [5-10]. Herein, we report a case of facial erythema induced by dupilumab.

CASE REPORT

A 21-year-old male, a case of atopic dermatitis present since childhood, was managed initially with a topical steroid, to which he was partially responsive. The patient had extensive AD involving the entire body, including the face. He was given cyclosporin in 2018 with a good improvement. In August 2019, he was started on dupilumab—given its safety when compared with cyclosporin—with a loading dose of 600 mg subcutaneously (SQ), followed by 300 mg SQ every two weeks as an outpatient. The patient noted an improvement after the second dose. However, he reported the development of facial erythema. After two weeks of starting the medication, he experienced the exacerbation of the facial lesions, which unresponsive to

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topical steroids. On examination, ill-defined, non-scaly, dusky erythematous patches were present on the face and neck (Figs. 1a – 1c). After reviewing the literature, we encountered two similar cases responding well to oral itraconazole. Thus, the patient was started on itraconazole 200 mg PO every day for four weeks. After one week of starting itraconazole, the patient reported the improvement of the facial erythema (Figs. 1d – 1f). However, he had a relapse before finishing the course (Figs. 1g – 1i). He was, then, started on topical miconazole with hydrocortisone cream twice a day for fourteen days with complete clearance of facial lesions, with a persistent response several months after stopping miconazole and hydrocortisone cream (Figs. 1k – 1l).

In addition to the facial erythema, the patient had developed conjunctivitis and was seen in ophthalmology. This was managed with eye lubricants: ophthalmic

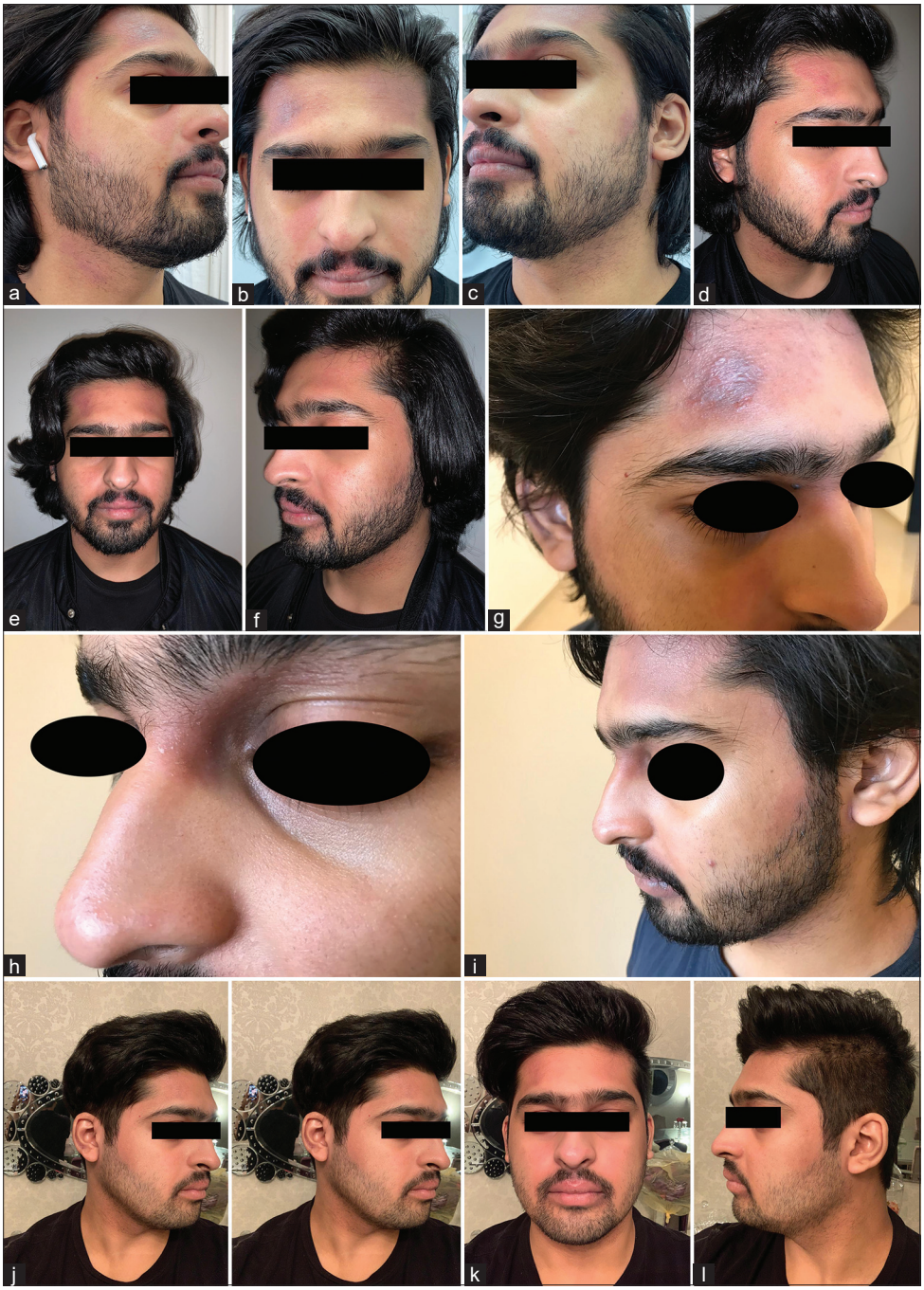

Figure 1: Dupilumab-induced facial erythema (a-c) two weeks after starting dupilumab, (d-f) with a partial improvement one week after starting itraconazole, (g-i) with a relapse after stopping oral itraconazole, and (j-l) with persistent results several months after stopping topical antifungal.

drops with 2% hyaluronic acid TID X 2 months in addition to tobramycin with dexamethasone ophthalmic solution TID for three weeks.

DISCUSSION

Dupilumab targets the alpha subunit of IL-13 and IL-14, thereby inhibiting T_h2 cytokines. It is used to treat T_h2-mediated diseases, mainly atopic dermatitis and bronchial asthma. The side effects reported by the pharmaceutical company include antibody development, local site reaction, conjunctivitis, eosinophilia, insomnia, and herpes simplex infection among others [2,10]. Nonetheless, facial erythema is not reported before phase III trials. We report this case to support the already reported cases and to show the superior results of topical antifungals over oral antifungals.

The exact pathomechanism of developing facial erythema is unknown [7]. However, the Malassezia spp. are believed to be involved, given the response to antifungals and the elevated level of serum *Malassezia*-specific IgE. It was hypothesized that T-helper 17 (T_h17) induced activation by dupilumab leads to the proliferation of the *Malassezia* spp. [6]. This might be counterargued, as the *Malassezia* spp. are part of healthy flora, yet the response to treatment supports this involvement. In our patient, the lesions were not scaly, thus scarping for a fungal culture was not done. Given the anatomic location, we preferred postponing the biopsy if no response was to be seen with oral and topical antifungals.

CONCLUSION

Based on our humble clinical experience, we suggest treating facial erythema with a topical antifungal initially, with a fungal culture from the scales if present. If no response is observed, we recommend adding oral itraconazole, thereby avoiding possible systemic side effects from oral itraconazole, with similar or even superior results. We also recommend delaying the biopsy, given the anatomical preference of this dermatosis, thus avoiding scars in a highly aesthetic area.

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

Coexistence of Parry–Romberg syndrome and lichen sclerosus et atrophicus in an adolescent female: A rare combination

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ABSTRACT

Parry–Romberg syndrome (PRS) is a rare form of localized scleroderma mainly affecting children and young adults, characterized by progressive hemifacial atrophy due to shrinkage and degeneration of tissues beneath the skin. Lichen sclerosus et atrophicus (LSA) is a rare chronic inflammatory skin disease that mainly affects preadolescent and perimenopausal females with anogenital and extragenital localization. Herein, we present a case of the coexistence of these two rare entities in a young adolescent female in the lower half of the face. To our knowledge, although there are numerous cases in the literature describing the coexistence of LSA and localized scleroderma, similar cases of the coexistence of PRS and LSA in the same site have not been discussed.

Keywords: Parry–Romberg syndrome; lichen sclerosus et atrophicus; extragenital lichen sclerosus; progressive hemifacial atrophy; localized scleroderma

INTRODUCTION

Parry–Romberg Syndrome (PRS) is considered an unusual variant of localized scleroderma [1], characterized by progressive hemifacial atrophy due to shrinkage and degeneration of tissues beneath the skin [2-5]. Cerebral disturbance of fat metabolism has been proposed as a primary cause. The syndrome usually manifests itself in the first decades of life, with a higher prevalence in females than males [4]. PRS may lead to serious deformities and, for this reason, immediate intervention is required in order to stop the progression of the disease.

Lichen sclerosus et atrophicus (LSA) is a rare chronic inflammatory skin disease that mainly affects preadolescent and perimenopausal females with anogenital and extragenital localization [6]. These patients develop characteristic shiny and pale atrophic plaques with concomitant pruritus and a burning sensation. LSA may coexist with other autoimmune diseases [7].

To the best of our knowledge, the cooccurrence of extragenital LSA with PRS in the same lesion is being discussed here for the first time in the literature, although the autoimmune nature of these two diseases may justify the simultaneous appearance of these disorders in the same patient.

CASE REPORT

A 14-year-old female presented with a five-month history of a solitary, sharply demarcated, pale, atrophic patch in the middle of the jaw, in conjunction with asymmetry and downward deviation of the lower lip (Fig. 1) and tongue (Fig. 2). A dermatoscopic examination of the lesion revealed findings compatible with those of follicular plugging. During the follow-up, within a four-month time period, there was a new, gradual appearance of pale plaques submandibularly and in the lower-left middle of the face (Fig. 3), while the patient also

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mentioned anogenital pruritus with vaginal discharge, erythema, and the partial disappearance of the clitoris. According to the patient's history, she suffered from dyslipidemia under medication. A recent immunization against HPV viruses had also been conducted.

Due to the progressive deterioration and tooth tearing reported, a punch biopsy from the plaque in the jawline was performed. The biopsy revealed results compatible with localized scleroderma, revealing diffuse dermal fibrosis with atrophy of the exocrine glands and moderate periadnexal lymphocytic infiltration (Fig. 4). A supplementary MRI brain scan was performed, without any pathological brain findings, apart from high signal intensity in cube flair images in the left condylar process of the mandible. Vaginal smear cultivation and IgG and IgM serum antibodies against *Borrelia burgdorferi* were negative. A wide serum immunological profile was held, including nRNP/Sm, Sm, SS-A, Ro-52, SS-B, Scl-70, PM-Scl-100, Jo-1, CENP B, PCNA, dsDNA, nucleosomes, histones, rib P-prot, and AMA M2, and gave normal results. The patient's clinical features regarding the white skin atrophy of the jawline in conjunction with the histopathological results and the partial loss of the clitoris led to the diagnosis of the nosological entities of the co-existence of PRS and LSA.

Firstly, topical corticosteroids and topical calcineurin inhibitors were administrated. However, there was a gradual worsening of the anogenital symptoms and the face lesions. Thus, a supplementary administration of prednisolone 20 mg per day for four weeks *per os* in combination with methotrexate 12.5 mg once a week *per os*, in conjunction with folic acid 5 mg a day before and a day after the initiation of methotrexate. During the first two-week follow-up, liver dysfunction was revealed, making it impossible to increase the

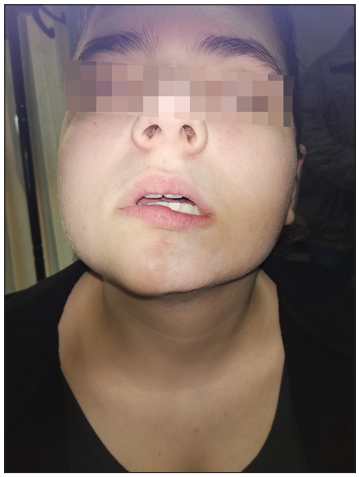

Figure 1: A solitary, sharply demarcated, pale, atrophic patch in the middle of the jaw in conjunction with asymmetry and downward deviation of the lower lip.

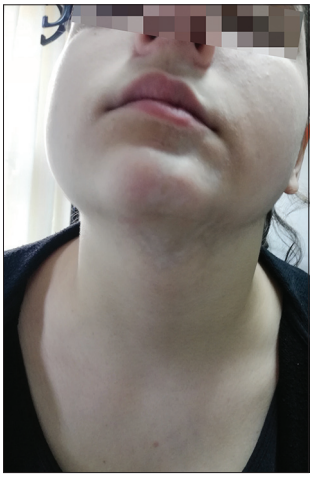

Figure 3: Pale plaques affecting the submandibular region and the lower-left middle of the patient's face.

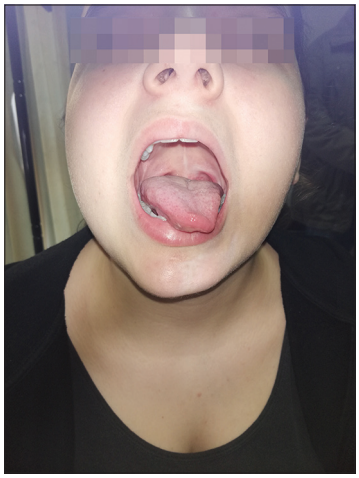

Figure 2: Deviation of the patient's tongue toward the side of the lesion.

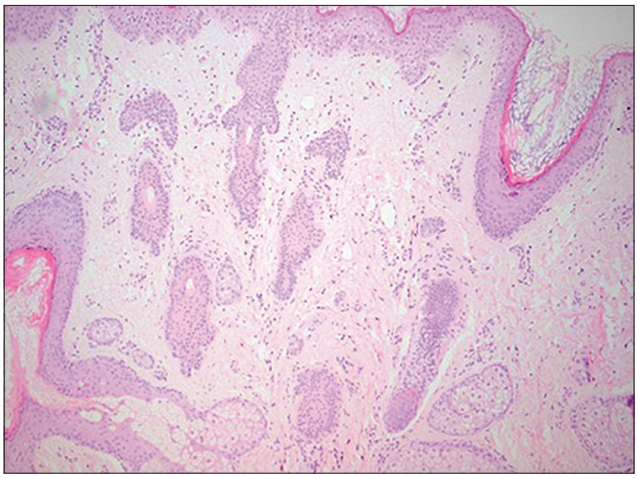

Figure 4: Diffuse dermal fibrosis with atrophy of the exocrine glands and moderate periadnexal lymphocytic infiltration.

dose of the *per os* regimens. After a period of four weeks, signs of partial disease inactivity were observed and the dose of the corticosteroid was tapered. Our patient, during 1.5 years of follow-up, has stabilized without deterioration of the skin lesions with a dose of methotrexate 12.5 mg weekly in combination with topical agents.

DISCUSSION

PRS is a rare, typically unilateral, acquired disease affecting mainly the face, leading to the atrophy of the skin, the subcutaneous layer, the musculature, and, in some cases, the cartilage and the bony structures of the facial zone. In some cases, there is also the involvement of the arms, trunk, and legs [4].

The age of onset seems to be the first twenty years of life, although a late onset has also been described. PRS progresses slowly and is self-limited, typically waning after 2–10 years and becoming stationary. PRS has a higher prevalence in females[4].

Atrophy of the skin and the underlying tissues is mainly unilateral and inferior to the forehead, usually involving the dermatomes of the branches of the fifth cranial nerve [2]. The structures of the oral cavity may also be affected.

Neurological and ocular manifestations and maxillofacial complications are the most common extracutaneous findings [3-5].

The aim of the treatment of PRS is to halt the disease activity. The most common drug administered is methotrexate, with doses varying from 0.3 to 1 mg/kg/week for 1–2 years, in order to avoid a relapse. Because of the delayed effect of methotrexate, high doses of systematic corticosteroids (prednisone 1 mg/kg/day) are also employed for three months, with a tapering dose at the third month [1,4].

A variant of scleroderma known as *en coup de sabre* (ECDS) shares common clinical and histopathological findings with PRS. Some authors attempted to separate the two entities by mainly clinical criteria, for instance, by the lack of previous induration, inflammation, and cutaneous atrophy in patients with PRS in contrast with the preceded hyperpigmentation and induration of the skin in ECDS that affects mainly the area above the brow [8]. Nevertheless, even in the same patient, overlapping of the clinical features of these two diseases may be observed [4,8]. A significant overlap of the histopathological features of ECDS and PRS is also present.

Connective tissue fibrosis, adnexal atrophy, and white mononuclear cell infiltrates are present not only in ECDS, but also in some of PRS biopsies [4].

Numerous authors suggest that these two entities fall into the same spectrum of the disease.

In our case, there was the overlap and coexistence of PRS not with a type of scleroderma, such as ECDS, but with LSA, which is a separate autoimmune disease.

LSA is a chronic inflammatory autoimmune disease, commonly affecting the anogenital region. Extragenital LSA may also be found. It affects mostly females, with a bimodal age distribution. The average age of diagnosis is 7.6 years in girls and 60 years in women [4].

The common clinical findings are ivory-white, shiny patches with concomitant atrophy, appearing predominantly in the anogenital area with an hourglass-like appearance. Pruritus or a burning sensation are often present. Morbidity may also occur in vulvar LSA [3]. Although there is often the coexistence of LSA and localized scleroderma (LS) in many patients, the relationship between the two disorders remains controversial. In some cases, the two disorders may appear in the same lesion [7].

Most of the time, histopathology may distinguish the two entities. In LSA, the epidermis is hyperkeratotic with hydropic degeneration of the basal layer. The elastic fibers are characteristically decreased [7].

Both LSA and PRS are of an unknown etiology and pathogenesis.

The possible role of HPV virus association in the development of LSA has been studied [9]. Our patient had undergone a recent immunization against HPV viruses.

Both diseases have a high rate of associated autoimmune diseases [3,10], and trauma seems to play a role in some cases [8].

CONCLUSION

To the best of our knowledge, this is the first case of the coexistence of PRS and LSA in the same extragenital site. Although the literature describes numerous cases of the concomitance of LSA with LS, similar cases of

the coexistence of PRS and LSA in the same site have not been discussed. The present findings support the autoimmune origin of the two diseases, the close relation of LS with PRS, and the theory that both entities lie in the same spectrum of a disease.

Consent

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

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

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Our Dermatology Online

Case Report

Congenital nevus comedonicus complicated by hidradenitis suppurativa-like lesions responding to isotretinoin treatment – A case report form Syria

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ABSTRACT

Nevus comedonicus (NC) is a rare hamartoma of the folliculosebaceous unit clinically characterized by linear lesions composed of numerous dilated follicular openings with keratinous plugs resembling classical comedones, seen mainly on the head and neck. Herein, we present here a case of congenital NC in a young Syrian female distributed along the Blaschko's lines only on the lower left limb and complicated by multiple hidradenitis suppurativa (HS)-like lesions. The case is unique because of an isolated involvement of a lower limb and a rare association with HS-like lesions, which responded greatly to oral isotretinoin.

Key words: Congenital nevus comedonicus; Hidradenitis suppurativa; Isotretinoin

INTRODUCTION

Nevus comedonicus (NC) is a type of epidermal nevus first described by Kofmann in 1895 [1]. Clinically, it is characterized by linear lesions composed of numerous dilated follicular openings with keratinous plugs resembling classical comedones, seen mainly on the head and neck, followed by the trunk and upper arm. NC associated with HS-like lesions is rare [2]. An isolated involvement of a lower limb, as in our case, has not been reported so far.

CASE REPORT

A fifteen-year-old Syrian female, born of a nonconsanguineous marriage, was referred to our hospital with comedo-like lesions distributed over the lower left limb extending from the lateral aspect of the left buttock up to the end of the left leg along the Blaschko's lines present since birth, which gradually increased in size and number (Figs. 1a – 1d). After puberty, the patient began to develop recurrent and intolerable painful nodules, abscesses, intercommunicating sinus tracts, and hypertrophic scars involving the buttocks, groin, and popliteal fold. These lesions relapsed or aggravated during hot weather. There was no family history of similar complaints. A physical examination revealed groups of dilated follicular openings filled with keratin distributed over the lower left limb with multiple nodulocystic swellings 2–4 cm in diameter with scarring and fibrous tracts scattered in between. General and systemic examinations were within normal limits, and there was no history suggestive of skeletal, ocular, or other systemic involvement. Routine laboratory investigations, including complete blood count, blood chemistry, and urinalysis were within normal limits. An examination of the lesions with a magnifying glass revealed groups of dilated follicular openings filled with keratin (Fig. 2). Because the patient refused a biopsy, the diagnosis was reached based on clinical manifestations as congenital nevus comedonicus (NC). The HS-like lesions involving the intertriginous areas were taken as being secondary to the NC. The patient was started

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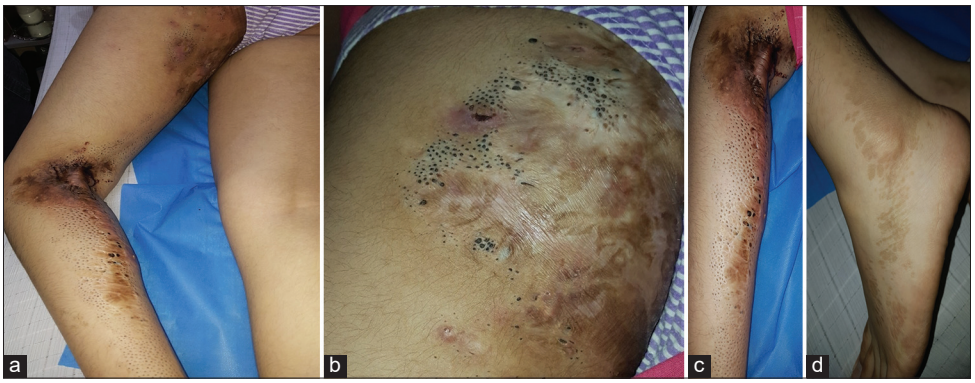

Figure 1: (a) Multiple comedo-like lesions and large atrophic pits, resulting in a classic sieve-like appearance present on the lateral aspect of the thigh and leg along the Blaschko's lines (note the multiple nodules, intercommunicating sinus tracts, and hypertrophic scars). (b) Nevus comedonicus on the left buttock with scars. (c) Nevus comedonicus with nodules, and intercommunicating sinus tracts in the popliteal fold (note the multiple hypertrophic cicatricial contractures). (d) Nevus comedonicus extending onto the left leg and foot.

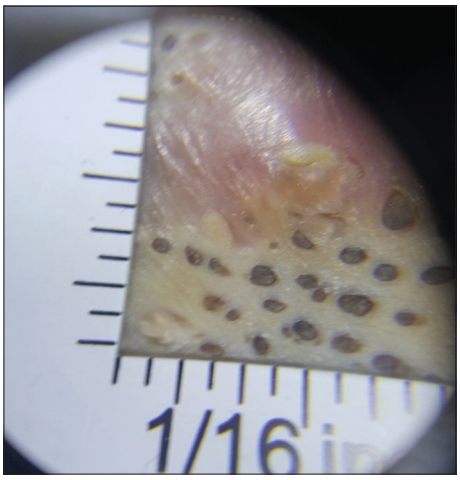

Figure 2: Magnification of the nevus revealing groups of dilated follicular openings filled with keratin.

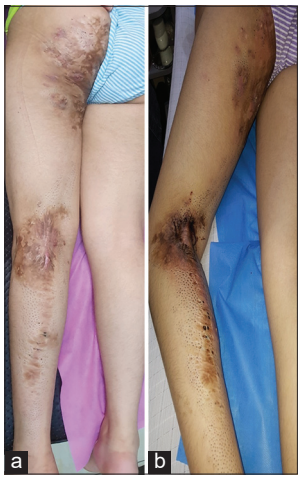

Figure 3: (a and b) The improvement of the cystic lesions after six months of treatment with oral isotretinoin.

on oral isotretinoin at a dose of 1 mg/kg/day and intralesional injections of triamcinolone with systemic antibiotics (clavulanic acid with amoxicillin) for ten days. The abscesses were incised and the pus drained. After six months of treatment with isotretinoin, there was a significant improvement in pus discharge and no new lesions developed; in addition, no severe side-effects of the treatment with isotretinoin were observed (Figs. 3 and 4).

DISCUSSION

NC is an uncommon skin abnormality caused by a defect in the development of hair follicles composed of keratin-filled pits. These lesions usually develop at birth or before the age of ten years, but may occur at any time from birth to middle age [3]. Clinically, NC is may be classified as either of two types: type one involves overwhelming numbers of comedones, while type two involves inflammatory changes with late sequelae such as scars, fistulae, and the formation of follicular cysts [4]. Our case was classified as type two. NC may be linear, interrupted, unilateral, bilateral, along the lines of Blaschko, or segmental. The lesions are most commonly located on the face, neck, upper arms, chest, and abdomen [5], and occasionally involve the palms and soles, scalp, female genitalia, and glans penis. The development of HS-like lesions in localized childhood NC is rare. HS is characterized by painful, inflamed nodules, abscesses, intercommunicating sinus tracts, and hypertrophic scarring in apocrine gland-bearing areas, most commonly the axillae and the inguinal and anogenital regions. Follicular plugging occurs congenitally and may be triggered by mechanical stress and hormonal changes, as in puberty [6].

The possible treatment of NC includes excision, dermabrasion, cryotherapy, coagulation, the extraction

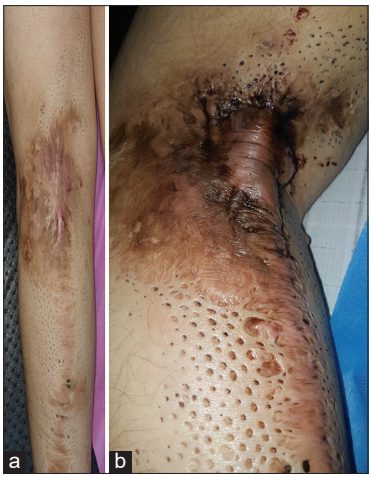

Figure 4: (a and b) The improvement of the cystic lesions after six months of treatment with oral isotretinoin.

of the comedones, and the use of topical agents such as retinoic acid, urea, tretinoin, ammonium lactate lotion, tacalcitol, tazarotene, and calcipotriene [7,8]. The therapeutic options for patients with NC complicated by HS include systemic antibiotics, intralesional corticosteroid injections, and oral isotretinoin.

Our patient was treated in all these therapeutic ways and, unexpectedly, showed a significant improvement of the inflammatory lesions and scars. However, there are several reports of NC in which isotretinoin was only minimally effective [9,10].

CONCLUSION

We present a case of congenital nevus comedonicus (NC) in a young Syrian female distributed along the Blaschko's lines only on the left lower limb and complicated by multiple hidradenitis suppurativa (HS)-like lesions. In contrast to previous reports, our case of NC is exceptional because of an isolated involvement of a lower limb and a rare association with HS-like lesions, which responded greatly to oral isotretinoin.

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

Generalized wooly hair with new associations: A case report

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ABSTRACT

Wooly hair is a structural anomaly of the hair shaft that affects scalp hair and manifests itself as tightly coiled hair. Wooly hair may be localized or generalized, but the generalized form is rare and may be limited to the scalp or complicated by cutaneous and extracutaneous features. A four-year-old female complaining of short, tightly-coiled scalp hair present since birth. An examination of the skin revealed the scalp hair to be fine, coarse, and lightly-pigmented. The cutaneous surface was dry, with multiple hypopigmented macules on the upper trunk and a larger, ash-leaf-shaped, located on the anterior trunk. Also, a large hyperpigmented patch, a congenital melanocytic nevus, was noted on the posterior trunk. An examination of the hair under a light microscope revealed various hair shaft abnormalities. To our knowledge, generalized wooly hair in association with an ash-leaf macule and a congenital melanocytic nevus has not been reported before.

Key words: Wool hair; Ash-leaf macule; Unruly hair; Melanocytic nevus

INTRODUCTION

Wooly hair is a disorder that results from a structural defect in the hair shaft, without increasing its fragility [1,2], showing as tightly-coiled, unruly hair in non-black races [3]. Wooly hair is generally a cosmetic problem but, in some, may threaten life [4]. It manifests itself either as the localized non-hereditary variant, a wooly hair nevus, or as the generalized hereditary form. Generalized wooly hair may be an isolated anomaly, affecting only the scalp hair, or associated with cutaneous and extracutaneous manifestations [5]. Herein, we present a case of generalized wooly hair in a four-year-old girl associated with skin anomalies but without systemic involvement.

CASE REPORT

A four-year-old girl brought by her father showed short, thin, light-colored, easily-fractured, tightly-coiled, and unruly hair that had not increased in length since birth. The child was born to a sanguineous marriage and was the seventh and the only affected among eight siblings: five daughters and three sons. There was no family history of the same condition, atopy, or other genetic disorders. On examination, the patient looked well, apart from the affected scalp hair. The hair was short, fine, light-colored, coarse in texture, and tightly-coiled into short locks. (Figs. 1a and 1b). The eyebrows and eyelashes were normal. The skin surface was dry, with multiple pityriasis alba lesions on the face associated with widespread keratosis pilaris. Multiple hypopigmented spots were present, mainly on the upper trunk and in a confetti-like distribution (Fig. 2). An ash-leaf-like hypopigmented macule was present on the anterior trunk (Fig. 3) and another macule, but hyperpigmented, on the posterior upper trunk (Fig. 2). There was no palmoplantar keratoderma. The nails, teeth, and eyes were not affected. Light microscopy revealed various hair calibers: fine hair, hair twisted on its long axis, fractured hair, hair with knots, and trichorrhexis nodosa (Figs. 4a – 4d). Echo studies and hematological and biochemical investigations were within normal limits. An examination of the hair with

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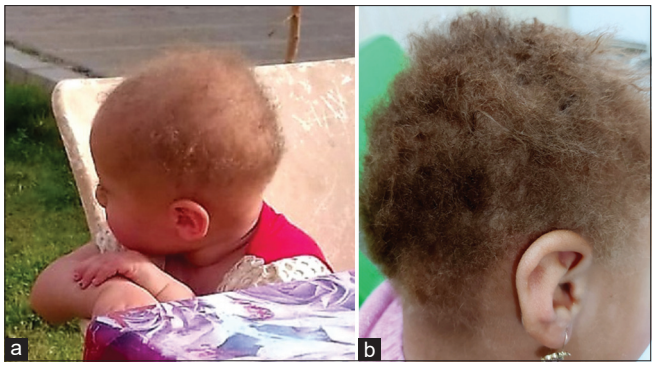

Figure 1: Wooly hair on the scalp in (a) a 1.6-year-old patient and (b) a 4-year-old patient.

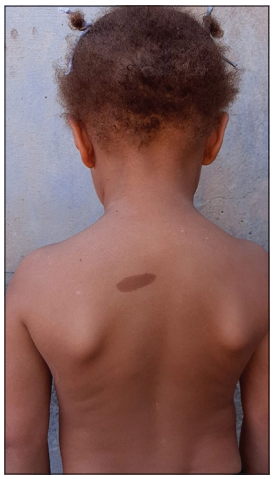

Figure 2: Hypopigmented spots on the posterior trunk in association with a hyperpigmented patch.

10% potassium hydroxide revealed no fungal elements. Growth milestones were normal for the patient's age and no abnormality was detected on systemic examination. Taking into consideration these findings, the case was mostly an autosomal recessive variant of generalized wooly hair with cutaneous anomalies, but without systemic manifestations.

DISCUSSION

Wooly hair is a hair shaft disorder either limited to a part of the scalp in the form of a wooly hair nevus or generalized as in familial wooly hair and hereditary wooly hair [6]. Wooly hair may be only a cosmetic concern if confined to the scalp or associated with fatal complications, such as cardiomyopathy [4]. Generalized wooly hair may be the only abnormality present or may be associated with injury to the skin, teeth, eyes, or heart [7]. Hair growth in generalized wooly hair of the scalp is normal or slower than in a healthy individual but the anagen phase is shorter, leading to shorter hair

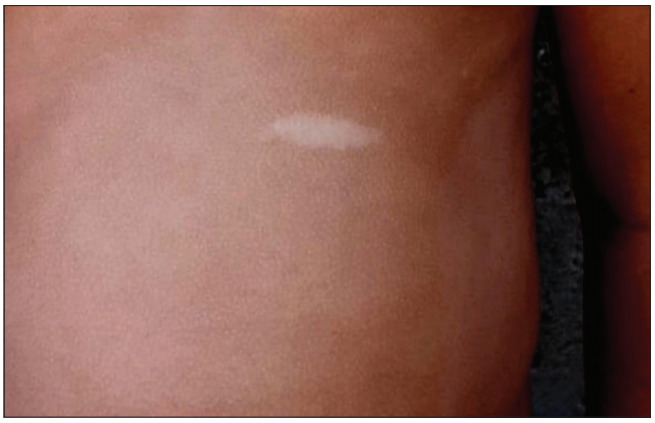

Figure 3: The hypopigmented ash-leaf-like patch on the anterior trunk and keratosis pilaris.

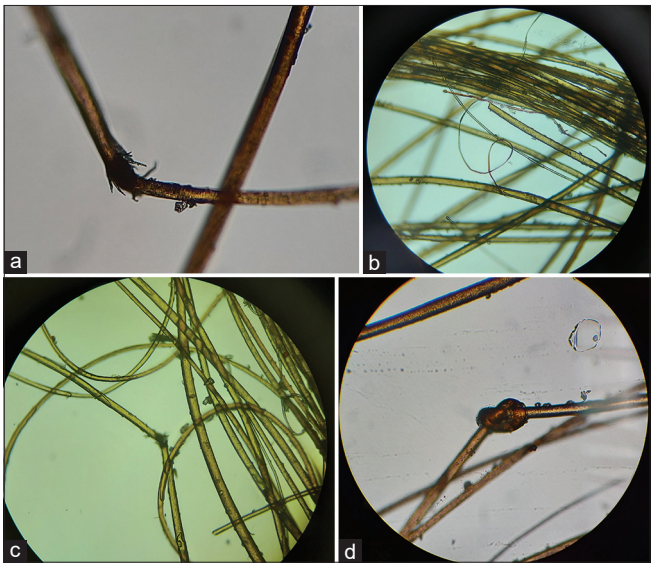

Figure 4: (a) Hair microscopy showing (a) a fractured hair, (b) different hair calibers (fine, thin, and twisted), (c) a fine and broken hair shaft, and (d) a hair with a knot formation.

that does not grow to be more than several centimeters long [7,8]. Also, the presence of trichorrhexis nodosa leads to the breakage of hair, effectively preventing hair growth [3]. Despite this, the length and condition of hair may improve with age [9] (as in the patient shown in Fig. 1). Keratosis pilaris is a disease that results from a keratinization abnormality in which the hair follicle is affected by a keratinous plug [10]. Widespread keratosis pilaris, affecting most of the skin surface, as in the patient shown in Fig. 1, was reported by Budhwar et al. to be a cutaneous anomaly manifested by generalized wooly hair [8]. Vasudevan B et al. described a four-year-old patient with widespread keratosis pilaris in addition to generalized wooly hair [11].

Xerosis and pityriasis alba are non-specific and minor criteria for atopic dermatitis [10]. Nonetheless, our

case was not atopic and there was no family history of atopy, so these may be considered a non-specific association with generalized wooly hair. Multiple hypopigmented spots were reported by Pavone et al. in a 29-month-old female, mainly between the shoulders [12]. In our case, the hypopigmented spots were more widespread, distributed as if confetti, and present on the shoulders and the upper and lower trunk. An ash-leaf-like hypopigmented macule was present on the anterior trunk. The macule was a white, oval lesion, which is a feature of tuberous sclerosis also seen in familial progressive hyperpigmentation and hypopigmentation [13,14]. This has not been previously reported in association with wooly hair. A hyperpigmented patch is a brownish patch with a well-defined border, generally a congenital melanocytic nevus (CMN) of medium size. A CMN is a nevus of melanocytic origin, its color varies from light to dark brown, may be of any size, and any site of the skin may be affected [15].

Although the examination of wooly hair with a light microscope usually shows non-specific features, different anomalies may be observed, such as varying calibers of hair and twisted hair on its long axis [11,16]. Trichorrhexis nodosa, hair with tapered ends, and knot formations may also be seen [4,16]. In our case, most of these hair shaft anomalies were present. Two important syndromes are associated with generalized wooly hair: Naxos syndrome and Carvajal syndrome. However, these diseases are associated, in addition to wooly hair, with palmoplantar keratoderma and cardiomyopathy [4].

CONCLUSION

Although, in such cases, genetic studies are important to reach an accurate diagnosis, they are not available at our location. Taking into account the history, clinical presentation, and investigations performed, our patient is mostly a case of generalized wooly hair of the scalp in association with cutaneous anomalies of ectodermal origin, but without systemic involvement. Some of these anomalies have been mentioned in the literature, such as keratosis pilaris and hypopigmented spots. However, to our knowledge, we are the first to report an association with an ash-leaf macule and a congenital melanocytic nevus.

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

Multiple eccrine hidrocystomas of the face (Robinson type): Response to topical hyoscine butylbromide

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ABSTRACT

Multiple eccrine hidrocystomas are uncommon benign cystic lesions with a non-remitting clinical course marked by episodic erythema, a burning sensation, and exacerbations during warm weather, which is often distressing. Females are affected more often than males aged between 30 and 70 years. Surgical excision is curative for solitary lesions but most treatments for multiple lesions remain frustrating for both the patient and the clinician. This 47-year-old female with classic multiple eccrine hidrocystomas became completely asymptomatic after treatment with topical 0.5% hyoscine butylbromide without the adverse effects of anticholinergic drugs. It appears to be a safe, effective, and cosmetically elegant treatment option for multiple eccrine hidrocystomas, but needs further evaluation.

Key words: Anticholinergics; Eccrine hidrocystoma; Hyoscine butylbromide

INTRODUCTION

Eccrine hidrocystomas are rare, benign translucent cystic lesions originating from the eccrine duct with an estimated prevalence of 1 in 1000 skin biopsies. They usually affect females between 30 and 70 years of age more often than males, but can also occur in children and adolescents [1,2]. They may occur as solitary lesions—known as Smith-type—or multiple lesions—known as Robinson-type—named after their illustrators. Treatment in most instances remains unsatisfactory. We describe the case of a patient with multiple eccrine hidrocystomas and share our therapeutic experience.

CASE REPORT

A 47-year-old female had developed numerous lesions on the face over a period of two years. Initially around the eyes, the lesions progressed slowly to involve the entire face. Although asymptomatic, the lesions became prominent and erythematous during warm weather and the associated burning sensation was uncomfortable. Spontaneous improvement occurred during cooler days. The rest of the patient's medical history was unremarkable and she denied any topical or systemic drug intake and the presence of similar problems in family members. Examination showed numerous smooth-surfaced, skin-colored, translucent lesions distributed predominantly over the periorbital skin and midface (Fig. 1a). A drop of clear serous fluid extruded when a lesion was punctured with a sterile needle. The mucous membranes, hair, nails, and a systemic examination revealed no abnormality. A complete blood count and serum biochemistry were normal. A biopsy of a skin lesion showed features of an empty cystic cavity lined with cuboidal cells in two layers, suggestive of eccrine hidrocystoma (Fig. 2). Topical 1% atropine ointment for bedtime application and a follow-up at two weeks was advised. However, the patient returned after four weeks feeling better and continued the prescribed treatment. She had developed dilated and fixed pupils with blurred vision and photophobia. Hyoscine butylbromide (Buscopan™) in a 0.5% concentration in calamine lotion was prescribed for twice daily topical application. The patient showed complete regression of the lesions on a four-week visit

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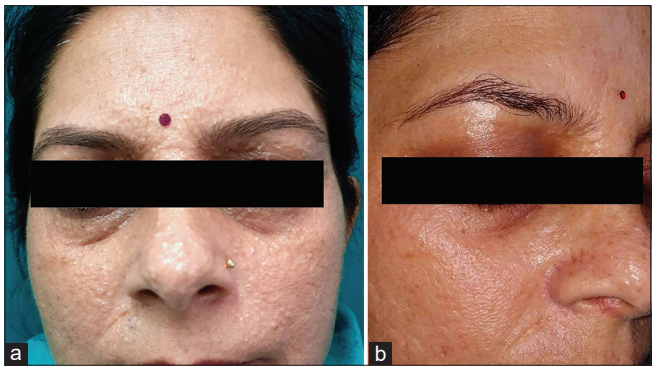

Figure 1: (a) Multiple skin-colored translucent papules of variable sizes and tense cystic consistency involving the whole face. (b) Complete clearance of lesions four weeks after topical 0.5% hyoscine butylbromide in calamine lotion applied twice daily.

without adverse effects (Fig. 1b). She was counseled about the benign but recurrent nature of the condition and advised to continue treatment intermittently during warm weather and to follow up regularly.

DISCUSSION

Eccrine hidrocystomas are cystic lesions measuring around 1 – 3 mm and predominantly involving the face, mostly the periorbital area. They usually remit in winters but show worsening in summers. Their etiopathogenesis is poorly elucidated but is imputed to obstruction of the eccrine duct and retention of sweat, as is evident from cystic dilatation and flattening of the lining ductal cells or adenomatous proliferation of the excretory duct [1]. Clinically, a syringoma or an epidermal inclusion cyst may sometimes mimic this, but apocrine hidrocystoma remains a major differential diagnosis. Apocrine hidrocystomas are solitary, rarely multiple, lesions usually 3 – 15 mm in size appearing as dark blue and localized in the inner canthus near the eyelid margin, as well as the forearms, chest, axillae, and labia majora, and show no seasonal variation [2]. Histologically, a multilocular cyst in the dermis shows papillary projections, lined with secretory columnar and myoepithelial cells with decapitation secretion and diastase-resistant periodic acid–Schiff (PAS) positive granules. In contrast, eccrine hidrocystomas are usually unilocular and the cystic cavity is lined with two layers of cuboidal cells. They lack papillary projections, myoepithelial cells, decapitation secretion, and diastase-resistant PAS positive granules [2]. Graves' disease, Parkinson's disease, Schöpf–Schulz–Passarge syndrome, Goltz–Gorlin syndrome, craniofacial hyperhidrosis, and prolactinoma are rare associations [3,4]. The case described shows characteristic clinicopathological

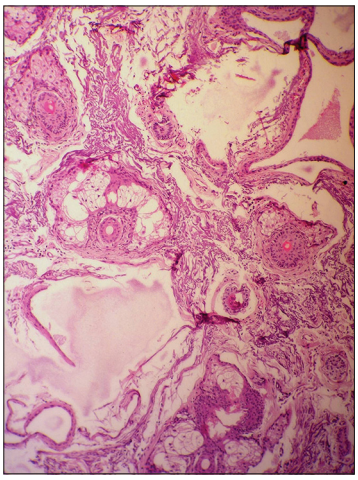

Figure 2: Multiple dilated unilocular cystic lesions with flattened cuboidal cells arranged in double rows unrelated to the surrounding eccrine glands (H&E, 40×).

features of multiple eccrine hidrocystoma without comorbidities.

Surgical excision of a small isolated lesion is curative but treatment of patients with multiple lesions remains largely unsatisfactory and recurrence occurs in up to 2.3% of cases [9]. Most cases have been treated with electrodessication, cryotherapy, microdermabrasion, needle puncture, lasers (pulsed dye, CO_2, erbium YAG) alone or in combination with isotretinoin, topical botulinum toxin type A, aqueous glycopyrrolate solution alone or in combination with microneedling, or oral oxybutynin with variable results [5-9]. However, these local ablative procedures are costly and pose risk of scarring. Topical atropine has been used for its anticholinergic effect, but may lead to mydriasis, blurred vision, and dryness in the mouth, as noted in our patient. Hyoscine butylbromide, or scopolamine, is another anticholinergic drug that blocks muscarinic receptors located on the gastrointestinal smooth-muscle cells to elicit an antispasmodic effect in abdominal cramps. The benefit of the use of its anticholinergic effect in treating multiple eccrine hidrocystomas remains under evaluation for the paucity of cases [9]. It provided symptomatic relief in our patient without the adverse effects associated with atropine. We feel that intermittent topical 0.5% hyoscine butylbromide is a low-cost, safe, effective, and cosmetically elegant treatment for multiple eccrine hidrocystomas, but its long-term use still needs further evaluation.

Consent

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

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

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

Our Dermatology Online

Case Report

Atypical and fulminant non-erythrodermic Sézary syndrome

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ABSTRACT

Sézary syndrome (SS) is a rare and aggressive type of cutaneous T cell lymphoma (CTCL) characterized by cutaneous and systemic dissemination of clonal CD4+T cells into the blood and lymph nodes. The majority of patients with SS present the classic symptoms of erythroderma, lymphadenopathy, and pruritus. However, there have been, in recent years, numerous reports of patients with SS and with non-classic signs. We report the case of a 67-year-old patient presenting non-erythrodermic Sézary syndrome with a particular clinical aspect made of diffuse and aggressive angiomatous lesions with a dermoscopic description.

Key words: Sézary syndrome; Non-erythrodermic; Angiomatous lesions; Dermoscopy

INTRODUCTION

Sézary syndrome (SS) is the leukemic subtype of cutaneous T cell lymphoma (CTCL) characterized by the triad of erythroderma, lymphadenopathy, and the presence of Sézary cells in the skin, lymph nodes, and peripheral blood [1].

In 2007, the International Society for Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) proposed the newest diagnostic guidelines for CTCL on the basis of developments in the understanding of T-lymphocyte tumor biology, along with molecular diagnostics and immunophenotyping advances [2]. The hematologic criteria recommended for Sézary syndrome are intended to identify patients with a worse prognosis as compared with other CTCL subsets and consist of one or more of the following: an absolute Sézary cell count of 1000 cells/mm^3 or higher; a CD4/CD8 ratio of 10 or higher caused by an increase in circulating T cells and/or an aberrant loss or expression of pan-T cell markers by flow cytometry; increased lymphocyte counts with evidence of a T-cell clone in the blood by the Southern blot or polymerase chain reaction technique; or a chromosomally abnormal T-cell clone [3]. In recent years, several cases have been reported in the literature of Sezary Syndrome (SS) fulfilling all the biological criteria but without erythroderma. The following non-classic symptoms of SS were identified as keratoderma, onychodystrophy, alopecia, leonine facies, ocular pathologies, peripheral neuropathy, burning or stinging pain, arthritis, papuloerythroderma of Ofuji, and lower-extremity edema [1]. We report the case of a 67-year-old patient suffering from SS with clinically absent erythroderma and atypical angiomatous lesions with a dermoscopic description. This is the first case in the literature of SS with such a clinical presentation. We also report the overwhelming evolution of the tumoral lesions in a short period of time, always confirming the very aggressive nature of this entity.

CASE REPORT

A 67-year-old male was admitted to our hospital with a one-year history of general itching, then the appearance of acutely pruriginous erythematous papules on the face and neck persistent for six months, which were formerly

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treated with topical steroids without improvement. A physical examination (Figs. 1–3) revealed multiple diffuse erythematous and angiomatous papules, nodules, and tumors on the face, scalp, trunk, axillary and inguinal folds, and upper and lower limbs, most of which had eroded surfaces and were surmounted by hemorrhagic crusts. The largest lesion was a rounded tumor with a six-centimeter long axis and with an eroded and bleeding surface at the nape of the neck. The face had a leonine appearance with several confluent angiomatous tumors. The affected skin surface was estimated at 70%. Dermoscopy revealed red lagoons separated by fibrous septa, confirming the angiomatous nature of these lesions (Fig. 4). We found pink-to-white structureless areas (Fig. 5) and, at very high magnifications, fine short linear vessels, dotted vessels, and spermatozoa-like structures in some tumor lesions (Fig. 6).

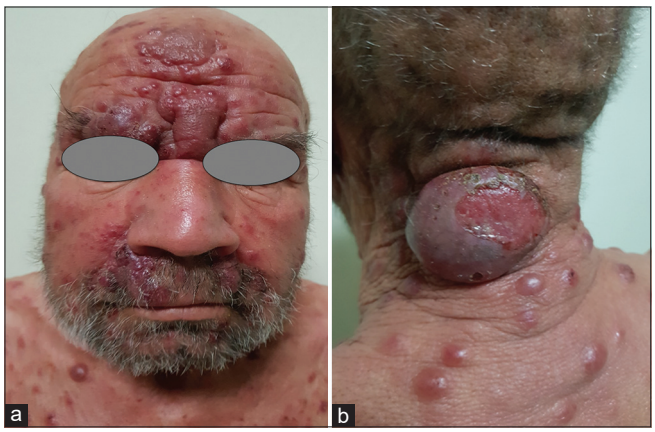

Figure 1: (a) A leonine appearance with the presence of several confluent angiomatous tumors. (b) A rounded tumor with a six-centimeter long axis with an eroded and bleeding surface at the nape of the neck.

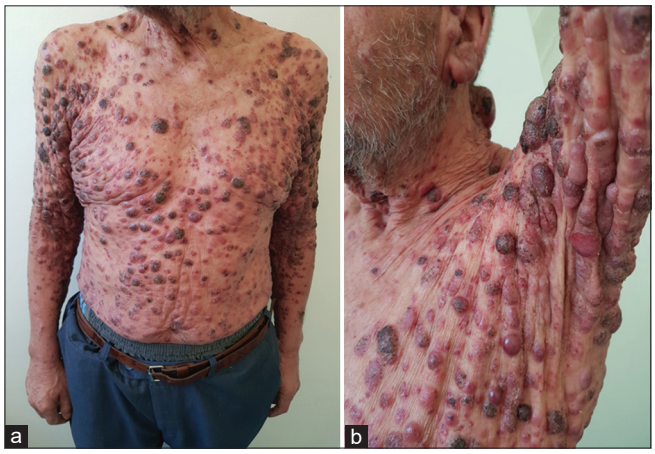

Figure 2: (a-b) Diffuse multiple erythematous and angiomatous papules, nodules, and tumors, most with eroded surfaces and surmounted by hemorrhagic crusts.

The patient also had bilateral angular cheilitis, multiple pinhead angiomatous papules in the scrotum and penis, fissuring plantar keratoderma, and diffuse nail onychodystrophy. An examination of lymph node areas revealed bilateral inguinal lymphadenopathy. The rest of the somatic examination showed homogeneous splenomegaly reaching as far as the umbilicus.

A skin biopsy specimen taken from the tumor lesion revealed infiltration of atypical lymphocytes in the upper dermis without epidermotropism. Blood count showed hyperlymphocytosis at 68,000 with normal differential cell counts of neutrophils and monocytes, but persistent eosinophilia and moderate thrombocytopenia were observed. A search for Sézary cells in the peripheral blood associated with lymphocyte immunophenotyping indicated the presence of an atypical T lymphoid population—$CD4^+$, $CD8^-$, $CD3^+$, $CD5^+$, $CD2^+$, $CD7^-$, $CD57^-$, $CD56^-$, $CD16^-$—expressing alpha-beta TCR; these cells represented about 95% of lymphocytes. Cytologically, they were medium-to-large cells with a cerebriform nucleus

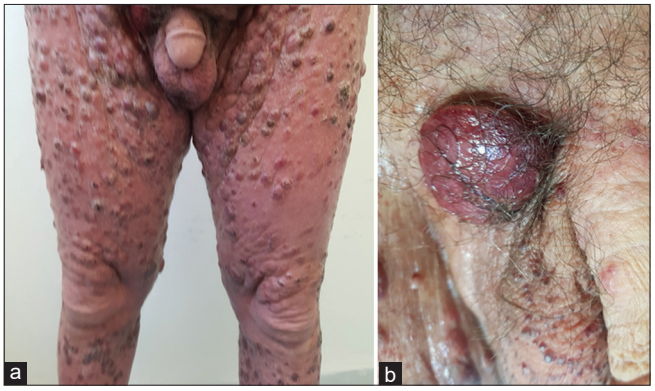

Figure 3: (a) Diffuse multiple erythematous and angiomatous papules, nodules, and tumors, most with eroded surfaces and surmounted by hemorrhagic crusts. (b) A rounded tumor with a four-centimeter long axis with an eroded and bleeding surface at the inguinal fold.

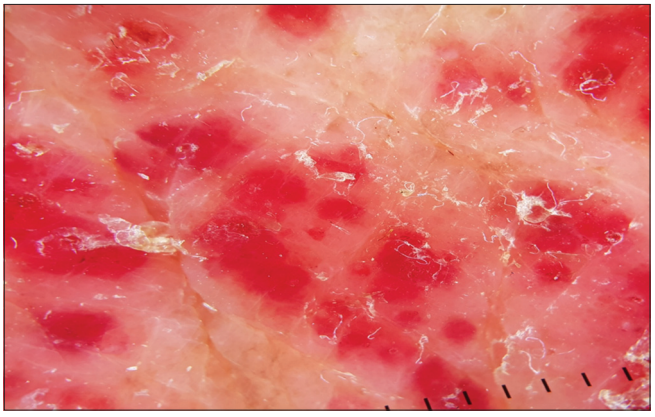

Figure 4: Dermoscopy revealing red lagoons separated by fibrous septa, confirming the angiomatous nature of these lesions.

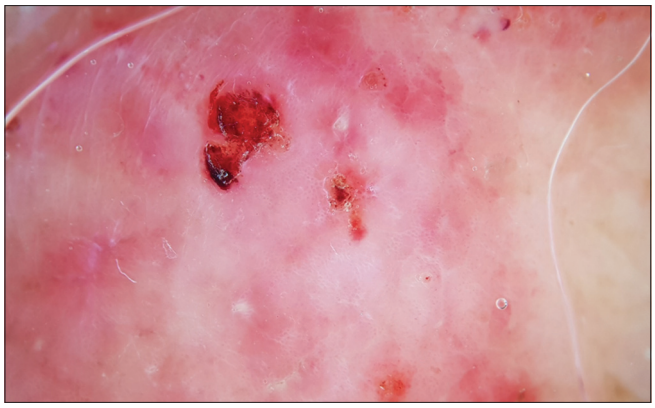

Figure 5: Pink-to-white structureless areas on the dermoscopy of a tumoral lesion.

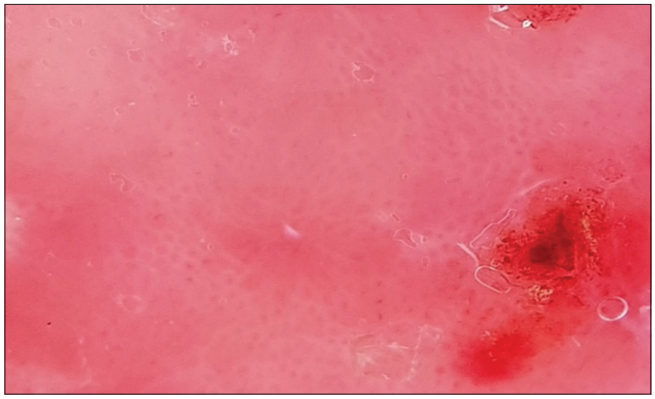

Figure 6: Fine short linear vessels, dotted vessels, and spermatozoa-like structures at very high magnifications.

(95% of Sézary cells). The CD4/CD8 ratio was 52.1. Beta-2 microglobulin was above 4 mg/L, and LDH was three times normal. In the absence of the availability of PCR, we retained Sézary syndrome on this cluster of clinical and biological arguments. The patient then underwent an extension workup consisting of an ultrasound scan of lymph node areas, which showed bilateral inguinal and axillary adenopathy suspected of malignancy. However, a cervico-thoraco-abdomino-pelvic CT scan and osteo-medullary biopsy were without particularity. The decision was to put the patient under CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine), prednisone) chemotherapy. Unfortunately, the patient died after a single course of treatment.

DISCUSSION

In 2000, Tokura et al. were the first authors to report a patient with SS without erythroderma. The clinical presentation was quite similar to our case, with multiple papules, nodules, and tumors, but it was an indolent form, which is the exact opposite of our case [4]. Lately, Thompson et al. identified a distinct and atypical population of SS patients with a high blood tumor burden of Sézary cells, fulfilling the criteria for SS but without fulfilling the criteria for erythroderma. Among the 16 patients identified, all had cutaneous findings consistent with cutaneous T-cell lymphoma, most commonly erythematous patches and plaques. Survival was not different between patients with SS with and without erythroderma. The authors confirmed that erythroderma may not be a necessary element in the diagnosis of SS and proposed that these atypical cases would be more precisely described with the TNMB classification [2]. Moreover, a retrospective, multicenter chart review was performed for 263 confirmed cases of SS diagnosed from 1976 through 2015; erythroderma was the earliest recorded skin sign of SS in only 25.5% of cases. In patients without erythroderma, during their initial visit, the first cutaneous signs of SS were nonspecific dermatitis (49%), atopic dermatitis-like eruption (4.9%), or patches and plaques of mycosis fungoides (10.6%). The mean diagnostic delay was 2.2 years for cases involving erythroderma on the initial presentation and 5 years for cases not involving erythroderma on the initial presentation. The authors conclude that early SS should be considered in cases of non-erythrodermic dermatitis that is refractory to conventional treatments [5].

This conclusion is very important for the daily practice of physicians. We would like to add to this that our patient presented chronic pruritus without any lesions for one year, then presented a nonspecific pruritic dermatitis for another six months, treated only symptomatically, which, unfortunately, considerably delayed the diagnosis and management of SS.

Several authors reported that all their patients with SS had eventually developed erythroderma, whatever their initial clinical presentation [6-7]. On the other hand, Henn et al. [8] reported that the six cases in their series never developed erythroderma throughout the course of the disease. Mangold et al. [5] also showed that 13 out of 23 cases did not develop erythroderma during the course of the disease. Thus, not all SS patients without initial erythroderma eventually progress to erythroderma. This is also the case in our patient, who developed several nodules and tumors during a follow-up but never erythroderma.

To characterize the clinical skin findings, Hiroaki et al. summarized 37 cases of SS without initial erythroderma; the skin manifestations varied from patches and plaques to tumors, often found in

patients with mycosis fungoides, as well as and other rarer findings, such as excoriations, palmoplantar keratoderma, and alopecia. Pruritus was reported in most patients. Interestingly, five cases of SS without erythroderma had no apparent cutaneous findings, while specimens taken from their skin tissue revealed dermal perivascular atypical lymphocyte infiltration, consistent with SS [1,9].

Our patient also had chronic pruritus without skin lesions for one year and then developed multiple diffuse and aggressive angiomatous tumors. Concerning dermoscopy, to our knowledge and based on a recent review of the literature, this is the first description of dermoscopy for non-erythrodermic SS reported in the literature [10].

SS is an aggressive epidermotropic CTCL with a five-year survival rate of 24% [11]. It is, therefore, interesting to know whether the survival of patients with non-erythrodermic SS would be different from patients with erythroderma. The results found so far in the literature remain contradictory. Henn et al. [8] showed a better survival rate for non-erythrodermic SS. Conversely, Thompson et al. [2] suggested that non-erythrodermic SS had a similar prognosis. In our patient, the evolution was dramatic with a spectacular extension of the tumors to the whole skin and death after one month from the diagnosis.

CONCLUSION

Sézary syndrome is a very aggressive cutaneous lymphoma, and the diversity of clinical aspects described in recent years leads us to consider it one of the great simulators of dermatology.

Awareness and information among dermatological practitioners and, especially, general practitioners are immensely important in the context of this syndrome, which may become fatal with delayed diagnosis, as our case illustrates.

We also suggest that erythroderma should no longer be linked to Sézary syndrome and that a new classification for this syndrome is necessary.

Finally, we report the clinical and dermoscopic aspect of these angiomatous tumors as a new atypical description of this syndrome.

Author Contributions

All authors read and approved the final manuscript.

Consent

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

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

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Our Dermatology Online

Review Article

Psoriasis, pityriasis alba, and vitiligo (PPV) are a triad of one disease: New observation

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ABSTRACT

Keratinocytes and melanocytes live in the epidermis, which is considered to be a very good environment for both. Therefore, any change in this regard will affect the function of both of them. Keratinocytes form the main bulk of the epidermis and are the only melanin storage as the dendrites of the basal melanocytes run between keratinocytes and gift melanin granules to surrounding keratinocytes. Consequently, any immunoinflammatory reaction in the epidermis will influence the function of both of them. Recent evidence has shown that psoriasis, pityriasis alba, and vitiligo are closely related diseases and might reflect one etiopathogenesis initially targeting the hair follicles and then extending into the epidermis proper. Hence, the three diseases form one condition: the so-called PPV triad. Consequently, the objective of the following work is to show how these three skin problems are closely related clinically, immunologically, and pathologically, thus constituting the PPV triad.

Key words: Psoriasis; Pityriasis alba; Vitiligo; PPV Sharquie triad; Follicular leukoderma

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF PSORIASIS

Psoriasis is a common chronic inflammatory skin disease affecting 1–3% of the population [1]. Psoriasis vulgaris, the most common variant, characterized by scaly erythematous plaques, mainly affects the epidermis and involves the extensor surfaces, although any cutaneous site may be affected. Follicular psoriasis, although common, is not well recognized in the dermatological literature [2]. This could be explained by the fact that the initial event in the clinical picture of psoriasis is minute or even microscopic, a transient lesion affecting the upper stable segment of hair follicles and progressing into ordinary psoriasis (Figs. 1 and 2). Psoriasis is a multifactorial disease with a complex pathogenesis. Normally, the skin epidermis shows regular and constant turnover, occurring every 26–28 days [3]. In comparison to a normal skin epidermis, a psoriatic epidermis manifests itself with hyperplasia, rapid turnover, and intensified mitosis [4]. Psoriatic skin turnover occurs every 3–4 days [5] leading to keratinocyte hyperproliferation, which is a characteristic feature of psoriasis. Several cell types and cell–cell interactions have been involved in the disease process, including keratinocytes, antigen-presenting cells, Langerhans cells, T cells, macrophages, and natural killer cells. In addition, various Th1 cytokines, keratinocyte growth factor (KGF), vascular endothelial growth factor (VEGF), and interleukins are suggested to play a role in psoriasis pathogenesis [6].

On the other hand, the genetic role is considered from the observation of a high concordance rate in monozygotic twins (63–73%) compared to a lower rate in dizygotic twins (17–20%). There is considerable heterogeneity in psoriasis, and different genetic loci have been identified (PSORS1–10) [7,8], although psoriasis susceptibility locus 1 (PSORS1) remains the

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most determinant genetic factor, accounting for 50% of genetic variance in psoriasis [9,10].

THE ROLE OF KERATINOCYTES IN PSORIASIS ETIOPATHOGENESIS

The exact sequence of events in the initiation of psoriasis remains unknown. Although activated T lymphocytes and IL-17 are crucial to the development and persistence of psoriatic lesions. The pathophysiology of psoriasis cannot be explained merely by T lymphocytes as other skin-resident cells, such as keratinocytes and dendritic cells, are also involved [11]. The epidermal skin plays a significant role in early skin lesions by activation and recruitment of immune and inflammatory cells. The psoriatic auto-antigen loop concept is considered in the pathogenesis of psoriasis [11]. Antimicrobial peptide LL37 (cathelicidin) is overexpressed in psoriatic skin and triggers the activation of innate immune cells. It has been found that 2/3 of moderate-to-severe psoriatic patients have LL-37–specific CD4 and/or CD8 T lymphocytes, which can produce INF-ɣ and Th-17 cytokines. The presence of LL-37–specific T cells in circulation correlates significantly with the disease process [12]. ADAMTSL5 (A disintegrin and metalloprotease domain containing thrombospondin type 1 motif-like 5), which is a melanocyte-derived protein, has also been observed to be strongly expressed in keratinocytes throughout the epidermis along with scattered expression in some dermal blood vessels and other perivascular dermal cells in psoriasis [13]. This protein has recently been implicated as an activating antigen for IL-17–producing T cells in psoriasis [14]. Both LL-37 and ADAMTSL5 autoantigens are downregulated following treatment with etanercept and IL-17 blockade [15]. Lande et al. identified the role of LL-37 in breaking innate tolerance to self-DNA as a fundamental player in the autoimmunological process of psoriasis. They found that LL-37 converts self-DNA into a potent trigger for INF production by forming aggregates and condensed structures that stimulate plasmacytoid dendritic cells (pDCs) through toll-like receptor 9 TLR9 [16,17]. Also, LL-37 binds to self-RNA and activates myeloid dendritic cells (mDC) through TLR7 and TLR8 in psoriatic lesions, leading to IL-6 and TNF production and differentiation of mDCs into mature DCs [18].

Furthermore, as keratinocyte autocrine stimulation by IL-1 exists in the epidermis, an experimental aberration of this highly controlled autocrine function has been tested using double transgenic mice, which show overexpression of the functional IL-1 receptor and 17 kD IL-1α in basal keratinocytes. It has been found that IL-1 has the ability to cross the basement membrane and activate dermal cells in addition to activating nearby cells such as keratinocytes, Langerhans cells, and melanocytes. Also, it leads to a wide variety of secondary responses, including the induction of secondary cytokines such as IL-6 and GM-CSF, leading to epidermal hyperplasia and dermal inflammatory cell infiltrate [19].

The characteristic histopathological findings of psoriasis include uniform elongation of the rete ridges, thinning of the suprapapillary plate, dilated blood vessels, intermittent parakeratosis, neutrophil aggregates in the epidermis, and perivascular infiltration of lymphocytes [20].

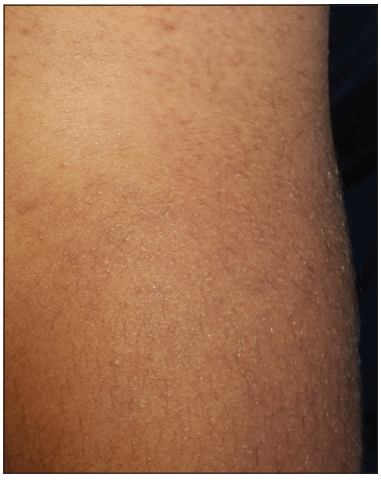

Figure 1: A 25-year-old male patient with follicular psoriasis involving the trunk.

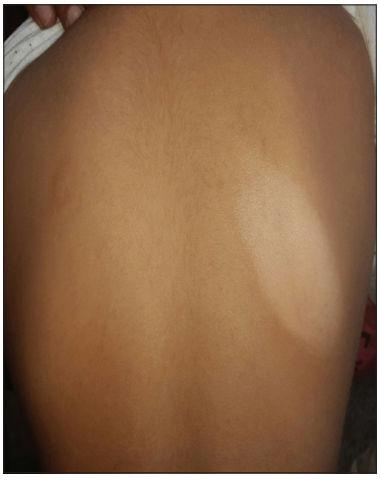

Figure 2: A 23-year-old male patient with follicular plaques of psoriasis involving the back.

VITILIGO: EPIDEMIOLOGY AND FOLLICULAR LEUKODERMA

Vitiligo is an acquired depigmenting skin disorder affecting approximately 1% of the population worldwide, and is considered one of the most common dermatoses [21]. Generally, two major types of vitiligo are categorized clinically. The more common type is the nonsegmental, or generalized, variant, which has a gradual onset of symmetrical and nondermatomal distribution. The less common variant is the segmental vitiligo, which has a rapid onset and unilateral semidermatomal distribution and stabilizes once fully developed [22]. Follicular vitiligo is not an uncommon variant, commonly seen in segmental and nonsegmental vitiligo [23]. Sharquie et al. observed that all types of vitiligo begin in the upper stable segment of hair follicles, and the initial lesions, similarly to psoriasis, may be minute or even microscopic and transient, leading to follicular leukoderma and progressing into ordinary vitiligo (Fig. 3). In the case of graying of hair, the loss of melanocytes is from the hair matrix, while in ordinary vitiligo, the loss of melanocytes is from the infundibulum and the basal layer of the epidermis. Another uncommon subtype is mucosal vitiligo, with a restricted involvement of the genital or oral mucosa [24].

Stages of Depigmentation in Vitiligo

Vitiliginous skin lesions usually progress in two stages of depigmentation. In stage one, the skin lesion is whitish-brown with a partial pigmentation loss and stays for weeks to months. In stage two, it turns ivory white and loses all pigmentation (Fig. 4). In both stage one and two, marginal and even normal uninvolved skin shows lymphocytic epidermal cell infiltrates, which are significantly higher than the normal skin control and are markedly higher in stage-one vitiligo specimens. This staging of pigmentation loss may be observed affecting the scalp hair as, in stage one, the hair appears blonde because of the partial melanin loss (Fig. 5).

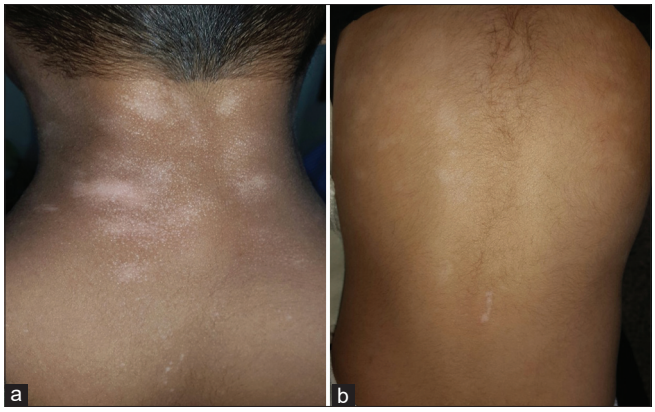

Figure 3: (a) A 25-year-old and (b) a 23-year-old patient with follicular vitiligo involving the back, showing follicular leukoderma, some coalescing to form patches of ordinary vitiligo.

Etiology of Vitiligo

The etiology of vitiligo is complex and the available data supports the development of autoimmune phenomena in genetically predisposed individuals [25]. Several theories have emerged to explain the pathogenesis of vitiligo, mainly including autoimmune, autodestructive, and neurohormonal theories [26-28]. Other studies have suggested a convergence theory, which claims that, in addition to the aforementioned theories, melanocytorrhagy, impaired melanocyte migration, and an altered cellular environment each contribute to the disease process and none is mutually exclusive [29].

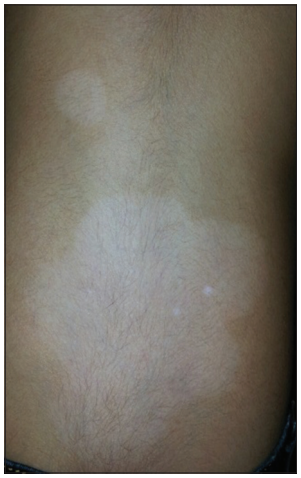

Figure 4: A 7-year-old male with vitiligo showing stage-one partial pigmentation loss progressing into stage-two complete pigmentation loss, with small ivory-white macules.

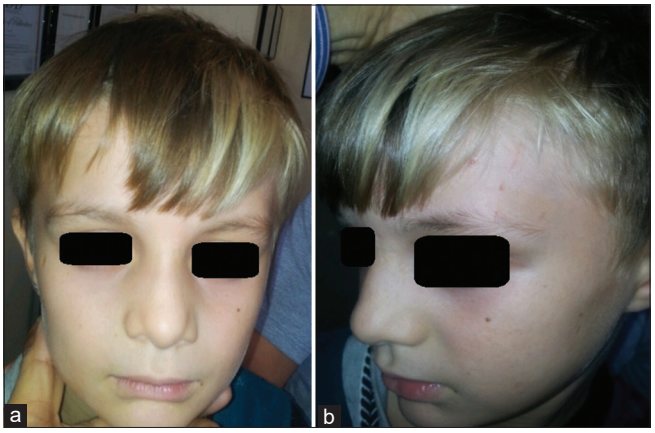

Figure 5: (a-b) An 8-year-old male patient with vitiligo showing stage-one pigmentation loss affecting the scalp hair, which changed into whitish-brown blonde.

A histopathological study of vitiligo lesions showed a significant decrease in or the complete absence of melanocytes and the presence of inflammatory cell infiltrates in vitiliginous skin, including the epidermis. Additionally, the inflammation may sometimes be more intense and severe in the epidermis, even forming Pautreier-like microabscesses with little inflammation in the dermis. This inflammatory reaction is more intense in stage-one pigmentation loss and in the marginal area. Other features, such as hyperkeratosis, acanthosis, spongiosis with exocytosis, melanophages, rete ridge elongations, and telangiectasia, may also be observed. Accordingly, vitiligo is considered an inflammatory skin disease and the epidermal lymphocytic infiltrate is most likely the primary immunological event [30]. This inflammatory reaction might begin in the hair follicles and then progress into the adjacent epidermis. This inflammatory reaction might be reflected clinically as an advancing erythematous ring at the peripheral border of the vitiligo area (Fig. 6).

The Role of Keratinocytes in Vitiligo Etiopathogenesis

Epidermal homeostasis is critical for organism survival and any changes or defects in skin barrier function may predispose to cutaneous inflammation [31]. Most studies concern themselves with the abnormalities of melanocytes rather than keratinocytes. In fact, the melanocytes in the epidermis form functional units with the adjacent keratinocytes [32], as each melanocyte in the basal layer serves multiple surrounding keratinocytes. *In vitro*, cell-to-cell interaction and cross talk are observed in the differentiation and proliferation processes of melanocytes [33]. Keratinocytes produce several growth factors as well as cytokines that affect melanocytes function, proliferation, and differentiation processes [32]. For instance, endothelin 1, stem cell factor, and GM-CSF (granulocytes–monocytes colony stimulating factor) stimulate melanocyte proliferation and melanogenesis, while IL-6 cytokines and tumor necrosis factor alpha secreted by adjacent keratinocytes inhibit melanocyte function [26,34,35].

A recent study demonstrated an associated role of keratinocytes in the pathogenesis of vitiligo by measuring the keratinocyte expression level of liver X receptor alpha (LXR-α), a member of the nuclear hormone receptors that acts as a transcription factor. It has been found that LXR-α was upregulated in perilesional and lesional skin [31]. Numerous genes that regulate melanocyte function are governed by LXR-α.

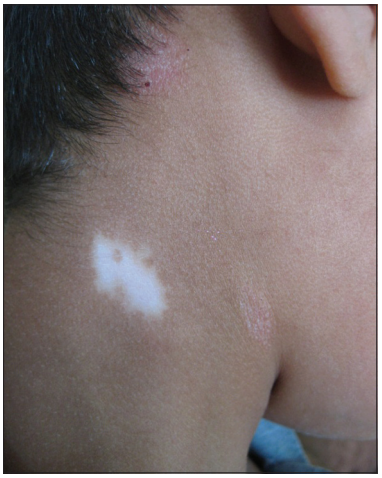

Figure 7: A 10-year-old male patient who developed a vitiligo lesion confined to a previously psoriatic lesion involving the right side of the neck.

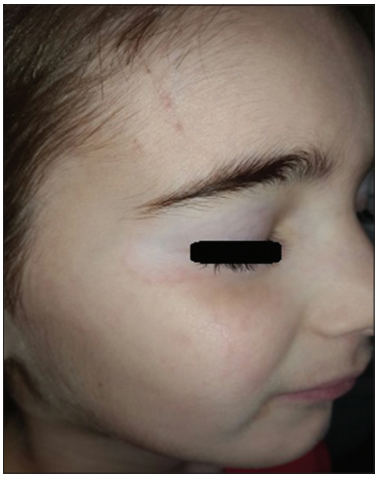

Figure 6: A 9-year-old female patient with vitiligo showing an advancing erythematous border of a vitiligo patch on the face.

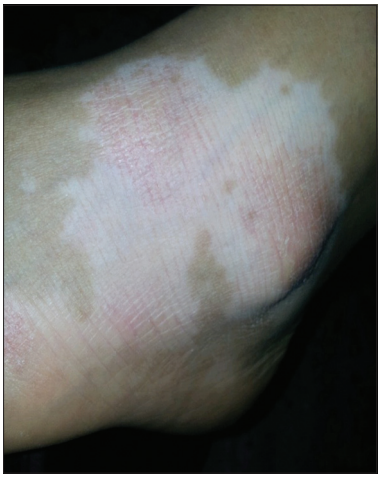

Figure 8: A 30-year-old female patient showing a coexistence of vitiligous and psoriatic lesions involving the left foot.

Activation of LXR-α by TO901317, a synthetic LXR ligand, inhibits melanogenesis through accelerated degradation of microphthalmia-associated transcription factor (MITF), a master transcriptional regulator of melanogenesis, by extracellular signal-regulated kinase (ERK) [36]. Reduction in the expression of KIT protein and its downstream effectors, including MITF-M, by melanocytes has also been detected by another study in lesional and perilesional sites of vitiligo [34]. Furthermore, structural keratinocyte abnormalities have been found to affect the growth and survival of melanocytes *in vivo*. E-cadherin, which mediates the adhesion between keratinocytes and melanocytes, has been shown to be absent or be in a discontinuous distribution across the melanocyte membrane in vitiligo patients. This defect is associated with the detachment of melanocytes from both basal and suprabasal epidermal layers [37]. Consequently, it leads to passive death of melanocytes due to loss of cell-to-cell contact and decrease in keratinocytes-derived growth factors [32]. These observations may explain the Koebner phenomenon in vitiligo under stressful skin conditions, such as trauma.

Psoriasis and Vitiligo as Close Relatives

Both psoriasis and vitiligo are inflammatory autoimmune skin diseases in which T lymphocytes play a role in their pathogenesis, and immune modulators, including topical corticosteroid, have been used successfully in their management [28,38]. A meta-analysis study conducted on a total of 120,866 psoriasis and 79,907 vitiligo patients found significantly increased odds for psoriasis in vitiligo patients, and vice versa [39]. In a study conducted on 1000 subjects, Sharquie et al. reported that the frequency of psoriasis among vitiligo patients was 6%, while 2% of psoriatic patients had vitiligo. Also, the frequency of reported family history of psoriasis among vitiligo patients and vice versa was 9.2% and 9.6%, respectively. In addition, it was found that psoriatic lesions were superimposed on vitiligo patches, and some lesions, especially in follicular psoriasis, had progressed into vitiligo (Figs. 7-10). This work suggested a close relative association between vitiligo and psoriasis [40].

Several case reports of vitiligo and psoriasis association have been mentioned in the literature. A case of vitiligo was observed in a patient who had guttate psoriasis and a positive family history of psoriasis with no other history of associated autoimmune diseases [41]. Menter et al. reported a case that developed multiple guttate psoriasis restricted totally to the areas of vitiligo lesions, suggesting that this pattern of anatomical cohabitation is sufficiently specific to make any coincidence unlikely [42]. Other cases of psoriatic lesions colonized with vitiligous patches have also been reported by other studies [43,44]. Such localization may be explained in several ways. Data from two research groups suggested the role of cytotoxic neurochemical mediators, such as substance P, as a possible mechanism of neuroecutaneous and dermatomal localization of affected areas in psoriasis and vitiligo [45,46]. In addition, the appearance of these two diseases may be due to expression of common cell surface markers that produces vitiligo as a result of autoimmune destruction and psoriasis as a result of autoimmune cellular stimulation through releasing of eicosanoids and lymphokine by keratinocytes [42]. Both diseases are affected by the pathogenic role of a high level of TNF-α [35,47]. In the case of vitiligo, TNF-α, IL-1, and IL-6 are powerful inducers of ICAM-1 in vitiligo and normal skin, which may

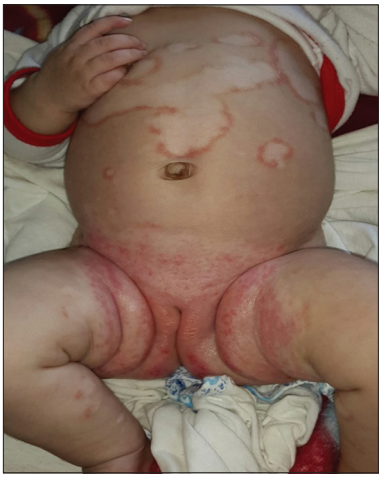

Figure 9: A one-year-old female patient with a coexistence of vitiligous and psoriatic lesions involving the napkin area and trunk.

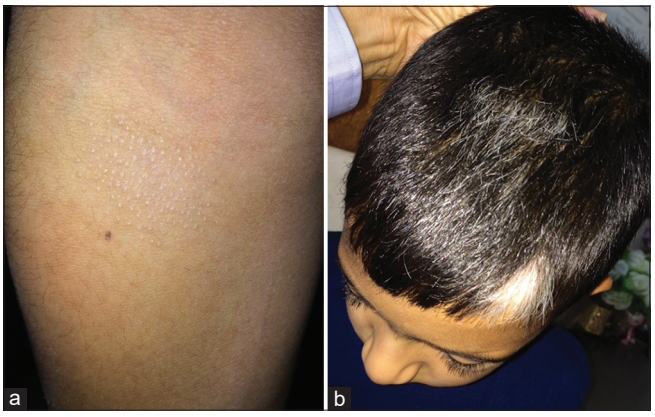

Figure 10: An 8-year-old male patient showing (a) follicular psoriasis of the thigh and (b) segmental vitiligo of the scalp.

enhance the target recognition of melanocytes by T lymphocytes, mediating cytotoxic damage [48]. The RNA released from necrotic keratinocytes might also act as an endogenous TLR3 ligand for the stimulation of ICAM-1 expression in human melanocytes [49]. TNF-α inhibits tyrosinase, tyrosine-related peptide 1 (TRP-1), and melanocyte proliferation in a dose-dependant manner [35,50]. In psoriasis, the elevated TNF-α level has been found in lesional skin and has been correlated with increased inflammation, which has successfully responded to TNF inhibitors [51]. Others have reported that this confined anatomical coexistence is possibly caused by the Koebner phenomenon [44]. Another explanation suggests the effect of cellular keratinocyte degeneration, which has been found in vitilignous skin [52]. This abnormality of keratinocytes may affect the uptake of melanosomes from adjoining melanocytes, which may lead to the accumulation of toxic intermediate metabolites in the melanin synthesis pathway. Hence, unchecked or aberrant melanin synthesis leads to cytotoxicity and destruction in a self-destruction mechanism not only to the melanocytes themselves but to the adjoining keratinocytes as well [52]. Melanocytes under stress undergo apoptosis, which also mediates the targeting of melanocytes by the immune system. If the immune response is sustained, melanocyte death may continue, leading to the spread of lesions to areas distant from the initial site [53]. Lastly, considering a genetic role, both diseases have been found to be linked by the same single-nucleotide polymorphism (SNP), rs9468925, at the HLA-C/HLA-B locus outside PSOR1 in the Han Chinese population [54].

Pityriasis Alba

Pityriasis alba is a common localized hypopigmenting disorder with numerous clinical variants [55], progressing in three stages. The first stage, or the early stage, begins as an erythematous patch with an elevated border lasting for several weeks. The second stage, or the intermediate stage, is characterized by the replacement of the patch with a smooth scaly layer (Fig. 11). Both of these two stages are marked by the presence of pinpoint follicular papules. Lastly, the third stage presents itself as a round hypopigmented macule with well-defined borders and loosely adherent scales [55]. This benign skin disorder predominantly affects children and adolescents between 3–16 years of age at a 5% prevalence rate [56]. It mainly affects the face, especially the cheeks. However, in 20% of affected children, the neck, arms, and shoulders are involved as well as the face. Less commonly, scattered lesions involve the trunk and limbs, sparing the face. Individual lesions are rounded, oval, or irregular hypopigmented patches that are usually not well marginated [57]. As pityriasis alba often coexists with atopy, it is considered a milder form of the disease [58]. However, pityriasis alba is not an entity by itself as it may be a manifestation of numerous other skin diseases, such as psoriasis, vitiligo, and other drying skin conditions, even as part of a tinea skin infection.

The pathogenesis of pityriasis alba remains a controversy. Some factors are reported to be associated with its development, including male sex, darker skin, exposure to sunlight, and atopy diathesis [59]. Other infectious causal factors, as microorganisms such as *S. aureus*, *Pityrosporum*, and *Aspergillus*, have been suggested but none has been confirmed [60]. However, in a study conducted in India and involving 200 patients, helminthic infestation and iron deficiency

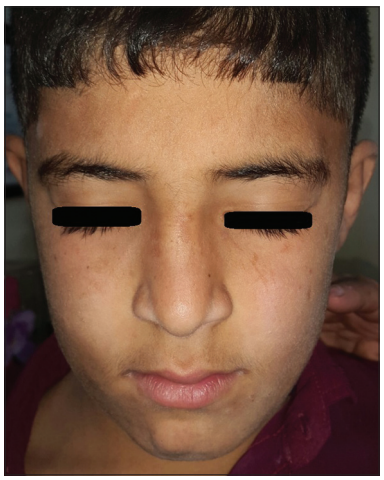

Figure 11: A 10-year-old patient with pityriasis alba showing scaly whitish erythematous patches with superimposed minute follicular papules involving the face.

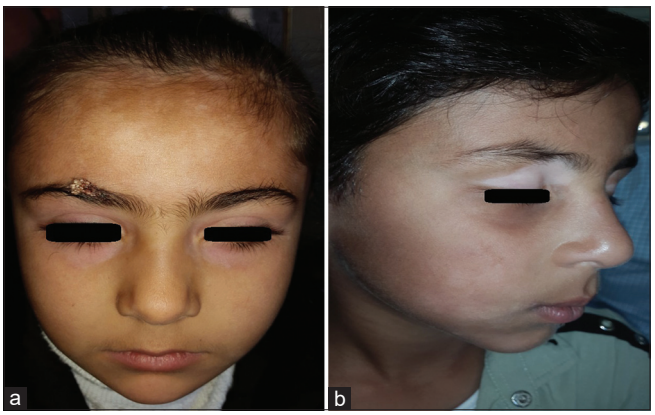

Figure 12: Coexistence of pityriasis alba and vitiligo in (a) a 9-year-old female and (b) an 11-year-old male.

anemia were detected in 15.5% and 16.5% of patients, respectively [61]. However, these findings might be coincidental as malnutrition is a common issue among the Indian population. A histopathological study involving 56 patients found a marked reduction of melanin with no significant differences in the number of melanocytes between lesional and normal skin. However, ultrastructural observations revealed a reduction in melanosomes in the keratinocytes and degenerative changes in the melanocytes. Other histopathological features of pityriasis alba were found to be spongiosis with exocytosis, hyperkeratosis, and acanthosis in decreasing order of frequency [60], and this histological picture may mimic that of early psoriasis and vitiligo [30].

Vitiligo and Pityriasis Alba

Both vitiligo and pityriasis alba are inflammatory hypopigmented skin diseases [62,63]. However, pigment loss differences can be observed. In pityriasis alba, it is usually partial, with a centrifugal extension beginning from the center of the lesion, and this partial pigmentation loss may be considered stage-one melanin loss as in vitiligo, while pigmentation loss in vitiligo is either partial (stage one) or complete (stage two) with well- or ill-defined demarcation from the surrounding skin. It is worth noting that both conditions may begin as a scaly erythematous dermatitis-like presentation and mimic each other [30,62,64].

In a study involving 134 patients with pityriasis alba, Sharquie et al. observed different variants: scaly hypopigmented patches in 44%, smooth hypopigmented patches in around 30%, and a combination of different stages in around 9%. Also, a coexistence of both pityriasis alba and vitiligo (Figs. 12 and 13) with a positive Wood's lamp test was observed in 14% of patients. Up to 57% of these patients with combined lesions had a positive family history of vitiligo. Furthermore, 14 (43.75%) patients out of 32 with pityriasis alba showed progression into vitiligo patches. Nine biopsies showed complete absence of melanin in lesional skin in Fontana–Masson stain [64]. Accordingly, there are 4 findings that may explain the possible association of pityriasis alba with vitiligo, including a positive family history and a possible genetic link, the development of both skin lesions in the same patient, a positive Koebner phenomenon in pityriasis alba, and lastly progression of pityriasis alba in the same patient into vitiligo during a follow-up.

Pityriasis Alba as a Manifestation of Psoriasis or Vitiligo

Hence, through clinical observation and research studies, we have found that vitiligo or psoriasis may present themselves in their early stages as pityriasis alba on the face (Fig. 14), and there have been several pityriasis alba cases coexistent with vitiligo lesions. Furthermore, some cases of pityriasis alba progressed, with time, into vitiligo [64] or psoriasis. In the same context, cases of pityriasis alba involving a lower limb in psoriasis distribution sites have also been reported [65]. In addition, a presentation of a follicular lesion involving the upper stable segment of hair follicles in the early stages of pityriasis alba, psoriasis, and vitiligo has been observed [2,23,66] along with the sharing of the same inflammatory cell infiltrates. All these findings suggest a shared pathology and an interchangeable behavior of these skin disorders.

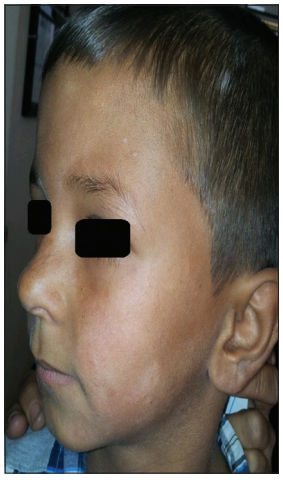

Figure 13: An 8-year-old male patient with pityriasis alba involving the face and vitiligo involving the scalp hair.

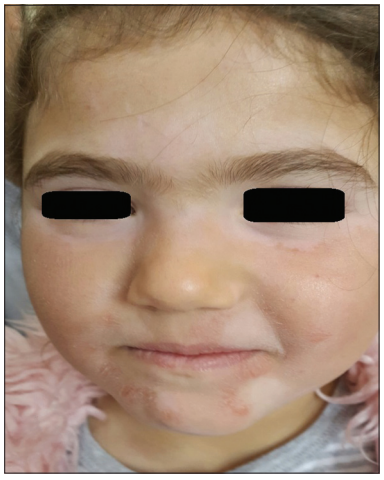

Figure 14: A 7-year-old female patient showing a coexistence of psoriasis, pityriasis alba, vitiligo lesions involving the face.

Hair Follicles as the Early Target Area for Psoriasis, Pityriasis Alba, and Vitiligo

Suspended inside the dermis, hair follicles have a more extensive surface area that is more exposed to surrounding pathological damaging processes. In addition, the hair follicle has its separate blood supply. This does indicate a more intense inflammatory reaction in the hair follicle in comparison with the neighboring basal layer of the epidermis, where there is only one surface for basal keratinocytes that is exposed to the dermis. Also, antigenic stimulation may be more intense in hair follicles than on the epidermis, as the density of the various antigens and receptors may be increased in the keratinocytes of the outer root sheath of hair follicles than those of the epidermis. Accordingly, the immunological and pathological reaction should be more florid in the hair follicles [23,67,68]. Hence, we expect that all inflammatory skin diseases where the epidermis is the target area may begin at the hair follicles and may be more intense than the surrounding epidermal cells. This inflammatory reaction will show as minute macules or papules that coalesce together to form plaques or patches, as seen in vitiligo, psoriasis, seborrheic dermatitis, and many other diseases [58,67-70]. The immunological and inflammatory damage may involve the bulb of the hair, as in alopecia areata and graying of hair, or involve the infundibulum and isthmus, as in lichen planopilaris and discoid lupus erythematosus. Similarly, with hyperkeratosis of the skin, it will be more obvious in the orifices of hair follicles than in the surrounding epidermis, as seen in many cases of keratosis pilaris [68]. Although the diseases begin as follicular lesions, this change may be microscopic and difficult to see with the naked eye, transient, or clinically obvious and easily seen.

The question, thus, should arise as to why follicular lesions cannot always be observed clinically or histopathologically in these diseases. The following points aim to offer answers:

1. The lesion might be so minute that it cannot be seen easily.
2. The pathological changes might be so minimal that they cannot be observed on a histopathological section.
3. The hair follicle involvement might have been missed during the sectioning of the biopsy.
4. The follicular lesion might be transient and then spread to the actual epidermis.

Finally, what about the areas with no hair follicles, such as the palms, lips, and mucosas? In this case, the orifices of the sweat and salivary glands will represent the orifices of the hair follicles [71].

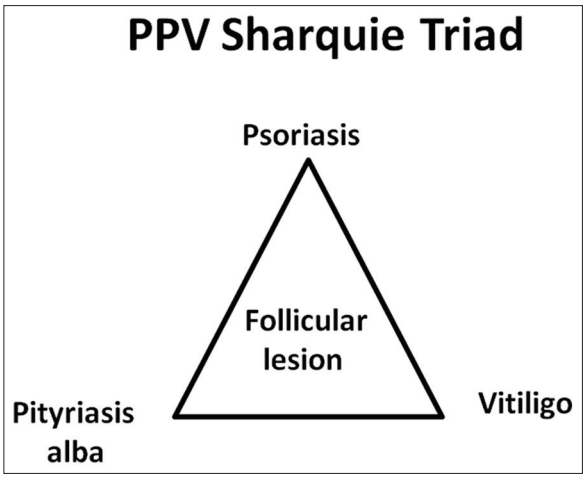

Figure 15: PPV Sharquie triad.

Hence, for the above reasons, the prevalence of actual follicular vitiligo, follicular psoriasis, and even follicular pityriasis alba cannot be well determined in the general population.

CONCLUSION

According to our clinical findings and research studies, in addition to a literature review, we have observed a close link between psoriasis, pityriasis alba, and vitiligo, wheras patients with pityriasis alba or psoriasis often develop vitiligo, and vice versa, or have a family history of psoriasis or vitiligo in favor of a common genetic background. Hence, this body of data supports our observation that psoriasis, pityriasis alba, and vitiligo constitute one triad on the basis of clinical, immunological, and histopathological findings (Fig. 15). Also, all these three diseases may begin in hair follicles and then progress to involve the epidermis. However, this may not be observed as the lesions might be transient, minute, or microscopic.

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Clinical Image

Chronic keloidal nodules of the hand: Don't forget the cutaneous leishmaniasis

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Cutaneous leishmaniasis (CL) remains endemic in certain regions of the world. Several atypical presentations have been described in the literature. Herein, we report an unusual case of CL due to *Leishmania infantum (LI)* manifesting itself as chronic keloidal nodules on the hand.

A 47-year-old patient from southeastern Tunisia presented at our department with non-healing nodules on the back of the right hand evolving for the last two years. The nodules recurred after surgical excision and antibiotic treatments. An examination revealed two non-ulcerated keloidal nodules on the back of the right hand, 2.5 cm and 1 cm in diameter (Fig. 1). A histopathological examination revealed hyperkeratosis, acanthosis, and dermal granulomatous inflammation with a predominantly histiocytic infiltrate containing small and spherical non-flagellated cells with bar-shaped paranuclear kinetoplasts. The diagnosis of chronic CL was retained. Species typing by polymerase chain reaction (PCR) revealed the presence of *LI MON-24* in the skin lesions. The patient was treated with meglumine antimoniate intramuscularly with a good response.

In Tunisia, CL is mainly caused by *Leishmania major*, *LI*, and *Leishmania tropica (LT)* [1]. Its clinical and progressive features depend on the infecting species and the immune response of the host [2]. Chronic CL (persistent for twelve months or more) is easily misdiagnosed because the lesions are often atypical and may be confused with other inflammatory and neoplastic skin diseases [3]. Furthermore, due to the low density of *Leishmania* bodies in this form, PCR is the most accurate diagnostic technique. The main causal agents of chronic CL are *LT* in the Old World and, less commonly, *Leishmania braziliensis* in the New World. Eroglu et al. reported *LI* to be a causal agent of the nodular form of chronic LC [3], as in our patient.

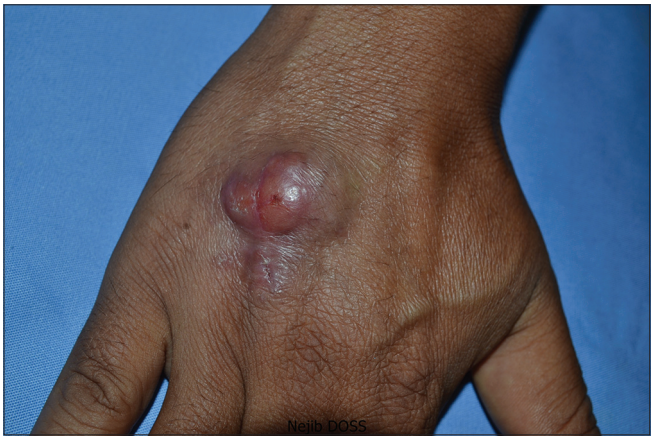

Figure 1: Non-ulcerated erythematous cutaneous nodules on the back of the right hand, without scales or crusts, 2.5 cm and 1 cm in size by the long axis.

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

Contact urticaria with a chemical burn caused by a hydroalcoholic gel with chlorhexidine

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Chlorhexidine is used as an antiseptic and disinfectant agent because of its wide antimicrobial spectrum. Immediate hypersensitivity reactions to chlorhexidine have rarely been reported in the literature [1]. One case of contact urticaria caused by chlorhexidine has been reported following dermal exposure to a hydroalcoholic gel.

A 45-year-old female with obsessive–compulsive disorder presented with an acute itchy eruption on the neck and cleavage, which appeared five days earlier, ten minutes after the frictional application of a hydroalcoholic gel to prevent a COVID-19 infection. The patient presented urticarial lesions with annular erythematous wheals on the neck and cleavage and extending to the submammary area. Brownish scales were also present, indicating the beginning of skin healing after the chemical burn (Figs. 1-3). There were neither angioedema nor respiratory symptoms. She reported a similar eruption located initially on the hands and forearms after the first

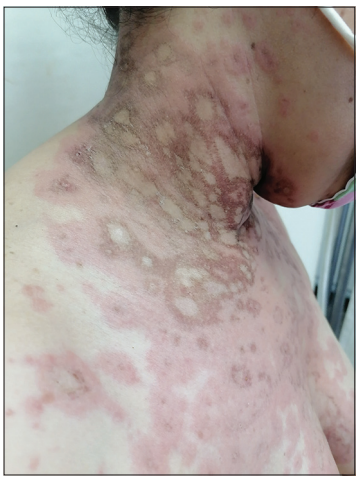

Figure 2: Urticarial lesions and annular erythematous wheals with brownish scales.

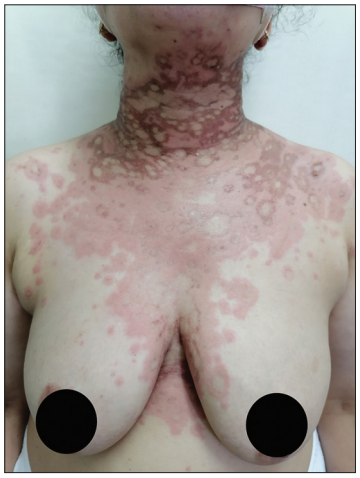

Figure 1: Urticarial eruption on the cleavage and extending to the submammary area.

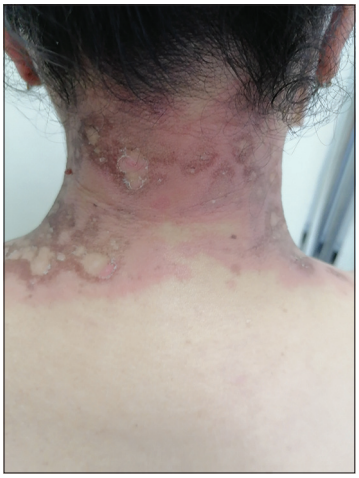

Figure 3: Circumferential lesions on the nape of the neck matching the area of application of the hydroalcoholic gel.

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application of the hydroalcoholic gel, which resolved spontaneously in several hours. She had never used any product containing chlorhexidine before and had no history of allergic reactions. Contact urticaria to the hydroalcoholic gel was suspected. The patient was treated with cetirizine at a dose of 10 mg once daily and scar creams, with a rapid resolution of the 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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Letter to the Editor

A case of resistant generalized verruca vulgaris treated with systemic isotretinoin

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Sir,

Verrucae are infections of the human papilloma virus (HPV) associated with the development of epithelial hyperplasia [1]. HPV is thought to be implanted in basal keratinocytes because of the mechanic damage to the skin barrier [2]. Out of the two hundred species of HPV, around twenty cause infection in humans [2,3]. HPV infections are spread worldwide [4]. HPV lesions are more common in immunodeficiencies such as lymphoma, chronic lymphocytic leukemia, AIDS (acquiredimmune deficiency syndrome) and in patients receiving immunosuppressants [5,6]. Although numerous treatments for verrucae exist, none isspecific to HPV. These include both nonsurgical and surgical methods, as well as keratolytic agents (salicylic acid), cryotherapy (liquid nitrogen), and lasers (pulse dye, CO_2, etc.) [1,4-6].

Herein, we report a case of treatment-resistant generalized verruca vulgaris and its excellent response to treatment with systemic isotretinoin.

A 32-year-old male was admitted to our outpatient clinic with warts on the hands, feet, and face persistent for the last nine years. A dermatological examination revealed diffuse verrucous lesions on the dorsum of the hands and feet, the palmar surfaces, the fingers, and the face (Fig. 1).

Previously, the patient underwent cauterization and cryotherapy for a period of three years at another clinic but the lesions continued to develop. Acitretin was used for four months and podophyllin for three months but the lesions did not regress. Similarly, after treatment with interferon alfa-2a at a dose of 4,500,000 IU three times a week for a total of eighteen times systemically and simultaneously, the localized lesions continued to develop and did not regress.

No defects in the immune system were detected, except for hypogammaglobulinemia, which was also detected by an allergy and immunology department. A CXCR4 gene mutation test was performed to consider WHIM syndrome but was negative. Finally, systemic isotretinoin therapy was prescribed. After systemic isotretinoin at a dose of 20 mg/day for twelve months and 10 mg/day for six months, the lesions almost completely regressed (Fig. 2).

After systemic isotretinoin, all verrucae from the body of the patient completely regressed, with only 1–2 pieces smaller than 1 cm remaining. Local treatment with fractionated CO_2 laser was administered to prevent relapse from the remaining foci on the feet. No recurrence was observed during a fourteen-month follow-up period. Informed consent regarding the use of this information in scientific publication was obtained from the patient.

Immunodeficiency states should be investigated if more than twenty verrucous lesions are found in more than one region of the body or if, in the case of acral localization, most of the fingers are affected [6]. Under these conditions, further investigation of the patient ought to be undertaken. Syndromes that a generalized verruca may accompany include Epidermodysplasia verruciformis (EV), WHIM syndrome (warts, hypogammaglobulinemia, immunodeficiency, myelokathexis), WILD syndrome

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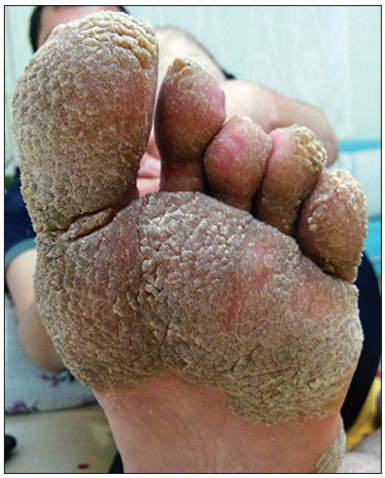

Figure 1: Diffuse verrucous lesions on the palmar surfaces of the feet.

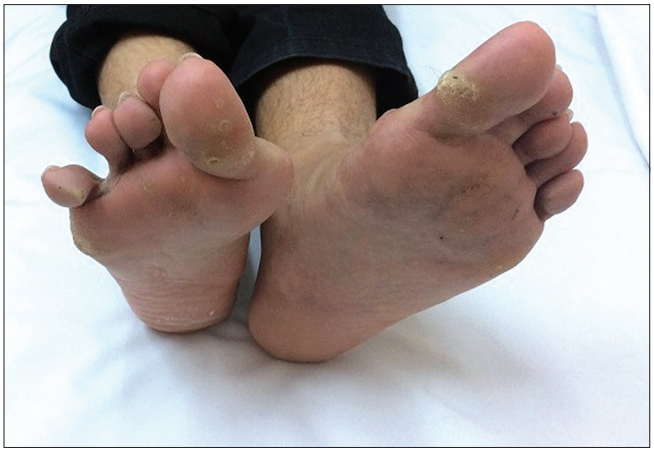

Figure 2: The lesions in almost complete regression.

(warts, immunodeficiency, lymphedema, dysplasia), severe combined immunodeficiency (SCID), hyper IgM syndrome, hyper IgE syndrome, atopic dermatitis, AIDS, and chronic lymphocytic leukemia [4-6].

Methods such as cryotherapy, electrocautery, lasers, and chemical agents (podophyllotoxin, 5-fluorouracil, bleomycin, dichloroacetic acid, formaldehyde, glutaraldehyde, cantharidin, lactic acid, monochloroacetic acid, salicylic acid, trichloroacetic acid, silver nitrate, etc.) are employed in the treatment of verrucae [6]. Immunotherapy methods may be preferred in patients unresponsive to commonly used treatments. Interferon alfa (IFN-α) is used systemically, topically, or intralesionally in the treatment of verrucae [7].

Systemic isotretinoin has been used to treat acne vulgaris for more than thirty years. However, isotretinoin also proves potentially helpful for numerous dermatologic disorders other than acne vulgaris. Diseases such as psoriasis, pityriasis rubra pilaris, sarcoidosis, condylomata acuminata, cutaneous T-cell lymphoma, skin cancer, rosacea, hidradenitis suppurativa, granuloma annulare, lupus erythematosus, and lichen planus have been shown to respond to its immunomodulatory, anti-inflammatory, and anti-tumor effects [8]. Isotretinoin also helps to prevent skin cancers such as basal cell carcinoma and squamous cell carcinoma. The literature provides cases of condyloma acuminata treated with systemic isotretinoin and cases of verruca plana treated with low doses of systemic isotretinoin (30 mg/kg) [8-10]. Reported was also a case of an immunosuppressed patient in whom a resistant genital wart was successfully treated with systemic isotretinoin [10]. Both immunosuppression and generalized verruca vulgaris distinguished our case from other cases.

Recalcitrant warts present a private therapeutic cause. Their duration may be lengthy and especially resistant to treatment [9]. We achieved positive results with long-term (eighteen months) and low-dose (10–20 mg) systemic isotretinoin. Because of these findings, oral isotretinoin seems to be the most effective therapy and one available at a reasonable cost for recalcitrant warts when compared with the findings of previous studies.

Here, we would like to stress that treatment with systemic isotretinoin is an inexpensive and more effective treatment option for patients with resistant verrucae than conventional treatments. Systemic isotretinoin may be an alternative drug for the treatment of verrucae so long as its potential for teratogenicity is taken into account.

Consent

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

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Letter to the Editor

One train hiding another: Antiphospholipid syndrome as a risk factor for Nicolau syndrome?

Stijn Maes[1], Joris Schollaert[1], Glenn Broeckx[2], Olivier Aerts[3], Niels Horst[3]

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Sir,

A 42-year-old female, known to have antiphospholipid syndrome (APS) and cutaneous lupus erythematosus, was hospitalized for type 2 non-ST segment elevation myocardial (NSTEMI) and bilateral adrenal infarction. She received 4.000 IE enoxaparin (low molecular weight heparin, LMWH) as secondary prophylaxis injected subcutaneously (sc.) at the anterior side of both upper legs. The day after, the LMWH dose was raised to 6.000 IE sc., after which the patient immediately developed an extremely painful and rapidly enlarging purpurous–necrotic skin lesion, albeit only in the upper right leg (Fig. 1). Duplex echography excluded deep vein thrombosis (DVT), and heparin-induced thrombocytopenia (HIT) was considered unlikely as no anti-PF4-heparin antibodies were present. Antigen tests equally excluded heparin-induced skin necrosis (HISN), a rare subtype of HIT with symptoms similar to Nicolau syndrome (NS). Moreover, the continued use of enoxaparin, without further worsening of the symptoms or the development of new lesions, equally argued against a diagnosis of HIT or HISN. A histopathological examination of a skin biopsy revealed acute, ulcerative, and pustular dermatitis with accompanying edema of the papillary dermis and steatonecrosis of the hypoderm. There was no clear vasculitis. Despite the absence of clearly visible emboli, easily missed in a small biopsy specimen, these characteristics were highly suggestive of NS (Figs. 2a – 2c). Despite the development of NS to enoxaparin sc., the latter was continued as the thromboembolic risks of APS were considered more important. Oral corticosteroids were administered to

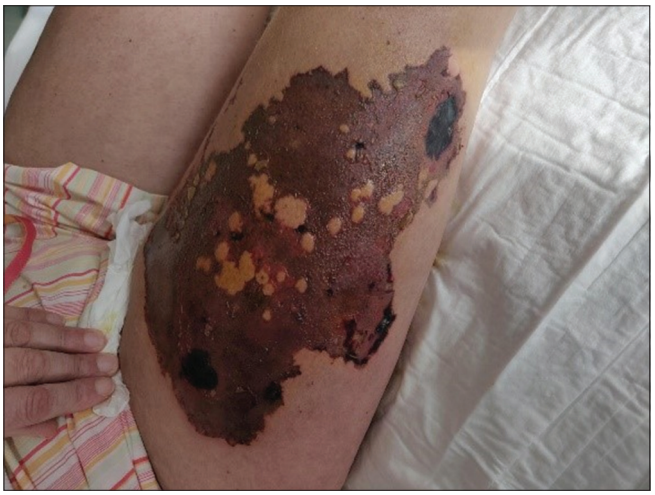

Figure 1: Acute, extremely painful, and necrotizing skin lesion on the right upper leg, immediately following subcutaneous (sc.) injection of low molecular weight heparin (LMWH; enoxaparin) in a patient with antiphospholipid syndrome (APS), with the clinical presentation and histology suggesting Nicolau syndrome (NS).

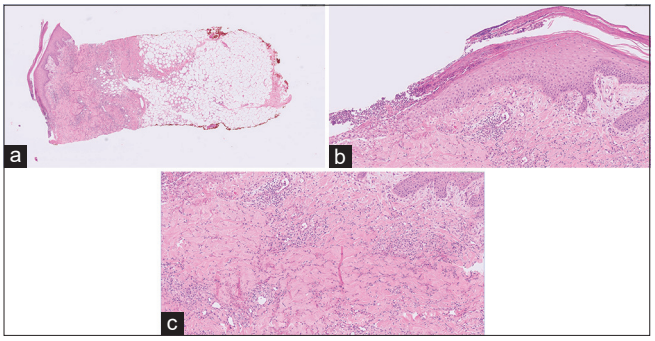

Figure 2: Histopathological findings from a skin biopsy with H&E staining: a) magnified overview (5×); b) detailed view of the epidermis and papillary dermis (20×) with ulceration on the left side accompanied by intracorneal pustulosis of the surrounding epidermis; c) detailed view of the dermis (20×) with acute perivascular inflammation and edema in the dermis and no clear vasculitis or emboli.

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prevent further progression of the affected area, and antibiotics (piperacillin/tazobactam, later switched to meropenem) to treat the bacterial superinfection. Also, because both legs became diffusely edematous, with extension toward the abdomen, an additional treatment with furosemide had to be initiated. Surgical debridement of the necrotic tissue was performed until vascular tissue was seen. Following the debridement, two months of vacuum-assisted closure (VAC) therapy was initiated and, eventually, the created skin defect was restored with a skin graft.

NS is a rare, acute, and iatrogenic dermatologic complication, predominantly following an intramuscular (im.) injection of certain medications and, more rarely, as in the present case, occurring after a sc. injection. This condition typically begins with immediate and extreme pain in the injection site, followed by a localized livedoid-like or violaceous plaque. After the acute phase—usually after three days—the skin begins to necrotize, often necessitating surgical debridement [1,2]. The diagnosis of NS is made clinically, sometimes supported by histology, and therapy should initially focus on pain reduction and the prevention of infection. Importantly, the application of ice should be avoided as cold temperatures cause vasoconstriction and may thus further aggravate necrosis. Besides, systemic corticosteroids and revascularization therapies—that is, anticoagulants, pentoxifylline, etc.—are often employed as well [3]. Depending on the evolution and the degree of necrosis, surgical debridement may become necessary. Although the exact pathogenesis of NS remains poorly understood, thromboembolic vascular lesions in the skin are believed to play a major role. The present case suggests that, in the setting of APS (a hypercoagulable state), the development of NS might be facilitated, as such becoming likely even after sc. injections and even if the latter concerns a (therapeutic) anticoagulant. Nevertheless, in view of the severe consequences potentially associated with untreated and symptomatic APS, continued treatment with the same sc. agent may then still be possible.

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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Letter to the Editor

Actinic porokeratosis effectively treated with nivolumab immunotherapy

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Sir,

Actinic porokeratoses form a heterogeneous group of dermatological conditions secondary to an epidermal keratinization disorder [1,2].

We report the case of a patient with actinic porokeratoses associated with a locally advanced squamous cell carcinoma of the face treated successfully with nivolumab (anti-PD-1).

A 71-year-old patient, followed for actinic porokeratoses for twenty years and treated with retinoids and vitamin B, was referred to the oncodermatology services of the University Hospital of Nantes for the management of an infiltrating squamous carcinoma of the right cheek.

A clinical examination found a patient, otherwise in good general condition, with an ulcerative mass on the right cheek with several diffuse erythematous scaly lesions throughout the body in relation to the patient's actinic keratosis. An examination of the areas of the lymph nodes failed to find adenopathy. The rest of the somatic examination was unremarkable. The biological balance was free of anomaly and a radiological examination did not find a metastasis elsewhere.

An anti-PD-1 treatment with nivolumab at a dose of 240 mg every two weeks helped to stabilize the patient's squamous cell carcinoma and cure his actinic porokeratoses after four months of treatment (Figs. 1a – 1c).

Actinic porokeratoses are generally resistant to usual treatments and pose a difficulty in their therapeutic management. The risk of degeneration varies depending on the clinical form, ranging from 7% to 19% [1]. The efficacy of anti-PD-1 therapy on skin squamous cell carcinomas and xeroderma pigmentosum has already been reported but has not yet been well illustrated in the management of actinic porokeratoses. The first resolved case of actinic porokeratosis under immunotherapy was reported by Salomon et al. in 2017 [1]. The etiopathogenesis of this condition is not yet well understood. Genetic factors have been suspected in familial forms. Other studies found chromosomal instability in fibroblasts in people with porokeratotic lesions after sun exposure. Treatment usually involves keratolytics, destructive agents, local chemotherapy with 5-fluorouracil, or immunosuppressing treatment with imiquimod, which rarely lead to a complete regression. In our case, immunotherapy led to the improvement of the

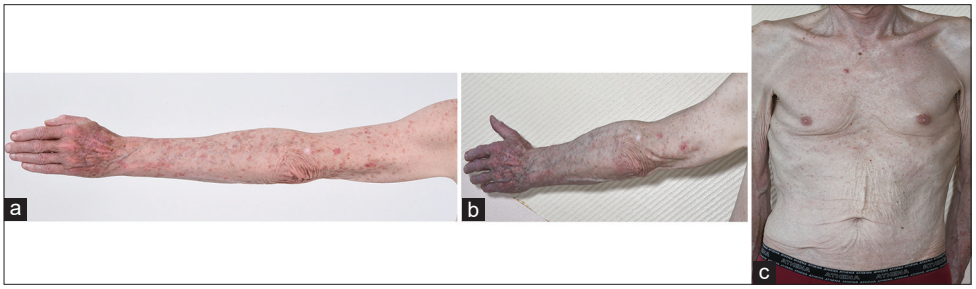

Figure 1: The good clinical evolution of the actinic porokeratosis under immunotherapy with nivolumab (anti-PD-1) (a) before and (b-c) after.

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squamous cell carcinoma as well as the healing of the patient's resistant actinic porokeratoses [2,3].

Further specialized studies would be necessary in order to explore the efficacy and pathophysiological mechanism of this therapeutic option.

CONCLUSION

Immunotherapy may be an effective therapeutic option for chronic porokeratoses resistant to usual treatments.

Consent

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

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

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Letter to the Editor

Hypertrichosis on the periphery of the scar of a thermal burn

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Sir,

The term *hypertrichosis* refers to the growth of hair that is considered excessive for the site and the patient's age [1]. It is classified into localized or generalized, both either congenital or acquired [2]. Herein, we report a case of localized hypertrichosis.

A 35-year-old Ethiopian male presented himself with chickenpox and was found to have excessive coarse hair on the periphery of an old scar that resulted from a thermal burn in childhood (Fig. 1).

The patient's family used to employ cautery as a traditional method of therapy for disease but he was incognizant of the reason for the cautery in his case.

He noticed the increased growth of hair around the scar a long time ago and failed to recall its first appearance. No hypertrichosis was found on the rest of the body. He had no history of medical issues and had not taken any medications before.

Box 1 lists selected causes, including conditions, associated with localized hypertrichosis [1-7], some only temporary and not persistent.

Several mechanisms have been proposed to explain the hypertrichosis in some of these conditions. For instance, a local increase in blood flow around the site of a fracture and the increased metabolism of the local soft tissues were thought to be the probable reason for the localized increase in hair growth after cast application [1].

Cases of hypertrichosis in relation to burns have been reported as early as 1965 in the indexed medical literature [7].

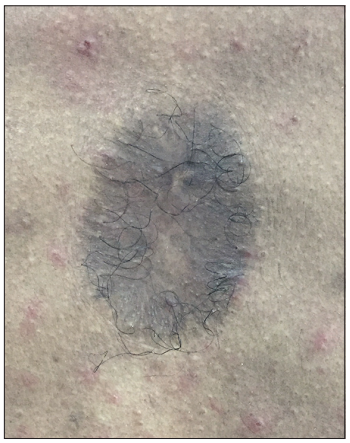

Figure 1: Hypertrichosis on the periphery of the scar of a burn on the chest.

Box 1: Selected causes, including conditions, associated with localized hypertrichosis [1-7]

Becker's nevus.
Cast application.
Infection and inflammation (areas overlying thrombophlebitis or chronic osteomyelitis and near inflamed joints in association with gonococcal arthritis).
Inflammatory dermatoses (after eczema and varicella).
Porphyria cutanea tarda.
Trauma (repeated friction and habitual biting).
Vaccination.

Shafir and Tsur reported a female who suffered a deep second-degree burn on the lateral aspect of the left thigh. She was hospitalized for one month after the accident due to the infection of the deep second-degree wound [4]. Meanwhile, the patient noticed that hair started growing on the periphery of the burned area. The area healed gradually and, on a follow-up six months later, it had remained hairy. The authors proposed that a burn may be regarded as a source of irritation, giving rise to localized hypertrichosis [4].

We believe that this phenomenon is not especially rare but it is reported less frequently as it is of lesser concern

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to the patient. We agree, however, that the question as to why some develop reactive hypertrichosis and most do not remains unanswered [4].

Consent

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Letter to the Editor

Lipedematous scalp: A possible association with Ehlers–Danlos syndrome

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Sir,

A 40-year-old male presented to the dermatology department with a history of a gradual diffuse swelling of the scalp felt as if underlaid with cotton. No previous trauma or surgery to the head or scalp were reported. He was not hyperlipidemic. The family history revealed no similar complaints in parents and siblings. The medical history included an unclassifiable form of Ehlers–Danlos syndrome (EDS) diagnosed at the age of 28 by the presence of a velvety, fragile skin, cutaneous hyperelasticity, peculiar cigarette-paper scars (Figs. 1a and 1b), subcutaneous molluscus pseudotumor formation, hypermobility of the joints (Fig. 1c), keratoconus, and mitral insufficiency. On examination, the surface of the scalp had an irregular appearance and was smooth, boggy, spongy, and fluctuant on palpation (Fig. 2). No clinical signs of inflammation were apparent. Hair density and length were normal. A histopathologic examination of a scalp skin biopsy revealed increased thickness of subcutaneous fat tissue close to the epidermis (Fig. 3) Thus, the diagnosis of a lipedematous scalp (LS) associated with EDS was reached. Therapeutic abstention happened to be the best management strategy since the patient was asymptomatic.

An LS is a rare disease characterized by a thick and boggy scalp due to increased thickness of subcutaneous fatty tissue. In 1935, Cornbleet described the first case in an African female. Up to date, about fifty cases of an LS have been reported, mostly in females [1,2]. To the best of our knowledge, only two male cases, excluding our patient, have been recorded [2,3]. Most patients with an LS are asymptomatic, as our case. The pathogenesis of an LS remains unknown. It is believed, however, that leptin, a hormone regulating fat masses and their distribution, may be inducing hyperplasia of subcutaneous fat [2]. Another theory explaining its pathogenesis involves metaplasia and displacement of adipose tissue [1,4]. EDS has not been reported in association with an LS but several women with lipedema of the lower body were reported to have a positive Beighton score (≥ 5) associated with joint pains, suggesting EDS hypermobility type (EDS-HT), formerly type III [5]. Furthermore, a single case of lipedematous alopecia, another entity that is part of the same disease spectrum associated with sparsity and shortness of the hair [3], was also described in association with significant hyperelasticity of the skin and hyperlaxity of the joints without other criteria to confirm true EDS [6]. No treatment was attempted in

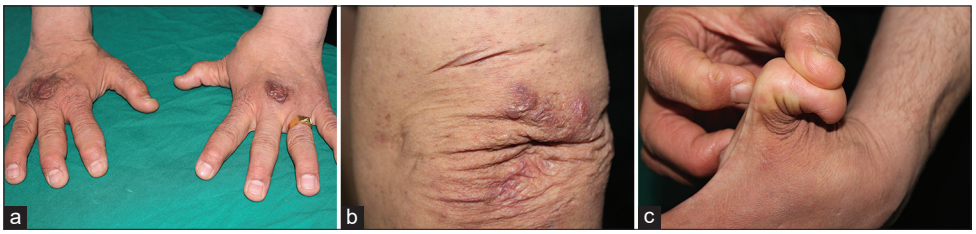

Figure 1: (a-c) Cutaneous hyperelasticity, fragile skin, peculiar cigarette-paper scars, hypermobile joints.

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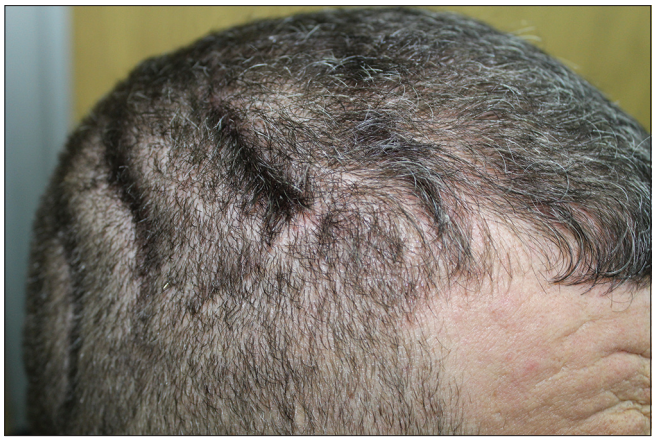

Figure 2: Clinical appearance with thickened skin but without alopecia.

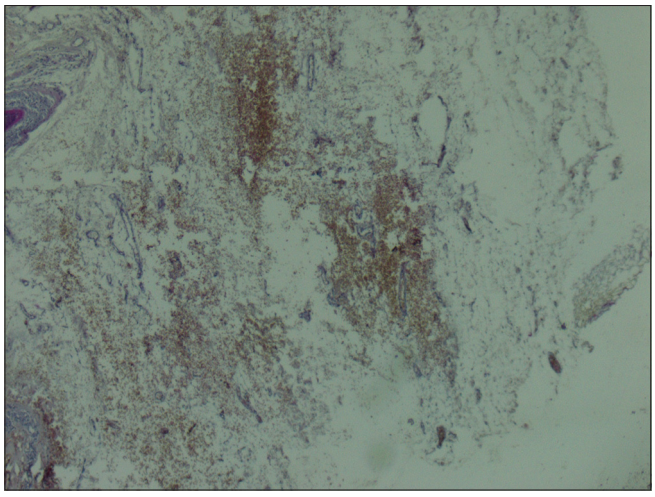

Figure 3: Histopathological examination revealing increased thickness of subcutaneous fat tissue close to the epidermis (H&E; 40×).

our case, although surgical intervention with debulking and scalp reduction have been proposed to treat an LS, but with variable results [1].

In conclusion, an LS is a rare disorder that dermatologists should be aware of, as it is not difficult to diagnose. Whether the coexistence of an LS and EDS is merely coincidental or a true association remains unclear. Further investigative studies are needed to assess a possible pathophysiological link.

ACKNOWLEDGMENTS

We would like to thank the patient for granting permission to publish this manuscript in the form of written consent.

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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Letter to the Editor

A pediatric case of scleroderma en coup de sabre and segmental vitiligo

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Sir,

Scleroderma *en coup de sabre* is a rare subtype of localized scleroderma in children that affects the face. Localized scleroderma is an autoimmune inflammatory sclerosing disorder, and thus the co-existence of secondary autoimmune disorders has been reported [1]. Herein, we report a rare pediatric case of the co-existence of scleroderma *en coup de sabre* and segmental vitiligo.

A 14-year-old female was referred to our department complaining of a facial lesion without a family history of connective tissue disease. A physical examination showed slightly reddish and slightly depressed longitudinal plaques on the forehead extending onto the scalp (Fig. 1). However, sclerotic lesions were not observed on the trunk and extremities. Hemiatrophy was not observed on the face. The patient had no medical history of seizures or epilepsy. Further examination revealed segmental vitiligo involving the left lower extremity (Fig. 2), but no vitiliginous lesions other than on the left leg. A biopsy specimen from the forehead revealed thickened collagen fibers in the lower dermis, and a specimen from the thigh revealed a loss of epidermal melanocytes. A laboratory examination detected antinuclear antibodies (1:80) but no anti-centromere or anti-Scl-70. Oral prednisolone 20 mg/day was administered, which was gradually tapered and ceased over the next three months. The facial erythematous lesion was sufficiently improved, whereas the depigmentation on the lower extremity remained unaffected.

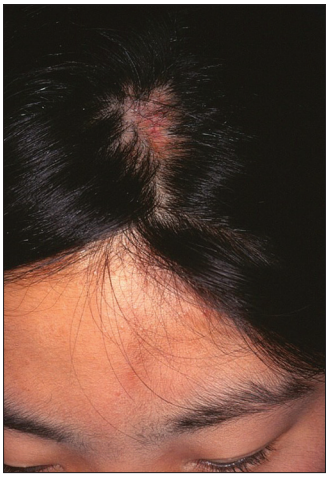

Figure 1: An en *coup de sabre* morphea on the forehead involving the scalp.

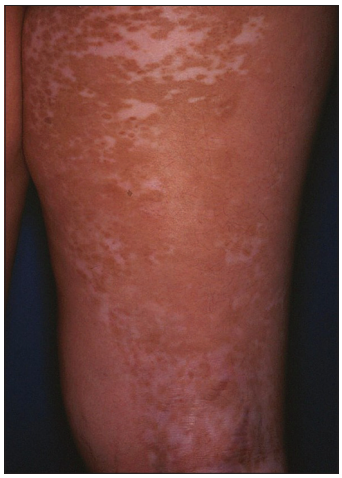

Figure 2: A depigmentation on the left lower extremity.

The co-existence of localized scleroderma and vitiligo is extremely rare, and the association of linear scleroderma with homolateral segmental vitiligo has rarely been reported [2]. Among 44 patients with linear scleroderma, vitiligo was noted in only one [3]. On the other hand, among 701 patients with childhood vitiligo, there were no cases of connective tissue disease [4]. Scleroderma *en coup de sabre* is a rare type of linear scleroderma affecting

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the forehead and sometimes the scalp in young people and impairing the patient's quality of life. Occasionally, the tissues deeper than the subcutis are involved, leading to functional limitations [5]. In a case reported by Ubaldo and Castro, a cleft lip was also observed on the same side with the lesions on the face, which may have been caused by embryological cell division, suggesting mosaicism [2]. In our case, linear scleroderma appeared on the face, whereas segmental vitiligo involved the lower extremity. Several pathogenic hypotheses of segmental vitiligo have been proposed, including a neuronal mechanism, somatic mosaicism, and microvascular skin homing, although without certainty as to whether or not leading to autoimmune destruction. In addition to trauma, neurological and infectious agents and immunological abnormalities have been postulated as the causative agents of morphea. Various pathogeneses have been proposed for these two entities, with the autoimmune mechanism common to both, although cutaneous mosaicism in linear scleroderma may not be confirmed on a molecular basis [1]. In conclusion, although the co-occurrence of scleroderma *en coup de sabre* and segmental vitiligo can be caused by sheer chance, the immunological, developmental, and neurological factors may have played a major role in our patient.

Consent

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Letter to the Editor

The first case of adalimumab-induced hypertrophic lichen planus

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Sir,

Tumor necrosis factor (TNF) alpha inhibitors are new therapeutics used to treat a range of rheumatological diseases refractory to conventional drugs. Several anti-TNF-α side effects have been described, especially cutaneous manifestations [1]. A number of so-called lichenoid eruptions have been reported in three different clinical patterns: lichen planus-like (LP-like), non-specific maculopapular eruption, and psoriasis-like. These cases are unified by a common lichenoid histology [2]. However, hypertrophic LP has never been reported in association with anti-TNF-α therapy.

A healthy 68-year-old male had suffered from arthropathic psoriasis for twenty-six years. His medical history involved multiple cutaneous psoriatic lesions almost on the entire body (body surface affected (BSA) = 60%), which had been resistant to topical treatment. The patient was treated with methotrexate. Three years later, we noted a slight improvement in both cutaneous (BSA = 40%) and arthropathic symptoms. We opted for one injection of adalimumab weekly. We noted rapid clinical improvement (BSA = 2%) and relieving of arthropathic symptoms. However, several months later, the patient presented himself with purplish nodular lesions on both forearms (Fig. 1). We noted neither mucosal involvement nor hair or nail lesions. A histopathological examination confirmed the diagnosis of hypertrophic LP (Fig. 2). Based on the clinical history and the histopathological findings, the diagnosis of adalimumab-induced hypertrophic LP was established. Adalimumab could not be stopped. The hypertrophic LP was treated with a topical corticosteroid with a slight improvement.

TNF is a pro-inflammatory cytokine produced by a wide variety of cell types, including keratinocytes, that plays a complex role in innate immunity and host defense, particularly against mycobacterial infections, and that may both enhance and suppress adaptive immunity. The main anti-TNF-α drugs (adalimumab, etanercept, and infliximab) have all been shown to be very effective in treating psoriasis [3].

Our patient presented an unusual side effect of adalimumab. A temporal association and a histopathological examination of our patient strongly suggested a causative relationship between the TNF blockage and the onset of the cutaneous lesions. With the Naranjo algorithm, a causality score of 6 was obtained and the case was categorized as a probable reaction to adalimumab.

Lichenoid eruptions induced by TNF-α inhibitors have, for the first time, been described by Vergara et al. in 2002 [4]. Since then, multiple cases of lichenoid eruption, including cutaneous and oral LP, lichen planopilaris, maculopapular eruption, and psoriasis-like LP, have been reported [1,2,4,7]. Only twenty cases of LP induced by TNF-α inhibitors have been described [1,2,4]. The three main TNF-α inhibitors (infliximab, etanercept, and adalimumab) were incriminated [5]. Some mechanisms have been suggested to explain the occurrence of lichenoid eruption due to TNF-α inhibitors therapy. In fact, the suppression of TNF may lead to the development

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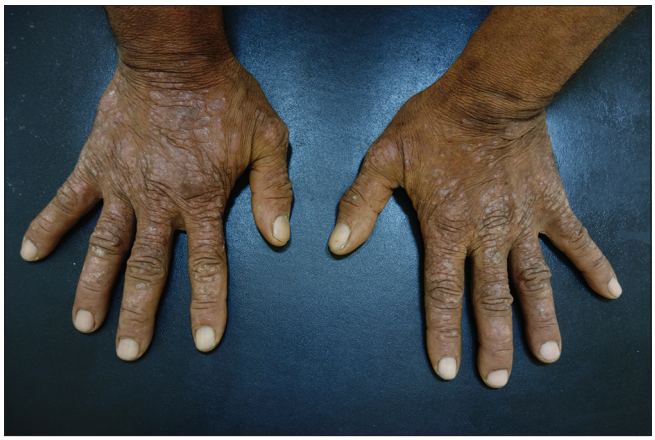

Figure 1: Hypertrophic cutaneous lichen planus with a nodular, polygonal, flat-topped, purplish plaque on both hands.

of opposing inflammatory cytokines, which may activate T cells and dendritic cells leading to lichenoid eruption [6].

Our patient presented hypertrophic LP, which is a particular clinical and histological form of LP. To the best of our knowledge, no case of hypertrophic LP induced by an anti-TNF-α drug has been reported [1,2,4]. Only one case of hypertrophic LP induced by anti-interleukin 17 (secukinumab) has been reported [7].

In conclusion, we witnessed the first case of hypertrophic LP induced by an anti-TNF-α drug. Physicians should be aware of this rare side effect. In fact, patients with cutaneous hypertrophic LP are prone to skin cancer. Therefore, we believe it to be worthwhile to monitor patients who use anti-TNF-α drugs for psoriasis against hypertrophic LP.

Consent

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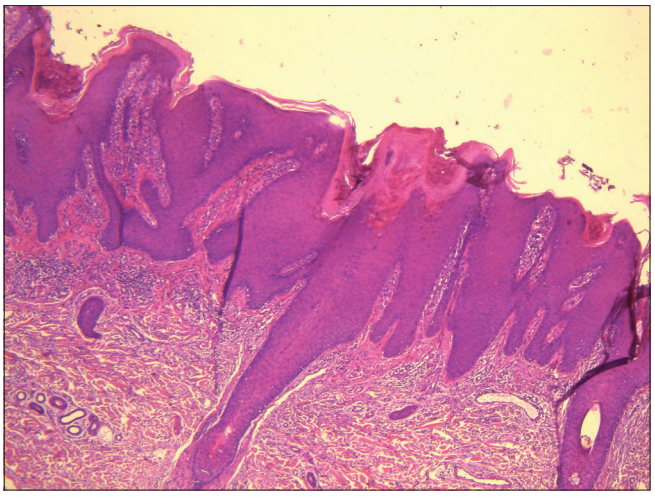

Figure 2: A thin, acanthotic epidermis with orthohyperkeratosis and wedge-shaped hypergranulosis with some necrotic keratinocytes associated with a dermal inflammatory lichenoid infiltrate and lymphocytes exocytosis in the basal layers of the epidermis (H&E, 40×).

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Letter to the Editor

Characterizing red dots in atopic dermatitis

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Sir,

A 7-year-old male presented himself with skin lesions on elbow and knee flexures persistent for six months prior. A physical examination revealed erythematous, excoriated plaques on these sites, along with scaling (Figs. 1a and 1b). Based on the clinical presentation, a diagnosis of atopic dermatitis was reached.

Dermoscopy (DermLite IV; 3Gen; Polarized, 10×) of the lesions revealed bands of erythema along the skin creases and patchy scaling. In addition, red dots were seen distributed along the skin creases as well.

Histopathology revealed spongiosis in the epidermis and superficial perivascular infiltrate typical of eczematous dermatitis.

Atopic dermatitis (AD) is a chronic, pruritic inflammatory dermatosis affecting predominantly the flexures. Upon dermoscopy, background erythema may be subtle or prominent depending on the stage of the disease. Patchy pinpoint vessels are characteristically seen in the active stage of AD [1,2]. The skin of atopic patients has been shown to contain thickened, flexuous blood vessels in the papillary dermis, which are responsible for the patchy pinpoint vessels seen on dermoscopy [2]. An interesting observation made is the distribution of red dots seen along the skin creases. The skin is relatively thinner in the flexural areas, more so in the skin creases, which explains the prominence of erythema and pinpoint vessels in this area (Fig. 2).

While red dots are most commonly seen in psoriasis, in which they tend to be regularly distributed, in atopic dermatitis, they appear in the form of dotted vessels arranged in a patchy distribution [3]. This is an important differentiating clue that should aid in proper diagnosis.

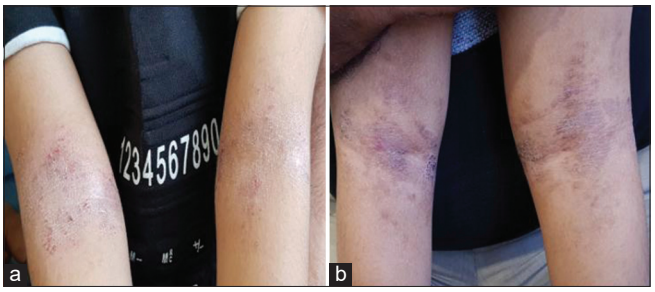

Figure 1: (a and b) Erythematous, scaly plaques with excoriations on elbow and knee flexures.

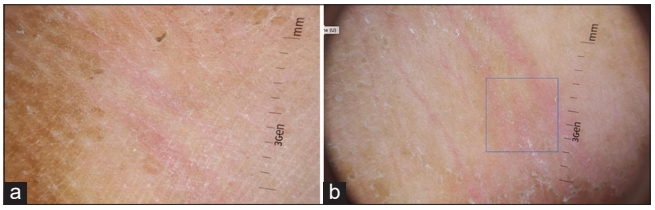

Figure 2: (a and b) Fine scales with subtle erythema (more prominent along the creases). Skin creases showing prominent pinpoint vessels (at the blue square) with a background of erythema and mild to moderate scaling.

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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Letter to the Editor

Leg ulcers and Klinefelter syndrome

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Sir,

Klinefelter syndrome (KS) is a rare sex chromosome disorder [1], associated with leg ulcers in 6% of cases. These ulcers are usually recurrent, refractory to treatment, and are a major socioeconomic handicap [2].

We report the case of a patient with a chronic leg ulcer associated with KS.

A 45-year-old patient, who underwent ligation of perforating veins of the left lower limb in 2005, was followed with endocrinology for KS for three years and put on androgens. He consulted with the dermatologist for a leg ulcer.

An examination found an elongated patient with large limbs (Fig. 1) as well as undeveloped sexual characteristics.

A dermatological examination revealed internal retromalleolar ulcers with plaques of ocher dermatitis associated with varicose veins of the lower limbs (Figs. 2 and 3).

A biological examination revealed hyper gonadotropic hypogonadism and osteoporosis. A thrombophilic and an immunological checkup were negative. Venous ultrasonography of the lower limbs showed staged venous thrombosis, which contraindicated any surgical procedure in view of the extent of thrombosis.

Treatment with platelet antiaggregant was initiated with fatty dressings and compression stockings in addition to the androgen treatment.

KS is the most common congenital anomaly causing primary hypogonadism [1,3], occurring in 1/500 to 1/1000 live births. The prevalence of leg ulcers in people with KS is 6%, 30 times higher than in the

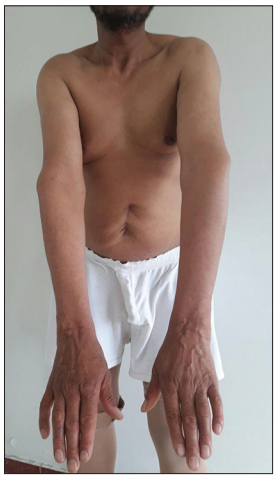

Figure 1: Long upper limbs in relation to Klinefelter syndrome.

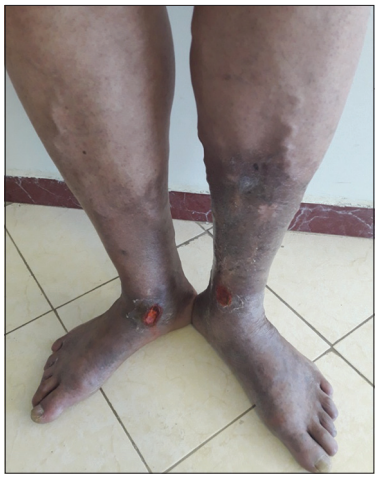

Figure 2: Ulcers of the lower limbs developed on a site of chronic venous insufficiency.

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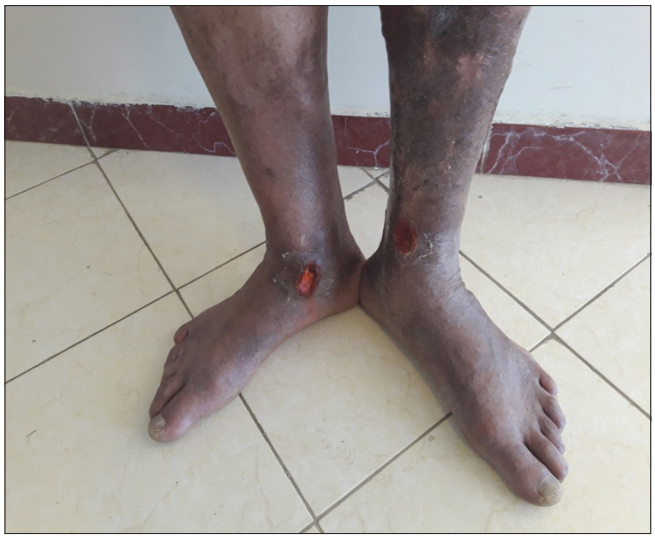

Figure 3: Perimalleolar ulcers of the lower limbs with associated ocher dermatitis.

general population. The pathogenesis of KS-associated leg ulcers is complicated due to a combination of factors: venous incompetence caused by an increase in venous pressure associated with long lower limbs, hormonal abnormality (inhibition of fibrinolysis caused by low levels of testosterone) [1,3], and abnormality of coagulation and the fibrinolytic system, which promotes thrombosis [3]. All these hemostatic abnormalities may explain ulcers by thrombosis of cutaneous microvessels and/or by venous thrombosis inducing postphlebitic disease, as in our patient. These leg ulcers are often refractory to treatment, require multidisciplinary therapeutic management, and involve the use of androgenic treatment, because improvement of leg ulcers in people with hypogonadism has been observed when on hormone therapy [2,3].

One must always keep in mind KS in young patients with recurrent venous ulcers refractory to treatment with a notion of sterility associated with the hypogonadism chart.

Consent

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

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

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Letter to the Editor

Grover´s disease reaches 50 years

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Sir,

An otherwise healthy 58-year-old female presented herself with an acute-onset eruption of red excoriated papules located on the upper part of the back (Figs. 1a and 1b) and proximal sites of the upper and lower extremities, worsening during periods of hot or humid weather. The patient complained of severe itching.

The correlation of clinical features added to the histological pattern of focal acantholytic dyskeratosis (Fig. 2) led to a diagnosis of Grover's disease (transient acantholytic dermatosis / TAD).

Systemic and topical steroids reduced the lesions and the patient was instructed to avoid such predisposing factors as heat, excessive sweating, and sun exposure.

Fifty years ago, Dr. Ralph Weir Grover, a NY dermatologist and dermatopathologist, uncovered the mystery of some unknown dermatologic cases hitherto regarded and diagnosed as atypical "Darier-like," "pemphigus vulgaris-like," and "Hailey–Hailey-like" disease most often affecting men over their fifties. These lesions occur due to the mechanism of separation of the skin's outer layers of cells, a process known as acantholysis; this, however, happens with no clear cause. Since Dr. Ralph had always been attracted by cytology and had an in-depth knowledge and a special taste for anatomopathology, it was not difficult for him to detect a unique feature of focal acantholysis and dyskeratosis in those laminas. He termed his discovery as *transient acantholytic dermatosis* and published a manuscript in the April 1970 issue of *Archives of Dermatology* [1]. The condition was soon known as Grover's disease (TAD) [2].

The origin of TAD is still unknown. What is known, however, is that that the proteins of the desmosomal attachment plaque are primarily affected, leading to desmosomal dissolution. More often than not, a history of atopic dermatitis, excessive sweating, and metal allergy is present. In our patient, irritative dermatitis and a very dry skin were noted. Since the disease is not rare, it might just be poorly diagnosed. Contrary to the term *transient* that forms part of the name, TAD is, in fact, chronic and some cases may last six to twelve months [3].

The purpose of reporting this case is to remind us of this poorly diagnosed pathology and also to pay tribute to Dr. Ralph, who passed away on May 25, 2008. As a sole practitioner, he uncovered the disease, making a dermatological history in a single-author manuscript, which has had a profound influence on the whole of the discipline.

To have been a solo practitioner of dermatology and to have identified a disease "missed" for centuries by "experts" in academe is no surprise to those who knew the brilliant turn of mind of Ralph. He was an original in every respect and a joy to work with. Not only did he have a marvelous, wry sense of humor, but he could be playfully puckish in selfdeprecation. As but one example, his middle name was "Wier," about which he commented to me, "they left off the 'd'!" It is regrettable that Ralph Wier Grover was not known personally to colleagues and trainees beyond Long Island. They would have reveled in his company and in his intellect, just as did I. — A. Bernard Ackerman, M.D.

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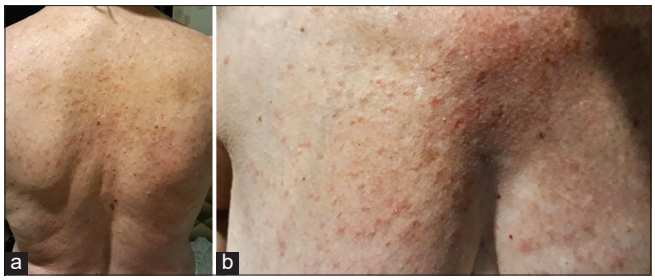

Figure 1: (a and b) Red excoriated papules located on the upper part of the back.

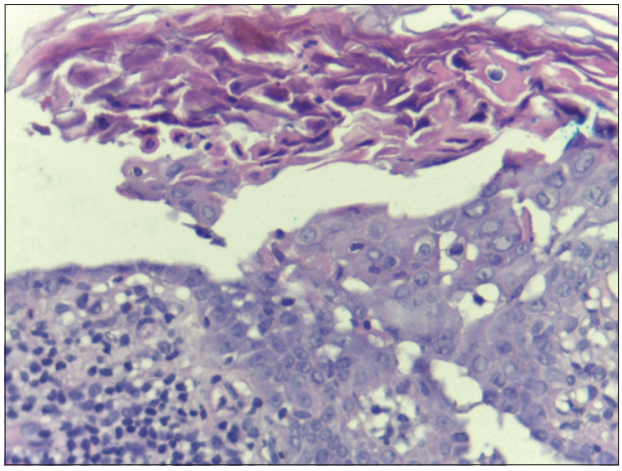

Figure 2: A biopsy showing focal acantholytic dyskeratosis, focal suprabasal acantholysis, and intense inflammatory infiltrate, composed mainly of lymphocytes, in the papillary dermis (H&E, 100×).

Whoever was lucky enough to be around him was brought to a higher level of understanding. And wherever he went he brought his humor and love. He will be missed and never forgotten, and all the people who learned from him will be carrying on his tradition of caring and joy. — James M. Krivo, M.D.

According to those who knew and worked with Dr. Grover, he was an example to be secretly followed with great generosity toward those in pain. A professional with such sensitivity is instantly rewarded with gratitude and, then, an endless virtuous circle is established. The expression *priceless* seems to have been coined to define this magical situation. Doctors lacking in affection will also have their own patients brought by the system; however, they will never discover one of the wonders of the medical profession, that is, the infinite joy of being chosen by the patient as *my doctor*.

Consent

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

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