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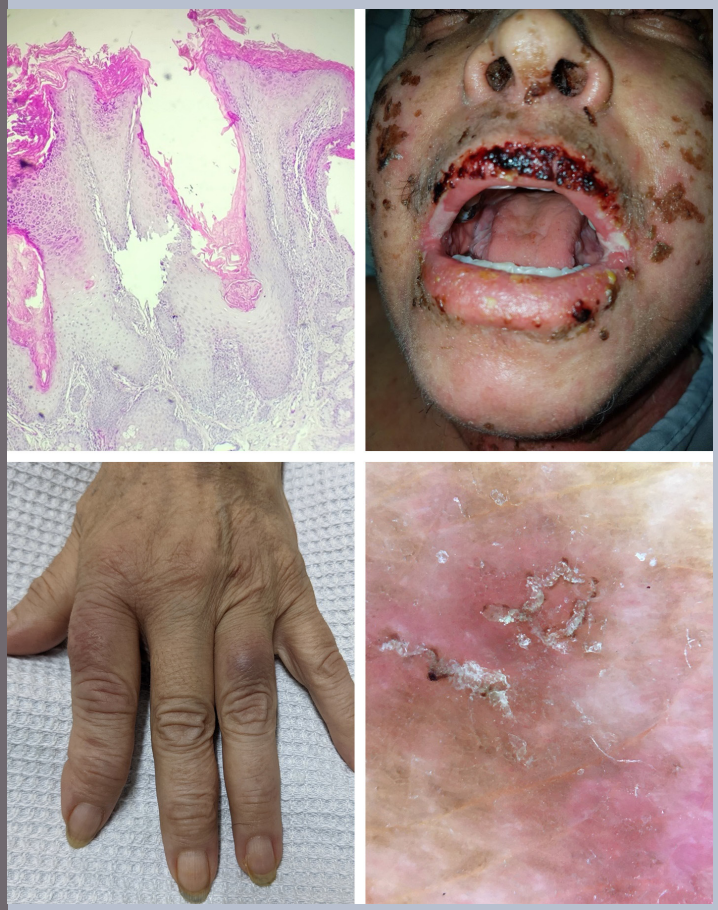

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Original Article

Sociodemographic and clinical characteristics of chronic urticaria among patients attending the dermatology clinic of a tertiary-care hospital

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ABSTRACT

Background: Chronic urticaria (CU) is characterized as the recurrent occurrence of wheals, angioedema, or both on most days of the week, for more than six weeks. Information available on this disease is mainly based on foreign studies. We observed the clinical characteristics of this disease among our population to fill the shortage of information. **Materials and Methods:** It was a hospital-based, cross-sectional, descriptive study conducted at the Department of Dermatology from July 2022 to March 2023. Patients diagnosed with CU were enrolled in this study after obtaining ethical approval from the Institutional Review Committee (IRC). The calculated sample size was 123. Sociodemographic features and clinical characteristics were recorded after taking consent from the patients. A descriptive analysis was performed and presented in frequency tables. **Results:** The majority (61%) had chronic spontaneous urticaria (CSU), 13.8% had chronic inducible urticaria (CINDU), and 25.2% had both CSU and CINDU. The mean age of participants was 35.86 ± 13.45 years. Females comprised 72.4% of the patients. A family history of urticaria was found in 16.2% of patients. The mean disease duration was 35.88 ± 60.2 months. Wheals occurred in the evening in 24.3% of cases. Angioedema was reported by 18.6% of the patients. Gastritis was the most common (11.4%) comorbidity. Physical factors precipitated urticaria in 39% of cases. Recurrence of the disease was seen in 17.8%. Prior to visiting the dermatologist, 76.4% had been taking antihistamines and 15% attempting an alternative medicine. **Conclusion:** Our findings were consistent with those of previous reports. CSU is more than three times more common than CINDU. Females and young adults were more affected by CU. Concomitant CSU and CINDU is also possible. As a chronic condition, it is often difficult to manage, and patients tend to explore alternative options.

Key words: Chronic urticaria, Clinical, Demography, Descriptive study

INTRODUCTION

Chronic urticaria (CU) is characterized as the recurrent occurrence of wheals, angioedema, or both on most days of the week for more than six weeks. CU is further divided into chronic spontaneous (no specific eliciting factor involved) urticaria (CSU) and chronic inducible (specific eliciting factor involved, for instance, cold, heat, or pressure) urticaria (CINDU) [1,2]. The prevalence of CU in Asia has shown an increasing trend, with reports of 3.08% in Korea [3], 0.79% in Taiwan [4], and 2.4% in Nepal [5]. It occurs most commonly in females and has a peak age of onset between 20 and 40 years [6]. Wheals have a more generalized distribution among Polish people, in whom CSU and a family history of CSU were twice more common than CINDU [7]. Likewise, 50% of the CUs were associated with angioedema in Brazilians, and stress was the most common aggravating factor [8]. Whereas Asia and the Middle East were found to have more comorbidity associated with CINDU than CSU [9]. Autoantibodies, infectious diseases, thyroid gland disorders, drugs, and numerous more allergens may precipitate CSU. However, the etiology largely varies in different geographical locations [1]. Only several studies from Nepal have focused mainly on the quality

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of life of patients with urticaria [10] or its association with autologous serum skin tests [11].

In view of the complex nature of CU, we wished to fill the void of the need for more information regarding the clinical characteristics of such a common disease among our own population.

Since CSU is associated with frequent hospital visits causing a burden to patients, families, and the health care system, as itching, wheals, and angioedema are often not sufficiently controlled [1], this study may help to find different clinical aspects of the disease in our own population, thereby helping in proper management.

MATERIALS AND METHODS

This was a hospital-based, observational, cross-sectional study conducted at the Department of Dermatology of the Patan Academy of Health Sciences, Nepal, from July 2022 to March 2023. After obtaining ethical approval from the Institutional Review Committee (IRC), patients diagnosed with chronic urticaria were included in the study. After briefly describing the study, data was collected from those who gave consent to provide information about their disease. The diagnosis of urticaria was clinical, and the required investigations were sent. Pregnant females, lactating mothers, children under fourteen years of age, wheals lasting more than twenty-four hours, acute urticaria, urticarial vasculitis, and mastocytosis were excluded from the study.

Information about the sociodemographic features of the patients and the clinical characteristics of CU was obtained. The confidentiality of the patients was maintained by not recording any data that would identify the patient as an individual (for instance, name, full address, photographs). Regarding occupation, those involved in laborious work (farmers, porters, field workers, etc.) were categorized as manual workers, and those whose work consisted of mostly sitting (secretaries, clerks, managers, etc.) were categorized as table workers. The place of residence was categorized as rural or urban areas according to the administrative division of Nepal. People from the Terai region and living in the river basin were categorized as from hot regions, and people from the hilly region were categorized as from cold regions. For comorbidities, already diagnosed diseases under treatment were recorded. Complete blood count, random blood sugar, serum creatinine level, stool R/E, urine R/E, and TSH (thyroid stimulating hormone) were sent as laboratory investigations to all patients with CU. A consecutive sampling technique was employed; the required calculated sample was 123. A descriptive analysis was performed and presented in frequency tables.

RESULTS

A total of 123 patients with chronic urticaria were included in the study. Out of the 123 patients, a majority (75; 61%) was diagnosed with CSU, while 17 (13.8%) and 31 (25.2%) were diagnosed with CINDU and both (CSU, CINDU), respectively.

The sex distribution revealed that the highest CU was observed among females (89; 72.4%), as compared to 34 (27.6%) males. All types of CU were predominant among females; CSU in 51 (68%), CINDU in 11 (64.7%), and both in 27 (87%) females.

The male-to-female ratio was 1:2.6. The mean age at presentation was 35.86 ± 13.45 years, ranging from 14 to 77 years. The highest number of cases was observed in the age group of 21 to 50 years, and only 4.8% were over 60 years old (Table 1).

In the CSU and CINDU groups, the highest number of cases was observed among the group of 21–40 years, while more cases were observed among the group of 21–30 years in both type groups.

Most of the patients were married (83; 67.4%), living in urban areas (75; 61%), and in cold regions (92; 74.8%) of the country. The majority of the CSU patients (47; 62.7%) were living in urban areas, whereas most of the CINDU patients (9; 53%) were from rural areas of the country. Regarding smoking, 16 (21.3%) of the participants with CSU were smokers, while 20 (26.6%) consumed alcohol.

Twenty-four (32%) of the patients with CSU were housemakers, while 8 (47%) patients with CINDU were table workers. Ten (32.2%) were manual workers in both types of groups.

The mean age at the onset of urticaria was 31.02 ± 13.61 years with an age range of 2 to 73 years. The most common age group for the onset of CU was between 21 and 30 years for all types of CU. The same applied to sex differences.

Table 1: Sociodemographic characteristics of the patients with chronic urticaria

Variables	Chronic spontaneous urticaria *n* = 75 (61%)	Chronic inducible urticaria *n* = 17 (13.8%)	Both *n* = 31 (25.2%)	Total *n* = 123
Sex				
Male	24 (32)	6 (35.3)	4 (13)	34 (27.6)
Female	51 (68)	11 (64.7)	27 (87)	89 (72.4)
Place of residence				
Urban	47 (62.7)	8 (47)	20 (64.5)	75 (61)
Rural	28 (37.3)	9 (53)	11 (35.5)	48 (39)
Hot region	23 (30.7)	3 (17.6)	5 (16.1)	31 (25.2)
Cold region	52 (69.3)	14 (82.4)	26 (83.9)	92 (74.8)
Marital status				
Married	55 (73.3)	11 (64.7)	17 (54.8)	83 (67.4)
Unmarried	16 (21.3)	4 (23.5)	12 (38.7)	32 (26)
Widow	4 (5.3)	1 (5.8)	2 (6.5)	7 (5.6)
Divorced	0	1 (5.8)	0	1 (0.8)
Age group (yrs.)				
14–20	4 (5.3)	3 (17.6)	7 (22.6)	14 (11.4)
21–30	21 (28)	5 (29.4)	12 (38.7)	38 (30.9)
31–40	20 (26.6)	5 (29.4)	4 (13)	29 (23.5)
41–50	18 (24)	2 (11.7)	6 (19.3)	26 (21.1)
51–60	7 (9.3)	2 (11.7)	1 (3.2)	10 (8.1)
>60	5 (6.6)	0	1 (3.2)	6 (4.8)
Smoking	16 (21.3)	3 (17.6)	2 (6.5)	21 (17)
Alcohol	20 (26.6)	3 (17.6)	8 (25.8)	31 (25.2)
Occupation				
Housemaker	24 (32)	2 (11.7)	8 (25.8)	34 (27.6)
Manual worker	15 (20)	3 (17.6)	10 (32.2)	28 (22.7)
Student	10 (13.3)	3 (17.6)	9 (29)	22 (17.8)
Table worker	21 (28)	8 (47)	2 (6.5)	31 (25.2)
Unemployed	5 (6.6)	1 (5.8)	2 (6.5)	8 (6.5)

A family history of urticaria was present in 20 (16.2%) patients with CU. Among these, 15 (20%) of the CSU patients, 1 (5.8%) of the CINDU patients, and 4 (13%) of those with both types of urticaria reported having first-degree relatives with urticaria (Table 2).

The mean disease duration was 35.88 ± 60.2 months, ranging from 1.5 months to 27 years, with patients with longer disease durations being less common.

Thirty-five (46.6%) patients with CSU had the disease for less than one year, and 13 (17.4%) had urticaria for over six years. Among the CINDU patients, 11 (64.7%) had the disease for less than one year, while in only 1 (5.8%) patient, the disease lasted for more than six years.

Out of the total patients, 84 (68.2%) reported daily occurrence of wheals, while for four (3.2%), the appearance of wheals was unpredictable. Everyday occurrence of wheals was primarily reported by patients with both types of urticaria 24 (77.4%) followed by patients with CINDU (12; 70.5%) and CSU (48; 64%).

The mean duration of wheals was 183.3 ± 249.5 minutes, and the duration of wheals ranged from 1 minute to 22 hours. Out of the 123 patients, 39 (31.7%) reported that wheals disappeared within one hour. Nineteen (25.3%) patients with CSU reported that wheals lasted for less than one hour, and in forty-one (54.6%), wheals lasted for 1–6 hours. However, in nine (53%) patients from the CINDU group, the wheals disappeared within one hour, while in seven (41.2%), the wheals lasted for 1–6 hours.

Regarding the distribution of wheals, 86 (70%) patients found wheals either in the upper or lower parts of the body. Seven (5.7%) reported wheals on the scalp, one had wheals on the sole, and twenty-one (17%) had generalized wheals. Thirty-two (42.6%) patients with CSU reported wheals on the lower parts of the body, while ten (59%) patients with CINDU had wheals on the upper parts of the body.

There was no preferential time of day for the occurrence of wheals in forty (32.5%) patients with CU. However, 30 (24.3%) and 21 (17%) reported having wheals during the evening and night, respectively. However, wheals appeared most frequently during the evening among 22 (29.3%) patients with CSU and 3 (17.6%) patients with CINDU. No female patient reported wheals during menstruation.

Urticaria was associated with angioedema in 23 (18.6%) cases, with a higher incidence in females than males (20 vs. 3). Among the 23, 17 (22.6%) had angioedema in

Table 2: Clinical characteristics of the patients with chronic urticaria

Variables	Chronic spontaneous urticaria *n* = 75 (61%)	Chronic inducible urticaria *n* = 17 (13.8%)	Both *n* = 31 (25.2%)	Total *n* = 123
Family history of urticaria	15 (20)	1 (5.8)	4 (13)	20 (16.2)
Duration of disease				
< 1 year	35 (46.6)	11 (64.7)	11 (35.4)	57 (46.3)
1–3 yrs.	21 (28)	4 (23.5)	13 (42)	38 (30.9)
3–6 yrs.	6 (8)	1 (5.8)	3 (9.6)	10 (8.1)
> 6 yrs.	13 (17.4)	1 (5.8)	4 (13)	18 (14.6)
Frequency of wheals				
Everyday	48 (64)	12 (70.5)	24 (77.4)	84 (68.2)
2–3 times a week	19 (25.3)	2 (11.7)	5 (16.1)	26 (21.1)
2–3 times a month	5 (6.6)	1 (5.8)	1 (3.2)	7 (5.7)
Monthly	2 (2.6)	0	0	2 (1.6)
Irregularly	1 (1.4)	2 (11.7)	1 (3.2)	4 (3.2)
Duration of wheals				
< 1 hour	19 (25.3)	9 (53)	11 (35.4)	39 (31.7)
1–6 hours	41 (54.6)	7 (41.2)	19 (61.3)	67 (54.4)
6–12 hours	12 (16)	0	0	12 (9.7)
> 12 hours	3 (4)	1 (5.8)	1 (3.2)	5 (4)
Site of wheels				
Head and neck	10 (13.3)	2 (11.7)	4 (13)	16 (13)
Upper body	21 (28)	10 (59)	11 (35.4)	42 (34.2)
Lower body	32 (42.6)	3 (17.6)	9 (29)	44 (35.7)
All	12 (16)	2 (11.7)	7 (22.5)	21 (17)
Angioedema	17 (22.6)	1 (5.8)	5 (16.1)	23 (18.6)
Time of appearance of wheals				
Morning	4 (5.3)	2 (11.7)	4 (13)	10 (8.1)
Afternoon	1 (1.3)	3 (17.6)	2 (6.5)	6 (4.8)
Evening	22 (29.3)	3 (17.6)	5 (16.1)	30 (24.3)
Night	14 (18.6)	1 (5.8)	6 (19.3)	21 (17)
During sleep	2 (2.6)	0	0	2 (1.6)
Mixed	8 (10.6)	1 (5.8)	5 (16.1)	14 (11.3)
Anytime	24 (32)	7 (41.2)	9 (29)	40 (32.5)
During menstruation	0	0	0	0
Dermographism	12 (16)	6 (35.3)	22 (71)	40 (32.5)
Visited emergency room	8 (10.6)	0	3 (9.6)	11 (8.9)
Comorbid conditions				
Gastrointestinal disorders	9 (12)	3 (17.6)	4 (13)	16 (13)
Respiratory disorders	3 (4)	1 (5.8)	3 (9.6)	7 (5.7)
Endocrine disorders	6 (8)	0	1 (3.2)	7 (5.7)
Cardiovascular	6 (8)	1 (5.8)	1 (3.2)	8 (6.5)
Headache	0	3 (17.6)	0	3 (2.4)
Multiple disease	5 (6.6)	4 (23.5)	2 (6.5)	11 (8.9)
Other	3 (4)	1 (5.8)	3 (9.6)	7 (5.6)

the CSU group. The most common site of angioedema was the lips, followed by the eye region. The rest of the patients reported mixed angioedema, affecting the lips, eyes, chin, tongue, or cheeks.

Eleven people (8.9%) were rushed to the emergency department due to generalized urticaria that was uncontrollable with oral antihistamines.

Dermographism was positive in 22 (71%) patients with both types of urticaria, followed by 6 (35.3%) patients with CINDU and 12 (16%) patients with CSU.

Besides urticaria, almost half of the patients (59; 48%) had other preexisting comorbidities. Among these, 16 (13%) diseases were related to the gastrointestinal system, with gastritis being the most common, reported by 14 (11.4%) patients. The other commonly reported comorbidities were hypertension and DM, followed by rhinitis, asthma, migraine, thyroid disorder, hyperlipidemia, dental caries, rheumatoid arthritis, irregular menstruation, and depression.

A routine biochemical test, complete blood count, erythrocyte sedimentation rate, urine, and stool test were performed on all patients on the first visit. Among the 123, 11 (8.9%) patients were found to have other diseases besides the pre-diagnosed disease. Among them, three were incidentally diagnosed with diabetes mellitus after showing high random blood sugar (> 220 mg/dL) and glycosuria. Meanwhile, one patient was found to be anemic (Hb 9.3 g/dL) and two were diagnosed with hypothyroidism. Additionally, four patients had UTIs, and one had hypertriglyceridemia (TG 400).

While most (42.2%) could not associate anything with the occurrence of urticaria, around 39% of the patients reported physical factors (heat, cold, tight clothing, rubbing during baths, exercise) as the precipitating factors for urticaria. One patient experienced wheals every time he sat for studying (Fig. 1).

Food was reported as a precipitating factor in 36 (29.2%) patients, with meat (48%) being the most common culprit for 17 (48%) patients, in which buffalo meat precipitated urticaria in ten (28%) patients (Fig. 2).

Recurrence of the disease was seen in 22 (17.8%) patients, with a higher incidence among females (16; 72.7%) than males (6; 27.3%). Most recurrences of urticaria were observed between the age of 21 and 50 years, more commonly in the age group of 21–30 years; among these, 18 (81.8%) patients with CSU had more than one episode of urticaria in their lifetime, and four (18.2%) patients with both types of urticaria had a recurrence of urticaria.

Other symptoms besides itching were reported by 39 (31.7%) patients, a burning and heat sensations being most commonly reported by thirteen patients; cough, throat irritation, and chest discomfort were reported by eleven patients, and dizziness, light-headedness, weakness, yawning, feeling irritated and restless, sleep disturbances were, among others, reported by fifteen patients. Such symptoms were primarily experienced by 26 (34.6%) patients with CSU.

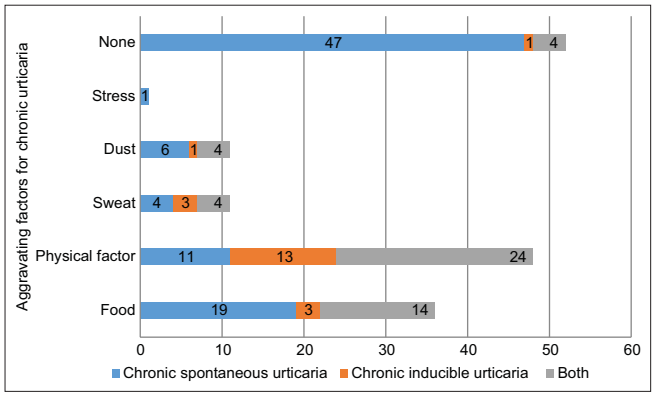

Figure 1: Precipitating factors or aggravating factors of chronic urticaria (multiple-response answers).

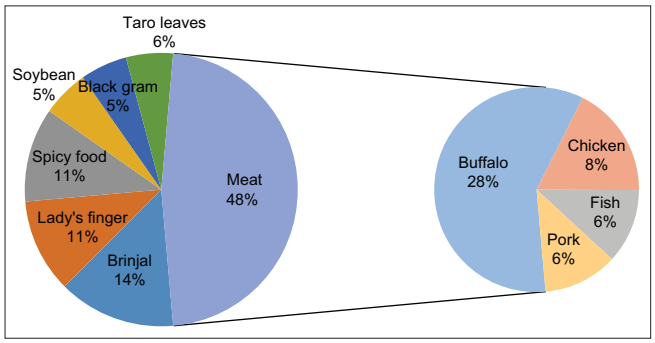

Figure 2: Types of food aggravating chronic urticaria.

The study found that 110 (89.4%) patients received some form of treatment prior to visiting the hospital, with only 23% continuing their medication. Among the patients who had previously taken medication, 94 (76.4%) had been taking only antihistamines at a therapeutic dose; sixteen (13%) had been multiple medications such as different H1 and H2 antihistamines, oral corticosteroids, montelukast, colchicine, and triple combination creams, and only five (4%) patients had been taking higher than the therapeutic dose of antihistamines. The duration of treatment for urticaria ranged from two days to twenty years, with only 82 (66.6%) patients being able to provide information or documentation about their previous treatment.

Among these, 53 (43%) obtained the medication from local medical shops, whereas 19 (15.4%) attempted alternative medicines such as herbal medicine, traditional healers, and worshipping the Naag god (Table 3).

DISCUSSION

The study included 123 patients diagnosed with CU and aimed to investigate the disease's various sociodemographic and clinical characteristics. The study found that CU was more common in females than males. The highest number of participants with CSU were females (72.4%), and the highest percentage of participants with CINDU were also females (64.7%), which is consistent with other authors' findings [6,7]. The male-to-female ratio was found to be 1:2.6, similarly to other study results [8]. However, in an Indian study on CU, more males (66) were affected than females (34), with a male-to-female ratio of 1.9:1 [12]. The actual reason for the sex difference is unknown yet thought to be due to the involvement of an autoimmune component in the occurrence of urticaria, with women being more susceptible than men to autoimmune diseases [13].

The mean age of our patients was 35.86 years, which was a similar finding in other studies [8,14,15]. In our study, the mean duration of the disease was 35.88 ± 60.2 months, ranging from 1.5 months to

Table 3: Treatment pattern of the patients with chronic urticaria

Variables	Chronic spontaneous urticaria *n* = 75 (61%)	Chronic inducible urticaria *n* = 17 (13.8%)	Both *n* = 31 (25.2%)	Total *n* = 123
Prior treatment				
Herbal medicine	4 (5.3)	0	0	4 (3.2)
Traditional healer	6 (8)	0	3 (9.6)	9 (7.3)
Worshiped the Naag god	3 (4)	1 (5.8)	2 (6.4)	6 (4.8)
Local pharmacy	28 (37.3)	5 (29.4)	20 (64.5)	53 (43)
Hospital	7 (9.3)	0	3 (9.6)	10 (8.1)
Medicine used				
Multiple	12 (16)	0	4 (13)	16 (13)
Antihistamines	56 (74.6)	12 (70.6)	26 (83.8)	94 (76.4)
Not known	7 (9.3)	5 (29.4)	1 (3.2)	13 (10.5)
Higher doses of antihistamines	4 (5.3)	1	0	5 (4)
Oral corticosteroid	6 (8)	0	1	7 (5.7)
Regularly on treatment	15 (20)	1 (5.8)	9 (29)	25 (20.3)

27 years, which was quite similar to an Indian study in which the mean duration of CU was 40 ± 40.93 months, and ranged from two months to twenty years [15].

The mean age at the onset of wheels was 31.02 ± 13.61 years, with an age range of 2 to 73 years in our study, similarly to the Indian study [15], yet lower than in a Spanish study in which the mean age at onset was 47.3 ± 16.2 years [16].

Maurer reported that CSU accounted for one-third of all CU cases [17]. Approx. 20% of cases experienced CSU and CINDU concurrently [16]. We also found similar results, with 61% of our patients having CSU, 13.8% having CINDU, and 25.2% having concomitant CSU and CINDU.

A similar proportion of CSU (667; 61.1%) was reported in a multicenter study from Poland, with more cases of CINDU (338; 35.1%) and much fewer of both (41; 3.8%) types of urticaria when compared to our study [7]. While in the U.K., the proportion of different urticarias varied from our study; they reported 217 (56%) patients with CSU, 59 (15%) with CINDU, and 57 (15%) with both CSU and CINDU [17].

Most (61%) of our patients with CU lived in urban areas, and it was found that the population living in urban areas was associated with a higher prevalence of urticaria [14]. A similar finding was observed in which lifestyle and environmental factors such as air pollution and urban living were associated with an increased incidence of allergic diseases among children [18].

In our study, 16 (21.3%) patients with CSU were smokers. No patient reported smoking as a triggering or aggravating factor in our study, unlike in China, where sixteen cases (3.1%) reported smoking-induced wheals [19]. It was interesting to note that smoking correlated with a reduced risk of urticaria when compared with the general population [14,20]. Studies have shown that nicotine modulates mast cell activation and inhibits the synthesis of pro-inflammatory cytokines [21]. However, no causal relationship was found between cigarette and alcohol use in the incidence of CU [8].

Thirty-one (25.2%) patients in our study consumed alcohol, unlike Zhong's findings in China, where 687 (25.4%) patients consumed alcohol, among whom 383 (55.7%) reported that alcohol triggered their urticaria. Alcohol as an aggravating factor was also reported by Salvaris in Brazil [8]. No patient in our study reported alcohol as a triggering factor for urticaria. There are few case reports of the induction of urticaria after consumption or contact with alcohol [22,23]. Yet, the exact pathogenesis of mast cell activation is not properly understood, whether it is an immunologic or non-immunologic reaction [23].

The observation is that CIU is much more frequent among first-degree relatives of affected individuals than in the general population [24]. In our study, twenty (16.2%) patients with CU reported a family history of urticaria, with CSU reported by fifteen (20%). However, a family history of urticaria varied in different studies; in Nepal, it was found in 24.6% of patients [25], 11.7% in Poland [7], and 4% in Italy. Such familial occurrence of CU suggests the existence of a genetic background for the disease [24].

In our study, more than one episode of CSU was observed in 22 (17.8%) cases, and all had one episode a long time earlier, which was consistent with the study from Spain [16]. Recurrence was observed in 13% of patients with CSU, mainly among alternative medicine users and antihistamine refractory cases [26].

Angioedema is a sudden, pronounced, circumscribed, non-pitting swelling of the deeper dermis and subcutaneous tissue or mucous membranes, presenting as pain or a burning sensation rather than itching [27]. Angioedema may occur with or without urticaria. In up to around 40% of cases, angioedema occurs concurrently with urticaria [13].

We found angioedema concomitant with urticaria in 23 (18.6%) patients, more than in a population-based, Chinese study in which angioedema was found in 6.16% of patients [14]. A higher frequency of urticaria angioedema was reported in patients from Brazil (50.4%) [8].

A systemic review revealed considerable regional differences in the occurrence of angioedema, which seemed more prevalent in Europe and the Americas than in Asia [28].

When the patients with angioedema vs. without angioedema were compared, it was found that angioedema seemed to be underreported and was associated with poor quality of life in terms of daily activities and work performance, with a negative impact on healthcare resource utilization [29].

Although the specific cause of urticaria may not be identified in the individual patient, it is often possible to identify non-specific aggravating factors in chronic urticaria, such as drugs, infections, physical factors, food additives, and stress [30].

In our study, 48% of the participants could recognize the aggravating factor of their urticaria, which was unknown for 52%. In contrast, 79.6% of patients from Spain and 84% from Brazil could tell the worsening factors [8,16]. In our study, physical factors and food were common causes of exacerbating factors, whereas in Curto's study, NSAIDs and stressful life events were the most common exacerbating factors. While stress, as an exacerbating factor, was reported in 15.2% of patients by Silvares [8], we had only one patient whose urticaria was aggravated by stress, which was, interestingly, the stress of school assignments.

Physical factors (heat, cold, tight clothing, rubbing during baths, exercise) were responsible for the aggravation of urticaria in around 39% of our patients, which was much higher than 10.4% of Silvares's [8], yet less than the 50% found by Sidbad [31].

We found food as an aggravating factor for CU in 36 (29.2%) patients, similarly to 30% in Juhlin's findings [32], and higher when compared to Ferrer's study, in which a food allergy was seen only in 4.8% of patients [33]. Our common urticaria-aggravating food was meat, especially buffalo meat, brinjal, lady's fingers, black gram, and taro leaves. The types of food-causing allergies are different in different countries; seafood, fish, prawn, crab, peanuts, eggs, and wheat were common food allergens in other Western countries, which is rare in our country. Seafood is generally unavailable to the general people in a landlocked country such as Nepal. This difference in food causing urticaria could also be due to differences in food culture and local beliefs regarding food articles.

In our study, 84 (68.2%) patients reported everyday occurrence of wheal, which was higher than 52% reported by others [8] and was primarily found in patients with both types of urticaria 24 (77.4%), followed by the CINDU (12; 70.5%) and CSU (48; 64%) groups of patients.

The signs and symptoms of CSU may occur spontaneously at any time of the day yet commonly during the evening, among 22 (29.3%) patients with CSU and 3 (17.6%) with CINDU, and at night (1; 5.8%), which was less than in a study from Europe (evening: 34%; night: 23%) [34]. The appearance of wheals during the evening and night may reflect the circadian variation in mast cell activation, which is crucial in developing allergic diseases [34,35].

Some patients with urticaria have only cutaneous symptoms, whereas some patients have systemic symptoms, such as headache, joint pain, and gastrointestinal complaints.

Thirty-nine (31.7%) patients had other symptoms besides itching in our study. Itching and burning sensations were expressed by 33% of our patients, supported (31%) by another study [23].

The frequency of arthralgia, abdominal pain, and fever was reported in the literature yet was non-existent in our study [8,29]. Contrary to our findings, Juhlin reported gastritis as a cause of CU in 44% of cases [32].

In our study, almost half of the patients (59; 48%) had other pre-existing comorbidities besides urticaria. The most common were related to the gastrointestinal system (16; 13%), with gastritis being the most

common disease reported (14; 11.4%). The other common comorbidities were hypertension and DM, followed by rhinitis, asthma, migraine, thyroid disorder, hyperlipidemia, and dental caries. However, other studies have reported that thyroid diseases and drug allergies were associated with urticaria [15]. Most of the other studies reported comorbid diseases, atopic diseases such as asthma, rhinitis, psychiatric diseases, type 2 diabetes, and hypertension [36]. It has been reported that the successful treatment of *H. pylori* infection may result in the remission of urticaria [37].

Most (89.4%) of our patients had been taking some form of treatment before visiting the hospital, which was slightly less than Chu's finding, in which nearly all patients (99.9%) were on treatment [9], yet similar to other patients from France, Germany, and Spain [16,34]. In our study, 76.4% took only antihistamines, less than in Chu's finding [9]. In ours, five (4%) had been taking higher doses of antihistamines, which contradicts Chu's finding, in which 12.4% of patients had been taking a higher dose of antihistamines. The higher rate of prior treatment before visiting the dermatologist in our study was because of the easy availability of antihistamines over the counter from a local medical shop, similarly to Maurer's finding, in which 78% of the respondents had been taking over-the-counter or prescription medication [34]. People visit the dermatologist only after taking OTC medicine for several weeks and not having their pruritus relieved. Moreover, dermatologists are not easily accessible to the general population who do not live in cities in Nepal. The other medicines, apart from antihistamines, were all prescribed by non-dermatologists or by local pharmacists in our study.

Few patients (7; 5.7%) were put on oral corticosteroids to control urticarial symptoms in our study, which was considered a second-line drug. No patient was treated with omalizumab in our study because the drug is unavailable in Nepal, and most of the general population could not afford it because of its high cost.

CU is a chronic disease in which wheals and itching are not adequately controlled, and patients tend to attempt alternative medicine in search of relief for itching. Almost 15% of our patients went for alternative medicine, mainly to traditional healers (7.5%), followed by worshiping the Naag god (4.8%) and using herbal medicine (3.2%). Whole plants, portions of plants, or single extracted active compounds are all used in phytomedicine [38]. These are widely employed in numerous Asian countries for various pathological conditions such as psychiatric diseases, gastrointestinal disorders, and skin diseases for their anti-inflammatory, anti-allergic, and antioxidant effects. Herbal formulas and single medicinal plants are valid alternatives to antihistaminic drugs in patients with CU, showing improvement in symptomatology and the quality of life of patients [38]. Although gradually on decreasing trend, one of the widely practiced treatment methods for any disease is visiting traditional healers such as *Dhaamis* and *Jhankris*, who chant mantras to chase off the offending spirit or to calm down God's anger, responsible for the deceased ailment, including skin diseases. One of the widespread beliefs in Nepal is that skin diseases result from the Naag god's anger. Thus, people worship the god and then only visit the hospital or other health facility if they do not feel relieved.

Apart from the aforementioned, a famous Chinese alternative medicine, acupuncture, was found to be effective in up to 90% of cases, reducing the mean duration of disease, suggesting it for the treatment of CU, especially the resistant forms [37].

CONCLUSION

In our study, as in previous studies, females outnumbered males, common in the age group of 21–40 years. Most patients were married homemakers, from urban areas, and from cold climates. A family history was positive in around one-sixth of all participants. Daily occurrence of wheals was the most common. Most urticarial wheals appeared in the evening and night. Angioedema was associated with almost one-fifth of the cases, with the lips being the most common site. Besides itching, nearly a third of the patients experienced other symptoms because of urticaria, commonly burning and heat sensations. The most common precipitating food was meat, especially buffalo meat. Most had been taking antihistamines before coming to a dermatology consultation.

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

Almond shells as a gel exfoliant

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ABSTRACT

Background: Natural cosmetics are becoming increasingly popular among the general public. Natural beauty products promote a holistic approach to environmental and health preservation. As a result, consumers seeking that type of cosmetics search for products that may ensure a genuinely natural effect. Over the last two decades, the number of studies demonstrating the benefits of natural ingredients in cosmetics for dermatologic and hair care, as well as disease treatment, has increased. For centuries, almonds have been employed in cosmetics. They increase the radiance and fairness of the skin. Almonds are widely available in the Portuguese region of Trás-os-Montes, and suggestions for using them in cosmetics should be made. This study presents a method of using almond shells as a cosmetic product easily reproducible at home. **Materials and Methods:** All equipment employed was cleaned and disinfected beforehand. Almond shells were ground to a powder and incorporated into a gel exfoliant formulation. **Results:** With a gentle rub, apply the almond shell exfoliation gel to the entire body. A sponge, lukewarm water, or damp cotton may be used to remove the product. The product may last for up to one month if properly stored and manufactured. **Conclusion:** As the demand for knowledge, acquisition, and the use of natural and organic cosmetics grows, the topic becomes increasingly relevant, as is the desire to stay young and seek accurate information in order to formulate organic and natural cosmetics.

Key words: Almond Shells; Exfoliant; Natural Cosmetics; Natural Ingredients; Trás-Os-Montes

INTRODUCTION

Natural cosmetics are becoming more popular among the general public. They promote an approach that connects environmental preservation and health protection. As a result, consumers of that type of cosmetic seek products that may guarantee a genuinely natural effect.

The number of studies proving the benefits of natural ingredients in cosmetics for dermatologic and hair care and disease treatment has increased over the last two decades. Colloidal oatmeal, for instance, has been shown to improve the treatment of psoriasis, and aloe vera shows benefits in the treatment of atopic dermatitis. Because of their antioxidative properties, licorice, green tea, arbutin, soy, açai berry, turmeric, and pomegranate have been shown to help reduce hyperpigmentation [1].

Almonds

Trás-os-Montes, Portugal, is bounded on the west by the Minho province, on the south by Douro, on the east by the Douro River, and on the north by Spain. The almond tree is one of the most widely planted tree crops in the Trás-os-Montes region [2]. *Parada*, *Casanova*, *Verdeal*, and *Pegarinhos* are the most common varieties [3]. It is also a region with the most organic farmers, and the region's climatic, topographic, and pedological differences favor agricultural diversity [4].

The *Rosaceae* family includes the almond tree. It is the oldest nut crop in southwest Asia and, therefrom, has spread to other areas and continents [5]. Hippocrates was the first to mention using almonds to treat colds and other phlegmatic disorders [6]. Almond cultivation spread in a narrow horizontal band westward through the Mediterranean Sea to Spain as a result of successive

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Greek, Roman, and Arab invasions [5]. Almonds may be consumed as dried fruit or employed in baking and liquors. The almond shell is converted into biofuel [7].

Sweet almond oil is widely used in cosmetics, particularly in dry skin creams and anti-wrinkle and anti-aging products. It improves the skin's radiance and fairness. It is present in over 280 cosmetic formulations at concentrations ranging from 1% to 50% [8]. It may be used to treat urticaria and wound healing when combined with white wine and honey [9]. Because it is suitable for all skin types, almond oil is one of the most popular oils used in aromatherapy and massage therapy. It promotes skin regeneration and elasticity due to high levels of vitamins E and K. [10]. An *in vivo* study in *Drosophila melanogaster* using the SMART and Comet assays revealed that almonds and almond shells have antigenotoxicological properties [11,12]. Antigenotoxicological properties have been linked to anti-aging properties [13,14].

This study presents a method for using almond shells as a cosmetic product that may be reproduced domestically.

MATERIALS AND METHODS

Chemicals

Glycerin (CAS: 56-81-5) and xanthan gum (CAS: 11138-66-2) were purchased from PlenaNatura (Amadora, Portugal).

Cosgard (INCI: benzyl alcohol and dehydroacetic acid; CAS: 100-51-6/69-72-7/56-81-5/110-44-1), melissa hydrosol (INCI: melissa officinalis water; CAS: 84082-61-1), and lemon essential oil (INCI: citrus limon peel oil; CAS: 8008-56-8/84929-31-7) were purchased from Aroma-Zone (Paris, France).

Equipment Cleaning and Disinfection

To reduce the risk of contamination, the equipment must be cleaned and disinfected. To do so, one needs a cleaning solution, denatured alcohol (70% alcohol by volume) in a spray bottle, boiled water, and clean rags.

The hair was tied back, and protective clothing was worn. The work surfaces were sprayed with alcohol after being cleaned with a cleaning solution. A single-use paper towel was used to dry the surfaces. Metal, silicone, and glass containers were disinfected and sterilized by boiling in water for twenty minutes and drying them with a single-use paper towel. Following that, each item was sprayed with alcohol, making sure it was contained in the containers and lids. A single-use paper towel was used to dry the items. Alcohol was sprayed on tools and non-heat-resistant plastic containers to ensure it reached the insides. The containers and tools were dried with air.

Almond Harvest and Preparation

Almonds (variety *Pegarinhos*) were chosen as natural ingredients in the Trás-os-Montes region and were obtained from an organic farmer in October 2022. The almond shells were separated from the almonds prior to the experiment. The almond shells were ground into powder (Fig. 1).

RECORDS

A traceability worksheet was created for each preparation (Table 1). This document was created in order to track the quantities and batches of each ingredient. In the event of a cutaneous reaction, it is beneficial to understand and research the irritant or allergenic component. The exact formulation is described in Table 2.

1. Xanthan gum, hydrosol, and glycerin were put in a recipient (Fig. 1a).
2. The preparation was mixed and left to rest for five minutes, then remixed until the xanthan gum dissolved completely and a dense gel formed (Fig. 1b).
3. Almond shells and Cosgard were added, and the preparation was mixed thoroughly (Fig. 1c).
4. Essential oil was added (Fig. 1d).
5. The preparation was transferred to a container (Fig. 1e).

Labelling

Following the cosmetic preparations, it is critical to label them in a reassuring manner. Conscientious labeling avoids confusion about the type of product and its use, secures cosmetics by clearly identifying their ingredients, and provides quick information on the date of manufacture and the shelf life of the preparation for use as directed. The following information should be included on the label:

1. Product name: The precise NAME of the preparation.
2. Composition: A list of all INGREDIENTS used in the formulation.
3. Date of manufacture and shelf life: The product's DATE OF MANUFACTURE and EXPIRATION

Figure 1: Steps of the preparation. a) Ingredients; b) mixture of ingredients; c) addition of almond shells and Cosgard; d) addition of essential oil; e) final exfoliation gel.

Table 1: Example of a traceability worksheet.

Date			02.12.2021
Ingredient	**INCI Name**	**Quantity**	**Batch No.**
Glycerine	Glycerin	2	0012385
Xanthan Gum	Goma xantana	3	202009B-G05
Melissa Hydrosol	Melissa officinalis water	88	21HY0076/5
Grounded almond shells	Prunus Amygdalus Dulcis (Almond) Shell Powder	5	N/A
Cosgard	Benzyl alcohol & dehydroacetic acid	1	22CG0226/2-2273
Lemon essential oil	Citrus Limon Peel Oil	1	21HE0094/5

Table 2: Almond shell exfoliation gel formulation.

Phase	Ingredient	%
A	Glycerin	2
A	Xanthan gum	3
A	Melissa hydrosol	88
B	Grounded almond shells	5
B	Cosgard	1
C	Lemon essential oil	1

DATE are calculated from the conservation period specified in the protocol. Light and heat should be kept away from the preparation.

4. Capacity: The label may be completed by indicating the container's CAPACITY. If necessary, the specific type of USE, skin type, or special PRECAUTIONS for use may be specified.

RESULTS AND DISCUSSION

The term *cosmetics*, according to the European Regulation, refers to a product applied to the body to keep the skin, and thus the body, in good condition, to protect it from environmental influences and aging processes, to change its appearance, and to improve the smell of the body [15]. Natural, conventional, and organic cosmetics all have the same definition yet differ in some ways. Conventional cosmetics do not require the inclusion of certified natural and organic ingredients [16]. A natural cosmetic product must contain at least one ingredient derived from a natural substance obtained directly from a mineral or a plant, and it must not be produced synthetically. Organic ingredients may be present in small amounts in natural cosmetics. However, natural products are not always organic [17]. At least 95% of the ingredients in an organic cosmetic must be certified organic. These raw materials are derived from approved cultivation and extraction methods. They must be biodegradable and chemically as natural as possible. The remaining 5% of the formulation may be water, agricultural raw materials, or non-certified extracting agents approved for organic formulations [18]. This is why only natural and organic ingredients were chosen to prepare this formulation.

Glycerin has hygroscopic properties and is used in numerous skin moisturizing products as it appears to help alleviate dry skin problems by attracting water from the underlying layers.

Melissa hydrosol has soothing and calming properties, ideal for uncomfortable and itchy skin. It helps to prevent the appearance and reduce the signs of aging. It is a tonic that cares for damaged skin and tones sagging skin.

Xanthan gum is a polysaccharide commonly used for the stabilization and consolidation of cosmetic products.

Cosgard is a preservative that effectively preserves all preparations containing an aqueous phase. It is

of synthetic origin yet is one of the few preservatives authorized by Ecocert and is widely employed in organic cosmetics.

Lemon essential oil provides purifying and tonic properties. Since lemon essential oil is phototoxic, we suggest using the distilled, furocoumarin-free form.

A certified organic farmer from the Trás-os-Montes region in Portugal provided the almonds.

The almond shell exfoliation gel may be applied to the entire body with a gentle rub. The product may be removed with a sponge, lukewarm water, or damp cotton. If well stored and manufactured in excellent condition, the product may last for up to one month.

CONCLUSION

Various societies, organizations, and digital influencers inform consumers on the advantages and benefits of using this type of product, addressing environmental, social, and ecological issues to make the population aware of environmental, social, and ecological concerns, as well as their own well-being.

The search for knowledge, acquisition, and use of natural and organic cosmetics is constantly growing, thus the topic is highly relevant, as is the interest in updating oneself and seeking accurate information to formulate organic and natural cosmetics.

Acknowledgments

The authors would like to thank Paula Santenico, an organic farmer, for providing the ingredients employed in this research.

Data Availability Statement

The data supporting this study's findings are available on request from the corresponding author, SG.

Statement of Human and Animal Rights

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

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Our Dermatology Online

Original Article

Dermoscopic pattern of the topical steroid damaged face: A cross-sectional, observational study at a tertiary referral center in south India

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ABSTRACT

Background: Unsupervised overuse of topical corticosteroids (TCs) is highly common in dermatological practice, leading to steroid abuse known as topical steroid damaged/dependent face (TSDF). Dermoscopy aids in the early detection of TSDF. **Aims:** The aim of this study was to evaluate the clinical and dermoscopic findings in patients with TSDF. **Materials and Methods:** The study was conducted on eighty patients presenting with clinical features suggestive of TSDF. Detailed history taking, clinical examination, and dermoscopic evaluation with a DermLite dermoscope were performed. **Results:** Out of the eighty patients included in the study, 64 (80%) were females and 16 (20%) were males. The most common age group affected was 18–30 years (52; 65%). Sixty-six were literate. Melasma was a common underlying condition for which a steroid was used by the patients (44; 55%). Betamethasone (34; 47.5%) was the most commonly used, followed by clobetasol (18; 22.5%). Relatives and friends were the common sources of recommendation (46; 57.5%). Most of the patients applied these for one year. Redness was the predominant presenting complaint, seen in sixty patients (75%). The common clinical findings were erythema (75%), hyperpigmentation (44; 55%), and hypertrichosis (50; 62.5%). The common findings observed on dermoscopy were telangiectasia (90%), red, diffuse areas (75%), brown globules (55%), and hypertrichosis (62.5%). In telangiectasia, the linear (60%), polygonal (30%), Y-shaped (25%), and serpentine (15%) types were seen. The other findings observed were white, structureless areas (37.5%), *Demodex* tails (25%), scaling (15%), pustules (10%), comedones (20%), and the breaking of the pseudo-reticular network (22.5%). **Limitations:** The limitation of this study was the lack of histopathological correlation. **Conclusion:** Dermoscopy aids in the early diagnosis of TSDF.

Key words: Dermoscope; Corticosteroid; Face; Telangiectasia; Hyperpigmentation

INTRODUCTION

The first topical corticosteroid (TC) was introduced by Sulzberger and Witten in the year 1952 as "Compound F" (hydrocortisone) [1]. Since then, a number of steroid molecules with varying potencies have been available on the market.

TCs have anti-inflammatory, antiproliferative, immunosuppressive, antipruritic, atrophogenic, melanopenic, and sex hormone-like effects on the skin, so they are useful for hyperproliferative, inflammatory, and immunologic disorders [2].

Due to their wide action and easy availability, TCs have been misused by pharmacists, general doctors, and patients. Yet, the other side of steroids remains largely unknown. They are rosacea acneiform eruption, hypertrichosis, demodicosis [3], red face syndrome [4], and addiction [5]. These effects occur due to the combined effects of the inhibition of action of nitric oxide and local immunosuppression leading to the overgrowth of microbes.

Topical steroid-damaged face is a relatively new entity, described in 2008. It is defined as "semi-permanent or permanent damage to face precipitated

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by indiscriminate, unsupervised, irrational or prolonged use of TCs resulting in a plethora of cutaneous signs and symptoms and psychological dependence on the drug" [6].

The face is commonly affected in TSDF as it is the most accessible site, and the facial epidermis (0.12 mm) is comparatively thinner than the rest of the body (0.60 mm), which results in increased percutaneous absorption of drugs [7].

Dermoscopy may help in the early detection of subclinical changes caused by topical steroid use and, thereby, tailor the treatment specific to every patient. The dermoscopic features searched for in TSDF are telangiectasia, white areas (atrophy), erythema, scales, and hypertrichosis [8].

The aim of this study was to evaluate the pattern of topical steroid abuse among patients attending the dermatology OPD, to characterize the clinical and dermoscopic findings in patients with TSDF and, to correlate them with the duration of steroid use.

There are very few studies conducted in relation to the dermoscopic features of TSDF, thus we decided to undertake this study.

MATERIALS AND METHODS

This was a cross-sectional, observational study conducted on patients above 18 years of age with clinical features suggestive of TSDF and H/O use of topical steroids for more than thirty days in the past three months. The study ran for a period of six months from March 2021 to August 2021.

The exclusion criteria were patients with pre-existing comorbidities (Cushing syndrome, PCOS, and thyroid disease), pregnant patients, patients under treatment with oral steroids, and patients unwilling to give consent.

Informed consent was taken from all patients. The sample size was 80. After detailed history taking regarding the nature of the steroid used, source, duration, and indication, clinical examination and dermoscopic evaluation were performed for all patients. Clinical and dermoscopic pictures were captured with an iPhone. Dermoscopy was performed by DermLite DL4. Statistical analysis was done with SPSS, version 22. Categorical variables were presented as frequencies and percentages. Quantitative variables were presented as means and SDs. Qualitative variables were compared with the chi-squared test. Ethical committee clearance was obtained.

RESULTS

A total of 80 patients were included in the study, among which 64 (80%) were females and 16 (20%) were males. The most common age group affected was 18–30 years (52; 65%). Sixty-six patients (82.5%) were literate and received basic education, while fourteen (17%) were illiterate. Melasma (44; 55%) was the common underlying condition for which steroids were applied (Table 1). Betamethasone (34; 47.5%) was the most commonly used by the patients, followed by clobetasol (22.5%). They were mostly used in combination with other creams, such as antifungal, antibacterial, and depigmenting creams. The cream formulation was used by most patients (90%) compared to ointments and lotions. The most common source of recommendation for the use of a topical steroid was relatives and friends (46; 57.5%) (Table 1). Most of the patients applied TCs for one year. The duration ranged from two

Table 1: Demographic characteristics

Characteristic	Number	Percentage
1. Age group (yrs.)		
18–30	52	65
31–40	16	20
>40	12	15
2. Sex		
male	16	20
female	64	80
3. Education		
illiterate	14	17.5
literate	66	82.5
4. Duration of TC application (yrs.)		
< 1	24	30
1–10	40	50
>10	16	20
5. Source of recommendation		
Relatives	46	57.5
Non-dermatologist doctors	10	12.5
OTC	18	22.5
Dermatologists	4-2	5-2.5
Practitioners of alternative systems of medicine		
Others (parlor, Internet)		
6. Type of steroid used		
Clobetasol	18	22.5
Mometasone	12	15
Betamethasone	34	47.5
Flutivate	4	5
combination	12	15
7. Indications		
melasma	44	55
fairness	22	27.5
acne	6	7.5
others	8	10

months to twelve years. Eighty percent of the patients employed topical steroids continuously, whereas only a small number of the patients (10%) employed them intermittently over a period of twelve years.

Redness was the predominant presenting complaint (60; 75%), followed by itching (50; 62.5%). Most patients had more than one clinical finding or side effect induced by steroids. The common clinical findings observed were erythema (75%), hyperpigmentation (44; 55%), hypertrichosis (50; 62.5%), acneiform eruption (26; 32.5%), telangiectasia (47.7%), and atrophy (4,5%) (Table 2) (Figs. 1a and 1b).

On dermoscopy, the most common findings observed were telangiectasia or vessels (90%), red, diffuse areas (75%), brown globules (55%), and hypertrichosis (62.5%). Telangiectasia and vessels were observed in the following patterns: linear vessels without branches (60%), polygonal vessels with multiple branches (30%), Y-shaped vessels with bifurcations (25%), and serpentine vessels (15%) (Figs. 2 and 3). The other features noted were white, structureless areas (37.5%), *Demodex* tails (25%) (Fig. 4), scaling (15%), pustules (10%), comedones (20%), and the breaking of the pseudo-reticular network (22.5%) (Table 3). Erythema, polygonal vessels, and white, structureless areas were seen more frequently in patients with long-standing use of topical steroids (Fig. 5). Brown globules were mostly observed in patients with a background of hyperpigmentation, such as melasma.

Table 2: Clinical symptoms and signs

	Number of Patients	Percentage
Clinical Symptoms		
1. Itching	50	62.5
2. Burning	40	50
3. Pigmentation	44	55
4. Acne	26	32.5
5. Redness	60	75
Findings		
1. Hyperpigmentation	44	55
2. Erythema	60	75
3. Hypertrichosis	50	62.5
4. Telangiectasia	38	47.5
5. Pustules	6	7.5
6. Papules	26	32.5
7. Scaling	4	5
8. Hypopigmentation	8	10
9. Wrinkles	4	5

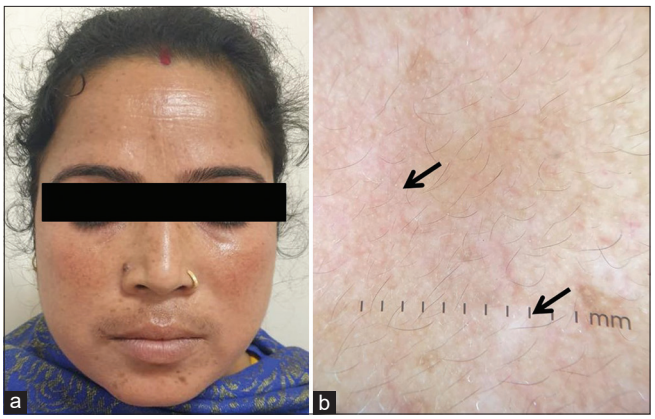

Figure 1: (a) Shiny skin with hyperpigmented macules on the face, hypertrichosis, telangiectasia on the bilateral cheeks. (b) Dermoscopic image showing erythematous and white, structureless areas (arrow), hypertrichosis.

DISCUSSION

TSDF is caused by patients and laymen applying TCs of the wrong potency to the face for a wrong indication and at the wrong age [2].

Topical steroid abuse is of great concern not only in India yet also in countries such as Africa, Iraq, and China [9-11].

The most common age group in our study was 18–30 years, which was in concordance with other studies [2,12,13]. At this age, social interactions and peer influence are more important. Yet, an Iraqi study found an age group of 15–19 years, which was a significantly younger population [9].

Abuse of steroids was more frequent in females in our study, similarly to other studies [11,12,14,15]. The reason could be cultural, ethnic, and social factors. In our study, 82.5% of the patients were literate, disproving the fact that steroid abuse is common among illiterates. This was also observed in other Indian studies [15].

Most of the patients employed TCs for more than one year, mostly due to feel-good effects and steroid addiction. The most common sources of recommendation were relatives and friends, followed by pharmacies, similarly to other studies [10,15]. This showed the unregulated OTC prescriptions common in India.

Betamethasone was commonly employed in our study and mostly in combination, as the Indian market is flooded with several combinations of steroids with antibacterial and antifungal agents. They are also cheaper. This finding was also observed in a multicentric study by Saraswat et al. and other studies [2,16].

TCs are mostly marketed as fairness creams, anti-acne medications, and general-purpose creams. In

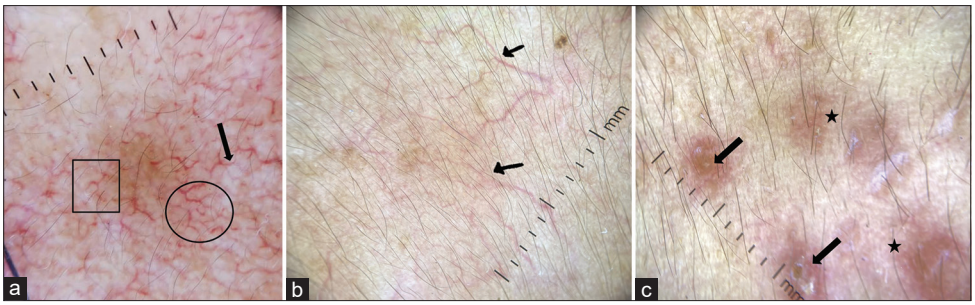

Figure 2: (a) Dermoscopy: white, structureless areas (arrow), polygonal telangiectasia (circle), Y-shaped telangiectasia (square). (b) Polygonal telangiectasia (arrows), brown globules, ill-defined white areas. (c) Follicular plugging and perifollicular telangiectasia.

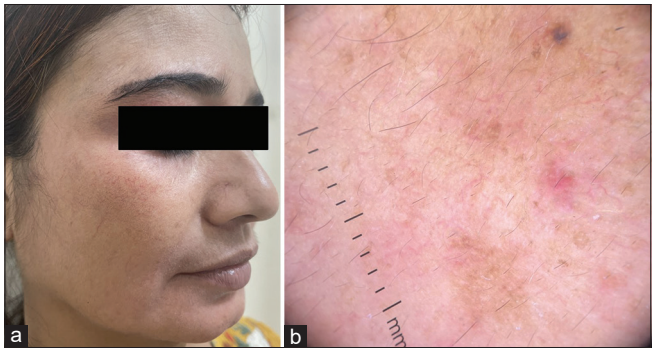

Figure 3: (a) Shiny skin, visible telangiectasia on the cheeks. (b) Dermoscopy showing perifollicular erythema, linear telangiectasia, an erythematous flare on white, structureless areas.

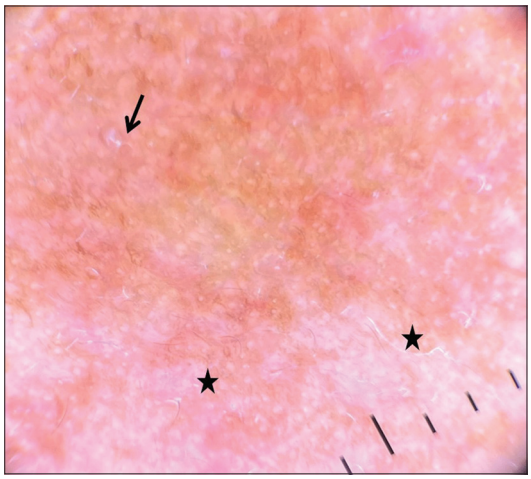

Figure 4: Dermoscopic image showing *Demodex* tails (arrow), brown globules, erythematous and white, structureless areas (asterisk).

our study, most patients used TCs for melasma and fairness.

According to the literature, the common clinical findings observed in patients with TSDF are erythema, dyspigmentation, and papulopustular lesions [11,12,14]. Hypertrichosis and atrophy were also observed in addition to the above findings. Most of the patients presenting with erythema may have been due to rebound vasodilation.

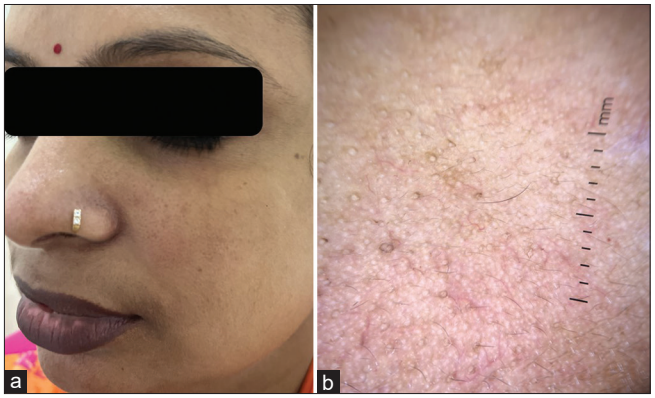

Figure 5: (a) Shiny skin with mild telangiectasia, freckles, and lentigines. (b) Dermoscopy showing polygonal telangiectasia, a perifollicular rim of hyperpigmentation, and blotchy, pink areas around telangiectasia.

Table 3: Dermoscopic findings

Dermoscopic Finding	Number of Patients	Percentage
Telangiectasia		
1. linear vessels without branches	48	60
2. polygonal vessels	24	30
3. Y-shaped vessels	20	25
4. serpentine vessels	12	15
Brown globules	44	55
White, structureless areas	30	37.5
Red, diffuse areas	60	75
Follicular plugging	6	7.5
Demodex tails	20	25
Hypertrichosis	50	62.5
White hair	4	5
Scaling (desquamation)	12	15
Breaking of the pseudo-reticular network	18	22.5
Comedones	16	20
Pustules	8	10

Some studies have documented the dermoscopic findings of TSDF. According to Sethi et al., the most common dermoscopy findings were brown globules (96.2%), red, diffuse areas (92.4%), vessels (87.1%), white, structureless areas (86.4%), hypertrichosis (80.3%), and white hairs (62.1%) [15]. Meanwhile, in a study on forty patients by Tatu, the dermoscopy findings observed were polygonal vessels (100%),

red, diffuse areas (100%), *Demodex* tails (80%), and pustules (80%) [8]. In our study, we observed vessels and telangiectasia (90%), red, diffuse areas (75%), brown globules (55%), and hypertrichosis (62.5%). Sethi et al. observed brown globules predominantly in their study along with red, diffuse areas [15], while brown globules were not predominant in our study. Vessels were common in our study, similarly to a study by Tatu et al., in which 100% of the cases had polygonal vessels [8].

Sonthalia et al., in a case report on TSDF, observed brown dots on a reddish-brown background, globules, clods, and ivory white to pinkish patches, multiple serpentine and branching linear vessels without branches with hypertrichosis [17]. In another case report, Jakhar and Kaur observed irregular, dilated, branched, serpentine vessels almost interconnecting, creating a polygonal pattern along with white, structureless areas and hypertrichosis [18]. In our study, we also observed various types of vasculature, linear, polygonal, Y-shaped, and serpentine vessels. Linear vessels without branches were the most common in our study. Polygonal vessels were seen in patients with long-standing use of steroids. Sethi et al. also observed Y-shaped vessels in patients using TCs for more than three months and polygonal vessels in patients using TCs for more than six months [15].

We observed *Demodex* tails in some cases, as *Demodex* infestation is common following the use of topical steroids.

In our study, predominant brown globules were seen more frequently in patients using TCs for melasma. As per the literature, dermoscopy of melasma shows a diffuse, light to dark brown background, brown granules, and globules with arcuate and annular structures.

Dermoscope is a valuable tool in the early diagnosis of damage caused by the use of topical steroids. When shown dermoscopic pictures, patients become more aware and vigilant on topical steroid use and adhere to future treatment.

If the patient is not giving a history suggestive of topical steroid use, a dermoscope may detect the changes and we may prompt the patient accordingly.

This study highlights the importance of awareness of the adverse effects of topical steroids and their addiction among doctors and patients. As these side effects are quite serious, early detection is essential. OTC sales of TCs should be banned in India, and the public should be highly educated about the topic.

Study Limitations

The limitation of this study was the lack of histopathological correlation.

CONCLUSION

Dermoscope is highly recommended as a non-invasive tool for the diagnosis of TSDF.

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

Epidemiological, clinical, and therapeutic aspects of dermatitis herpetiformis at Yalgado Ouédraogo University Hospital Centre, Burkina Faso

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ABSTRACT

Background: Dermatitis herpetiformis is a rare autoimmune bullous dermatosis that predominantly affects Caucasians, adults or children, with a sex ratio of 1.8. **Materials and Methods:** The aim of this study was to document the clinical and epidemiological profiles of dermatitis herpetiformis and to detail its treatment in a hospital setting in order to increase our knowledge about this disease in our context and so to improve its management. We conducted a retrospective, cross-sectional study of the records of all patients seen in consultation or hospitalized at the dermatology department of Yalgado Ouédraogo University Hospital Centre, Ouagadougou, a public hospital in Burkina Faso, from January 2016 to December 2020. **Results:** We collected 14 cases (0.12%) of dermatitis herpetiformis among 11,456 patients seen. The mean age was 8 years (ranging from 4 to 27 years). The sex ratio was 1.33. The majority of the patients were schoolchildren living in rural areas (8 cases). The duration of the disease ranged from five days to one year (mean duration: 59.35 days). Eight patients had a history of digestive problems such as abdominal pain and diarrhea. Pruritis was the principal functional sign. In all patients, the lesions were polymorphous: disseminated vesicular bullae, papules, erosive, and excoriated lesions, sometimes forming clusters. Mucosal involvement was rare (3 cases). A gluten-free diet and dapsone 2 mg/kg/day were proposed to all patients and resulted in the improvement of the lesions. **Conclusion:** Our study confirmed that dermatitis herpetiformis is rare in our context. It is more frequent in young children and predominantly affects boys. It is intensely pruritic, and generalized polymorphous lesions were present in all our patients. Treatment is essentially based on a gluten-free diet and dapsone, which is a therapeutic test in the absence of supplementary investigations to establish a definitive diagnosis.

Key words: Dermatitis Herpetiformis; Clinical Medicine; Dapsone; Gluten Intolerance

INTRODUCTION

Dermatitis herpetiformis (DH) is a rare, recurrent auto-immune bullous dermatosis classically associated with gluten enteropathy. It predominantly affects Caucasians, with a sex ratio of 1.8 [1]. The prevalence is higher in northern Europe, ranging from 11 to 66 cases per 100,000 inhabitants [2,3]. In Black Africa, studies of this bullous dermatosis are highly sparse. Two hospital studies conducted in the Ivory

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Coast and in Sudan found a prevalence of 20.9 for 100,000 patients [4] and 5 cases in 16 years [5], respectively. In view of the rarity of African data and the difficulties of diagnosis in our context, we undertook the present study to document the sociodemographic, clinical, and therapeutic aspects of DH in a hospital setting.

MATERIALS AND METHODS

This was a descriptive, cross-sectional study in which we retrospectively examined the records of patients with a clinical or histological diagnosis of DH during the five-year period from January 1, 2016, to December 31, 2020, at the dermatology and venereology department of Yalgado Ouédraogo University Hospital Centre, the national reference hospital in Ouagadougou, Burkina Faso. The variables collected were sociodemographic (age, sex, place of residence), clinical (history, gastrointestinal problems, pruritis, type of primary lesions (location), therapeutic (dapsone), and on the course of the disease (healed, stationary, death of patient, lost to follow-up).

RESULTS

Epidemiological Data

We collected 14 cases of DH among 11,456 patients who had been seen in consultation or admitted to the hospital. The prevalence of DH at the dermatology department was 0.12%. The mean age of the patients was 8 years (range: 4 to 27 years). Eight patients were male and six were female (sex ratio: 1.33). Most patients were in the 6–10 year age group (7 cases) (Table 1) and were schoolchildren (8 cases) living in a rural environment.

Clinical Data

The duration of the disease ranged from five days to one year, with a mean duration of 59.35 days. A history of gastrointestinal disturbances, such as abdominal pain and diarrhea, was observed in eight patients. Pruritis was the main functional sign observed and was present in twelve patients. The general condition remained good in ten patients. All patients presented with generalized polymorphous lesions consisting of vesicular bullae, papules, and erosive and blackish excoriated lesions in clusters in some areas (Fig. 1). Mucosal involvement was present as vesicular stomatitis (2 cases) and conjunctivitis (1 case).

Table 1: Age and sex distribution of the fourteen patients

Age group (yrs.)	Female	Male	Total
[0–5]	1	0	1
[6–10]	2	5	7
[11–15]	0	2	2
[16–20]	3	0	3
[21–25]	0	0	0
[26–30]	0	1	1
Total	6	8	14

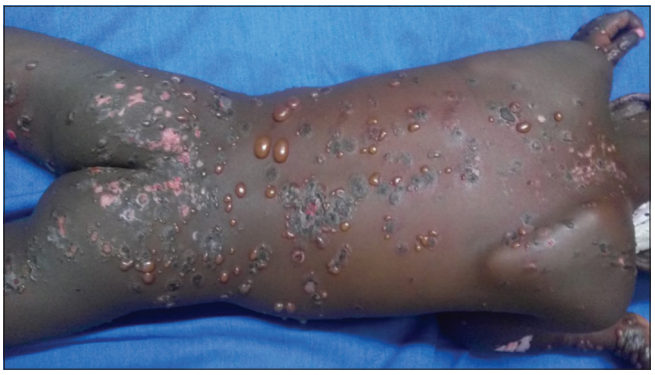

Figure 1: Multiple vesicular bullae on the trunk in clusters in the lumbar area.

Paraclinical Data

A biopsy of the bullous lesion was performed in six patients and the findings were consistent with DH in 5 cases. Four patients had anemia, as shown by a full blood count. G6PD was measured in two patients yet showed no deficiency.

Treatment

A gluten-free diet (GFD) and dapsone (2 mg/kg/day) were proposed in all patients. Systemic corticotherapy was administered in association with dapsone in one patient who did not respond to dapsone alone after one month.

Course of the Disease

After one month of treatment, six patients were clinically healed and the episode of vesicular-bullous lesions had cleared. The episode persisted in seven patients and one patient was lost to follow-up. After three months of follow-up, five patients had no recurrence of bullous lesions. A new outbreak occurred in two cases, and six patients who lived in rural areas were lost to follow-up.

DISCUSSION

Epidemiology

We recorded 14 cases (0.12%) of DH at the dermatology department of our institution during the five-year period. Kaloga et al. in the Ivory Coast and Akakpo et al. in Togo found a lower prevalence at their departments, with 7 patients in 5 years and 11 patients in 8 years, respectively [6,7]. Zaraa et al. in Tunisia observed 9 cases in 11 years [8]. Our findings confirmed the rarity of DH.

The disease predominantly affected males. Ouattara and Sidigg et al. also found a male predominance, with sex ratios of 1.56 and 1.03, respectively [4,5]. On the other hand, Akakpo et al. and Zaara et al. found a female predominance, with sex ratios of 0.8 [7] and 0.5 [8], respectively. A female predominance was also reported by Smith et al. in the U.S. [9].

The age of our patients ranged from 4 to 27 years, with a mean of 8 years. The disease was most frequent in the 6–10 year age group. This was similar to reports in the literature indicating that DH most often develops between the second and seventh year of life, as found by Ermacora et al. [10]. Other studies, however, have shown a predominance of DH in adults aged between 25.6 and 66 years [2,5,6,11].

Clinical Aspects

The duration of the disease before the specialist consultation ranged from five days to one year, with a mean of 59.35 days. This delay was long and is explained in our context by initial neglect by the patients of their skin problems, the use of phytotherapy before seeking medical advice, and the lack of access to dermatologists. This long time to diagnosis has also been reported in some developed countries, sometimes being as long as two years [12].

Pruritis was the principal functional sign, reported by the majority of the patients. In the literature, DH is classically accompanied by intense pruritis [1,4,7,13,14].

Eight patients presented with gastrointestinal signs. However, confirmatory gastrointestinal endoscopy was not performed. Akakpo et al. observed no signs of gluten enteropathy, nor did they conduct supplementary investigations to detect one [7]. Ouattara reported a case of associated coeliac disease [4]. Zaraa et al. reported two cases of coeliac disease among four patients who had undergone supplementary tests [8]. Dermatitis herpetiformis is considered as the cutaneous manifestation of gluten intolerance, invariably accompanied by coeliac disease [10,14].

Generalized polymorphous lesions were present in all our patients. The same observation was made by Akakpo et al. [7] and by Ouattara, who reported polymorphous and symmetrical lesions in 73.9% of cases [4].

Three patients (21.4%) had oral and ocular mucosal involvement. Akakpo et al. also reported such involvement in 36.4% of cases [7] and Ouattara in 17.4% [4]. Zaara et al. found no mucosal involvement [8]. It is rare in DH [1].

Paraclinical Aspects

A biopsy of the lesions was performed in six patients, and the histology was compatible with GH in five cases. Ouattara confirmed this observation in 52.2% of biopsies [4]. Histology makes little contribution to the diagnosis. The reference diagnostic test for DH is direct immunofluorescence (DIF) [1,14], which is unavailable in our context.

Treatment

A gluten-free diet was initiated in all patients. It is indispensable for the management of DH [1,14], yet is difficult to follow. Treatment with dapsone (2 mg/kg/day) was offered to the fourteen patients. This molecule is the mainstay of DH treatment [1,14,15] and was effective in obtaining rapid regression of the cutaneous signs, generally within several days.

Evolution

After three months of follow-up, seven patients who came from a rural environment were lost to follow-up. This could be explained by financial difficulties and the use of phytotherapy. Better therapeutic education could considerably reduce the number of patients lost to follow-up.

CONCLUSION

This study shows that DH is a rare disease that, in our setting, mainly affects children of school age. It usually manifests as generalized polymorphous lesions.

Diagnosis is essentially clinical and management is based on dapsone, which is a diagnostic test.

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

Lipid profile and carotid intima–media thickness in xanthelasma palpebrarum: A case–control study in Northeast India

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ABSTRACT

Background: Xanthelasma palpebrarum (XP) is a common cutaneous xanthoma often associated with dyslipidemia. Carotid intima–media thickness (CIMT) is a non-invasive method of monitoring subclinical atherosclerotic plaque formation and its progression. This study was conducted to assess the cardiovascular comorbidities in patients with XP by measuring the CIMT and serum lipid profile. **Materials and Methods:** A total of eighty patients aged between 18 and 80 years diagnosed clinically with XP and the same number of apparently healthy, age- and sex-matched controls were included in the study after giving informed consent. Detailed history taking, examinations, and investigations were performed for all patients. **Results:** Significantly raised triglycerides and LDL levels were seen in 56.3% and 66.3% of the cases, respectively. HDL levels were elevated in 63.8% of the cases and 95% of the controls, which was statistically significant. The mean levels of total cholesterol, triglyceride, LDL, and HDL were 169.68 ± 39.91 mg/dL, 159.68 ± 28.61 mg/dL, 121.23 ± 30.13 mg/dL, and 43.09 ± 8.76 mg/dL, respectively. Elevated CCAIMT and ICAIMT were seen in 87.4% and 72.8% of the cases, respectively, which was significant. **Conclusions:** There was a significant elevation of triglyceride and LDL and a decrease in HDL among the patients with XP when compared to the controls, thus making lipid profile testing compulsory for all patients with xanthelasma. They also have an increased risk of subclinical atherosclerosis, as assessed by the significantly higher values of CCAIMT and ICAIMT. Hence, all xanthelasma patients should undergo CIMT as a screening procedure for the early detection and primary prevention of cardiovascular complications.

Key words: Xanthoma; Xanthelasma palpebrarum; Dyslipidemia; CIMT; Cardiovascular morbidity

INTRODUCTION

Xanthelasma palpebrarum (XP) is the most common cutaneous xanthoma, commonly seen in middle-aged individuals [1]. It is characterized clinically by sharply demarcated, yellowish, flat plaques bilaterally on the upper and lower eyelids, usually near the inner canthus.

The exact cause is unknown, yet several factors, such as lipid abnormalities, hormonal factors, local factors, and macrophages, are attributed to play a role in its etiopathogenesis [2,3]. It may occur as a result of disturbed lipid metabolism or essential familial hypercholesterolemia, in which LDL levels are raised due to a defect in the LDL receptors, resulting in a defective uptake and degradation leading to skin lesions [1,2].

Patients with XP may have lipid abnormalities, ranging from 9.1% to 67.9% [2]. A high prevalence of atherosclerotic, vascular, and heart diseases have been reported in patients with XP with both elevated and normal lipid levels [2,4]. Meanwhile, according to other authors, it seems to have no significant relation with lipid metabolism [5].

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Carotid intima–media thickness (CIMT) is a non-invasive method of monitoring subclinical atherosclerotic plaque formation and its progression. An increased intima–media thickness (IMT) correlates with an increased risk of cardiovascular events, such as myocardial infarction and stroke. An increase in IMT of 0.1 mm has been reported to increase the relative risk of coronary disease by 11%. It is considered a surrogate marker of more generalized atherosclerosis and a risk factor for cardiovascular disease [6,7].

Although XP is a benign lesion producing no functional defects, we have to be aware of the possible cardiovascular and metabolic comorbidities that may be associated with it.

In our study, in addition to assessing the lipid profile pattern associated with XP, we also included a measurement of CIMT. Only several studies have been conducted on CIMT in patients with XP. Hence, this study was conducted to assess the association of XP with atherosclerosis and other cardiovascular abnormalities by measuring the CIMT and serum lipid profile. This association, if significantly present, may prove to be an aid in the early intervention and proper management of patients to prevent unwanted cardiovascular complications.

MATERIALS AND METHODS

This was a case–control, observational study conducted over a period of two years at the outpatient department (OPD) of Dermatology, Venereology, and Leprology in collaboration with the Department of Radiodiagnosis of the Regional Institute of Medical Sciences (RIMS) in Imphal, India. A total of eighty patients aged between 18 and 80 years clinically diagnosed to have XP and the same number of healthy, age- and sex-matched controls were included in the study after giving informed consent. Patient confidentiality was maintained throughout the study.

The exclusion criteria were:

- Study subjects on drugs known to interfere with the lipid levels in the blood;
- Pregnant and lactating mothers;
- Study subjects with comorbid conditions, such as hypothyroidism, hyperthyroidism, and nephrotic syndrome, and females on oral contraceptive pills.

Consecutive sampling was performed. Both cases and controls were subjected to proper history taking, clinical examinations, laboratory tests, and CIMT measurements.

The serum lipid profile was measured after a fasting period of eight hours at minimum. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were measured with the enzymatic endpoint method.

Dyslipidemia was diagnosed based on the NCEP ATP III guidelines:

- TC: > 200 mg %;
- HDL: < 40 mg %;
- TG: > 150 mg %;
- LDL: > 100 mg %.

CIMT was measured with B-mode ultrasonography for carotid IMT measurement (Samsung Medison SonoAce X8; Seoul, South Korea). Intima–media thickness was measured as a distance between the leading edge of the first echogenic line of the wall of the carotid artery (lumen–intima interface) and the leading edge of the second echogenic line (media–adventitia interface) during the end of the diastole (peak of the R wave on electrocardiogram) at two segments: at the point of proximal 1 cm and distal 1 cm from the common carotid artery bifurcation (Figs. 1a and 1b). Measurements were taken only on longitudinal scans and not on transverse scans. The cutoff for the upper limit of the normal for carotid intima–medial thickness was 0.8 mm [7].

Data analysis was performed with SPSS, version 21.0. For inferential statistics, the chi-squared and Fisher exact tests were employed and a p value of < 0.05 was considered statistically significant. Student's t-test were employed for comparing between means. The strength of association was presented by odds ratios at a 95% confidence interval.

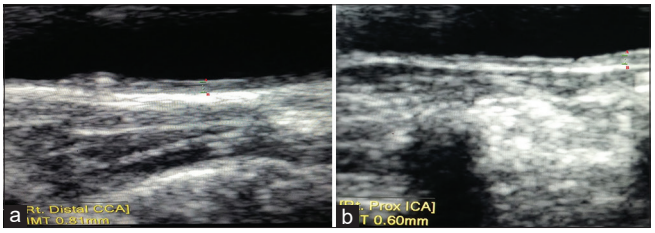

Figure 1:(a) Longitudinal scan of the common carotid artery on B-mode ultrasound. The measurement was taken as the distance between point A—the leading edge of the first echogenic line of the wall of the carotid artery (lumen–intima interface)—and point B—the leading edge of the second echogenic line (media–adventitia interface). (b) Longitudinal scan of the internal carotid artery on B-mode ultrasound. The measurement was taken as the distance between point A—taken at the lumen–intima interface—and point B—taken at the media–adventitia interface.

Ethics Statement

Ethical approval was obtained from the ethics committee of the institute.

RESULTS

A majority of the cases and controls were in the age group of 41–50 years (43.8%; $n = 35$), followed by 51–60 years (26.3%; $n = 21$), and 31–40 years (21.3%; $n = 17$). The age range was 33–64 years.

A majority were females (60%; $n = 48$), while the rest (32%; $n = 32$) were males.

A majority of the patients had a disease onset between 41 and 50 years with the mean age of onset of 43.90 ± 8.04 years. 88.7% of the patients had XP for more than two years (Table 1).

Hypertension was found in 40% of the cases and 26.3% of the controls, while diabetes was found in 21.3% of the cases and 28.8% of the controls. However, these findings were not statistically significant.

A history of smoking was present in 25 cases (31.3%) and 11 (13.8%) controls, which was statistically significant ($p = 0.008$). A sedentary lifestyle was present in 85% of the cases when compared to 68.8% of the controls, which was also statistically significant ($p = 0.015$). Low, moderate, and heavy alcohol intake was found in 18.8%, 11.3%, and 5% of the cases and 6.3%, 8.8%, and 3.8% of the controls, respectively. A habit of oral tobacco intake was present in 46.3% of the cases and 37.5% of the controls.

A positive family history of xanthelasma was found to be more common among the cases (22.5%) than among the controls (7.5%), which was significant ($p = 0.008$) (Table 2).

The mean BMI of the cases and controls was 25.75 ± 3.03 and 25.40 ± 2.81, respectively (Table 3).

The unilateral eyelid was affected only in 10% of the cases, with most cases (42.5%) having bilateral eyelid involvement (Table 4). All four eyelids were involved in 33.7% of the cases (Fig. 2).

The most common morphological type of xanthelasma was the plaque type (85%; $n = 68$), followed by the papule type (15%; $n = 12$).

Elevated cholesterol was found in 15.1% of the cases ($n = 12$) when compared to 12.5% ($n = 10$) of the controls. The mean levels of serum cholesterol among the cases and controls were 169.68 ± 39.91 mg/dL and 169.09 ± 36.32 mg/dL, respectively, which was not significant.

Triglyceride levels were elevated in 56.3% of the cases ($n = 35$) and 13.8% ($n = 11$) of the controls, and the distribution was found to be statistically significant ($p < 0.001$). The mean triglyceride levels among the cases and controls were 159.68 ± 28.61 mg/dL and 141.14 ± 13.96 mg/dL, respectively.

LDL levels > 100 mg/dL were found in 66.3% of the cases ($n = 53$) and 42.4% of the controls ($n = 34$), which was statistically significant ($p = 0.009$). The mean LDL levels in the cases and controls were

Table 1: Duration of XP in months in the study population

Duration of XP (months)	No. of patients	Percentage (%)
< 24	9	11.3%
24–47	31	38.7%
48–72	28	35.0%
➢ 72	12	15.0%
Total	80	100.0%

Table 2: Distributions of family histories in the two groups of the study population

Family History	Cases ($n = 80$)	Controls ($n = 80$)	*p* value
Xanthelasma palpebrarum	18 (22.5%)	6 (7.5%)	0.008**
Diabetes	22 (27.5%)	17 (21.3%)	0.357
Hypertension	32 (40%)	41 (51.3%)	0.153
Dyslipidemia	17 (21.3%)	10 (12.5%)	0.140
Obesity	20 (25%)	12 (15%)	0.114
Ischemic heart disease	11 (13.8%)	9 (11.3%)	0.633
Cerebrovascular accident	14 (17.5%)	7 (8.8%)	0.101

Table 3: BMI (kg/m^2) distribution in the two groups of the patients studied

BMI (kg/m^2)	Cases	Controls
< 18.5	0 (0%)	1 (1.2%)
18.5–24.9	33 (41.2%)	32 (40%)
25–30	43 (53.8%)	47 (58.8%)
➢ 30	4 (5%)	0 (0%)
Total	80 (100%)	80 (100%)

Table 4: Pattern distribution in the two groups of the patients studied

Pattern	Cases	Percentage
Unilateral	8	10%
Bilateral	34	42.5%
Three eyelids	11	13.8%
Four eyelids	27	33.7%
Total	80	100%

121.23 ± 30.13 mg/dL and 105.59 ± 25.13 mg/dL, respectively.

HDL levels were elevated in 63.8% ($n = 51$) of the cases and 95% ($n = 76$) of the controls, which was statistically significant ($p = 0.001$). The mean levels of HDL in the cases and controls were 43.09 ± 8.76 mg/dL and 50.41 ± 7.87 mg/dL, respectively.

A majority of the cases (87.4%; $n = 70$) had an elevated CCAIMT when compared to controls (4.9%; $n = 4$), which was significant ($p < 0.001$). A majority of the cases (72.8%; $n = 59$) also had an elevated ICAIMT when compared to the controls (1.2%; $n = 1$), which was significant ($p < 0.001$).s

Table 5 shows the mean values of CCAIMT and ICAIMT in the cases and controls, which were statistically significant ($p < 0.001$).

DISCUSSION

Females outnumbered males in our study, with a male-to-female ratio of 2:3, similarly to studies by Sharma et al. [1] and Kampar et al. [3]. This may have been due to the fact that females are cosmetically more conscious. A majority of the patients belonged to the age group of 41–50 years (43.8%), followed by 51–60 years (26.3%), similarly to findings by Nair et al. [8] and Kavoussi et al. [9]. In our study, a majority of the patients (38.8%) had xanthelasma for 24–48 months,

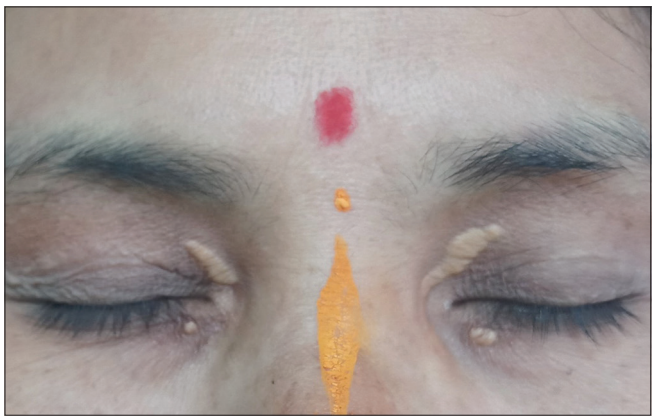

Figure 2: Well-defined, soft, yellowish papules and plaques around the medial canthus of the upper and lower eyelids.

Table 5: Comparison of CCAIMT and ICAIMT in the cases and the controls.

Variables	Cases	Controls	Total	*p* value
CCAIMT	0.90±0.12	0.49±0.12	0.69±0.24	< 0.001
ICAIMT	0.86±0.15	0.48±0.11	0.67±0.23	< 0.001

although Shankar et al. [10] found the duration of less than one year to be more common.

Hypertension was found to be more common among the cases, whereas diabetes mellitus was found to be more common among the controls, although it was not a significant finding. A history of smoking and a sedentary lifestyle was more commonly observed among those with xanthelasma, which was also significant statistically. However, no association could be found between alcohol intake and xanthelasma. Oral tobacco use was present in 46.3% of the cases, which was much higher than that reported by Dey et al. (13.1%) [11].

A family history of xanthelasma palpebrarum was found in 22.5% of the cases when compared to 7.5% of the controls, which was statistically significant ($p = 0.008$), implying that there is a higher proportion of a positive family history of xanthelasma among the cases than the controls.

There was no significant difference between the mean BMI of the cases and the controls.

A majority of the patients had plaque morphology (85%), followed by papule morphology of XP (15%). Bilateral eyelids involvement was found in a majority of the cases (42.5%), similarly to the findings by Dey et al. [11].

In our study, 15.1% ($n = 12$) of the cases and 12.5% ($n = 10$) of the controls had elevated serum cholesterol levels. The mean levels of serum cholesterol were almost equal in the cases and controls. The cases having total cholesterol ≤ 200 mg/dL were 19% less likely to develop xanthelasma when compared to the controls.

Significantly elevated triglyceride levels were seen in 56.3% of the cases ($n = 45$) and 13.8% ($n = 11$) of the controls. The cases with triglycerides ≤ 150 mg/dL were 88% less likely to develop xanthelasma when compared to the controls. The mean triglyceride level among the cases was found to be higher than among the controls, which was consistent with findings by Aggarwal et al. [12].

LDL levels were elevated in 66.3% of the cases ($n = 53$) and 42.4% of the controls ($n = 34$). The cases having LDL ≤ 100 mg/dL were 63% less likely to develop xanthelasma when compared to the controls, and the mean LDL level was higher among the cases than the controls. This finding was similar to a study by Shankar

et al. [10], who reported statistically significant elevated LDL in 82% of the cases. This was higher than the findings by Platsidaki et al. [13].

HDL level was found to be elevated in 63.8% ($n = 51$) of the cases and 95% ($n = 76$) of the controls with higher mean levels in the controls than the cases, which was significant statistically. The cases with low HDL were ten times more likely to develop xanthelasma when compared to the controls. This observation was in contrast with that by Sharma et al. [1], who reported no difference in HDL between the cases and the controls.

A majority of the cases (87.7%; $n = 70$) had an elevated CCAIMT when compared to the controls (4.9%; $n = 4$). Similarly, a majority of the cases (72.8%; $n = 59$) had an elevated ICAIMT when compared to the controls (1.2%; $n = 1$), which was also statistically significant ($p < 0.001$). The cases with CCAIMT and ICAIMT ≤ 0.8 mm were 99% less likely to have xanthelasma when compared to the controls. The mean values of CCAIMT and ICAIMT were significantly higher ($p < 0.001$) in patients with xanthelasma. This result was in agreement with that by Pandhi et al. [14], who reported significantly higher mean values of CCAIMT and ICAIMT in patients with xanthelasma in addition to more elevated ICAIMT and CCAIMT in the cases than the controls. Esmat et al. [15] reported a higher IMT in patients with XP, especially in those with hyperlipidemia. However, Chan et al. [5] reported that the presence of XP was not associated with an increase in CCAIMT.

CONCLUSION

There were significant abnormalities in LDL, HDL, and triglyceride levels in the patients with XP when compared to the controls. Hypertension and diabetes mellitus were the commonly associated comorbid diseases. Our result also indicated that patients with xanthelasma also had an increased risk of subclinical atherosclerosis as assessed by the significantly higher values of CCAIMT and ICAIMT. Hence, it is advisable for patients with XP to undergo lipid profile testing and CIMT measurements as a screening procedure for the early detection and primary prevention of CAD.

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

DRESS syndrome: A descriptive series of 62 cases

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ABSTRACT

Background: Drug reactions with eosinophilia and systemic symptoms (DRESS) are rare, yet potentially life-threatening, adverse drug reactions. This retrospective study aimed to analyze the epidemiological, etiological, therapeutic, and evolutionary characteristics of DRESS in the context of the dermatology department of Ibn Sina Hospital in Rabat, Morocco. **Methods:** A retrospective descriptive study was conducted over a period of fourteen years (January 2009 thru December 2022). All archived records of patients hospitalized for DRESS syndrome at the dermatology department of Ibn Sina University Hospital were collected. Cases were identified with the RegiSCAR criteria and, for each patient, epidemiological, anamnestic, clinical, paraclinical, therapeutic, and evolutionary data was collected. **Results:** The study included 62 patients, with a female predominance (67.7%). The average age was 48.59 years. The average time to onset of symptoms after drug intake was 27 days, and the duration of symptoms after the discontinuation of the suspected drug was more than two weeks in 80% of the cases. Clinically, all patients had pruritus and maculopapular rash, and 78% had erythroderma. Facial swelling was found in 66.1% of the cases, and 56.4% presented with at least one mucosal involvement. Hematological abnormalities consisted of hypereosinophilia in 85.36%. The most commonly implicated drugs were allopurinol, phenobarbital, and Salazopyrine. **Conclusion:** This study provides important epidemiological, etiological, clinical, therapeutic, and evolutionary data of patients hospitalized for DRESS syndrome in the context of the dermatology department of Ibn Sina Hospital in Rabat. The results of the study may be used to improve the diagnosis and management of DRESS syndrome in similar settings.

Key words: Toxidermia; Dress Syndrome; Epidemiology

INTRODUCTION

Toxidermias are undesirable drug effects that may be potentially serious [1]. Severe forms include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), also known as Lyell's syndrome [2].

DRESS syndrome is a rare drug-induced idiosyncratic hypersensitivity reaction that combines skin manifestations and systemic involvement [3].

In this retrospective study conducted at the dermatology department of Ibn Sina Hospital in Rabat, we aimed to analyze the epidemiological, etiological, therapeutic, and evolutionary characteristics of DRESS syndrome in our context by comparing our data to the literature.

MATERIALS AND METHODS

This was a retrospective, descriptive study covering a period of fourteen years (January 2009 thru December 2022). All archived records of patients hospitalized for DRESS syndrome at the dermatology department of Ibn Sina University Hospital were collected. Cases were identified with the RegiSCAR criteria, which allows cases to be classified as possible, probable, certain, and excluded. All cases classified as possible, probable, or certain were included. For each patient, we collected epidemiological, anamnestic, clinical, paraclinical, therapeutic, and evolutionary data.

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Ethics Statement

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.

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

RESULTS

We collected 62 patients, 42 females (67.7%) and 20 males (32.3%), indicating a clear female predominance with a male-to-female sex ratio of 0.47. The average age was 48.59, ranging from 22 to 75 years.

Fifty-four patients (87.80%) had at least one medical history, with the most frequent ones being: arterial hypertension found in 15 patients (27.7%), autoimmune diseases (rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis) found in 8 (14.8%), diabetes in 6 (9.67%), heart disease in 7 (12.96%), recent neurosurgical intervention (extra-dural hematoma, spontaneous cerebral hematoma, schwannoma, pituitary adenoma) in 4 (6.45%), depression in 4 (6.45%), chronic renal failure in 4 (6.45%), head trauma in 4 (6.45%), and epilepsy in 2.

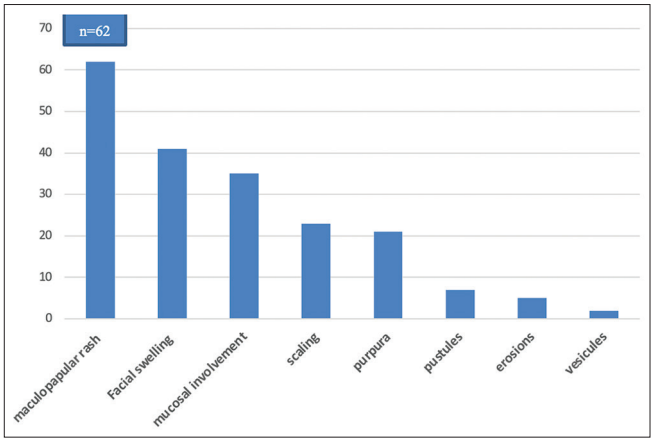
The average time to the onset of symptoms after drug intake was 27 days. The duration of symptoms after the discontinuation of the suspected drug was more than two weeks in 80% of the cases.

Clinically, pruritus was noted in all patients. Fever was observed in 68.29%, and fatigue in 32 (51.61%). Burning sensations were reported in four patients, dysphagia was in three, dyspnea in two, and dysphonia in one.

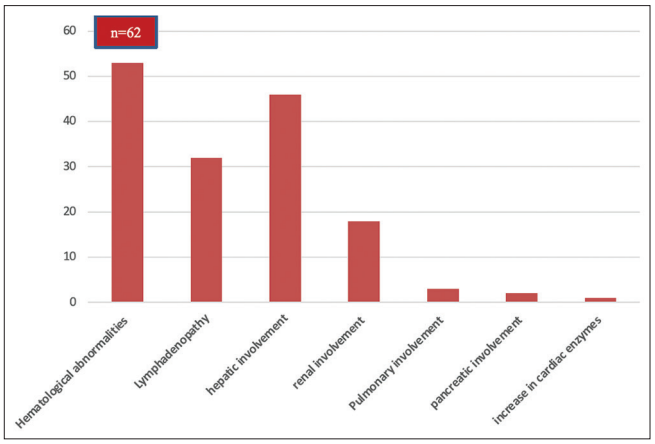
A maculopapular rash was present in all patients, among which 78% had erythroderma. Facial swelling was found in 41 patients (66.1%), scaling in 23 (37.09%), purpura in 21 (33.8%), pustules in 7 (11.29%), skin erosions in 5, and vesicular lesions in 2. Thirty-five patients (56.4%) presented with at least one mucosal involvement. The oral mucosa was the most affected, mainly with cheilitis, in 17 cases (48.57%). Stomatitis was noted in 6 cases. Conjunctivitis was noted in 9 cases (25.71%), oral erosions in 2 cases, and genital erosions in 2 cases (Graph 1).

Lymphadenopathy was present in 51.22% of the cases. Hematological abnormalities consisted of hypereosinophilia in 85.36% of the cases, leukocytosis in 63.2%, and abnormal lymphocytes in 26.7%. Visceral involvement was dominated by hepatic involvement, present in 75% of the cases, followed by renal involvement in 29.26%. Pulmonary involvement was noted in 3 cases, pancreatic involvement in 2, and an increase in cardiac enzymes in one (Graph 2).

RegiSCAR score calculation identified 30 certain cases, 29 probable cases, and 3 possible cases (Graph 3). The most commonly implicated drugs were allopurinol (43.34%), phenobarbital (22%), and Salazopyrine (17%). All implicated drugs were prescribed by a medical professional. Allopurinol was prescribed by various physicians (general practitioners, cardiologists, nephrologists, rheumatologists, traumatologists, and endocrinologists) for hyperuricemia in 18 cases, suspected gout in 5, and actual gout attack in 4. Phenobarbital was prescribed by neurosurgeons prophylactically after



Graph 1: Types of skin lesions.



Graph 2: Systemic involvement.

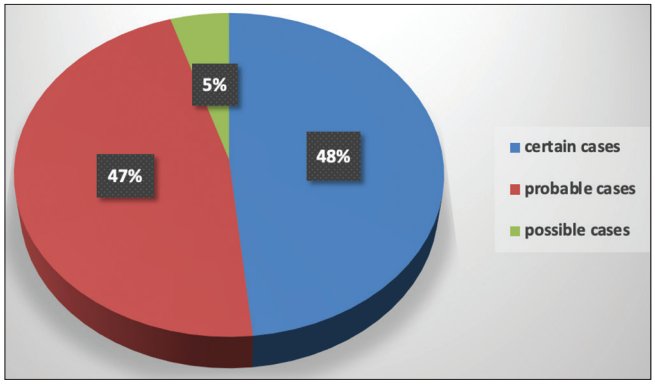
a neurosurgical procedure in 8 cases and after a head trauma in 4. It was only indicated for epilepsy treatment in 2 cases. Salazopyrine was indicated for the treatment of chronic inflammatory rheumatism and ulcerative colitis. Carbamazepine was prescribed by psychiatrists for neurogenic pain and psychiatric disorders (Graph 4).

The discontinuation of the suspected medication(s) as well as any non-essential medication was recommended for all patients. Local care and emollients were also recommended for all our patients.

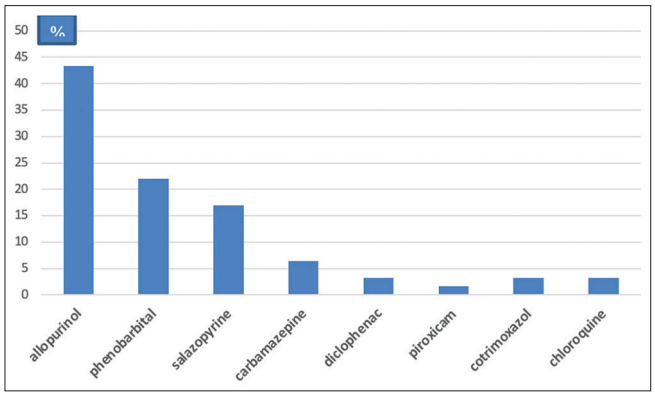
Hydroelectrolytic resuscitation was indicated in 12 patients (29%), mainly in cases of renal impairment or dehydration.

Treatment was mainly based on oral corticosteroids, which were indicated in 63.4% of the cases. The corticosteroid doses ranged from 0.5 to 1 mg/kg/day depending on the severity of systemic involvement. The total duration of corticosteroid therapy was estimated to be around one year.

The evolution was favorable in 95.1% of the cases. However, three deaths were recorded (Table 1).



Graph 3: Distribution of the cases according to RegiSCAR score.



Graph 4: Implicated drugs.

Short-term complications were mainly infectious: one case of pneumonia, two cases of nosocomial urinary tract infection, and three cases of soft tissue infection (abscess, lymphangitis, and erysipelas), which responded well to antibiotic therapy, yet with worsening rash and cytolysis in two cases.

Long-term complications could not be determined due to the retrospective nature of our study. One case of thyroiditis was noted (patient readmitted to our department). One case of relapse was reported four months after the discontinuation of corticosteroid therapy.

DISCUSSION

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), also known as drug-induced hypersensitivity syndrome, is an uncommon severe systemic hypersensitivity drug reaction. It is estimated to occur in 1 for every 1000 to 10,000 drug exposures [1]. It may affect patients of all ages and typically presents 2 to 6 weeks after exposure to the culprit medication [4].

Several reports state that, generally, there is no sex predominance. Mizukawa et al. described a female predominance with a male-to-female ratio of 0.71 [4]. In our study, we also noted a clear female predominance, with a male-to-female ratio of 0.46.

There is also no seasonal variability or specific atopic background in patients. However, Mizukawa et al. reported a history of mainly viral infection in half of their patients in the month preceding DRESS syndrome [5].

Its complex pathophysiology is now better understood, involving a predisposing immunogenetic background and a dominant reactivation of herpesviruses, specifically the HHV6 virus. Its pathophysiology has been clarified by the demonstration of reactivations of herpes viruses, which explains the seriousness of the clinical manifestations, in particular, the systemic attacks, as well as the biological modifications of DRESS syndrome [6,7].

DRESS syndrome has some highly specific characteristics, particularly chronological. Patients typically develop symptoms three weeks after the initiation of the triggering drug. The latency period of DRESS syndrome is longer than that of other delayed hypersensitivity drug reactions (SJS/NET, PEAG,

Table 1: Characteristics of the death cases

	Case 1	Case 2	Case 3
Age	70	75	67
Medical history	Arterial hypertension, diabetes, heart disease	Heart disease, chronic renal failure	Arterial hypertension, depressive syndrome
Incriminated drug	Allopurinol	Allopurinol	Allopurinol
Indication	Hyperuricemia	Hyperuricemia	Hyperuricemia
% of skin surface affected	90%	65%	more than 90%
Systemic involvement	Hepatic and renal, an increase in cardiac enzymes	Hepatic, renal, and pulmonary	Hepatic, renal, and pancreatic
Cause of death	Cardiogenic shock	Septic shock due to nosocomial infection	Septic shock

fixed pigmentary erythema, maculopapular rash). The duration of symptoms is also prolonged, generally lasting more than fifteen days after the discontinuation of the implicated drug, with an episodic course that may be interspersed with periods of remission [8].

The clinical presentation is highly polymorphic, characterized by the presence of fever, ranging from 38°C to over 40°C, which evolves in spikes. The fever is present in 90% to 100% of cases. A more pronounced fever is found in cases of erythroderma. Fever usually precedes the skin rash by several days, yet both symptoms may occur simultaneously [9,10]. Pruritus is also almost always present. Dysphagia may also be associated. The general condition is usually impaired. Some authors describe a high frequency of prodromes, such as upper respiratory tract infections, which they believe could support the role of viral infections [11]. In our series, pruritus was present in all patients. Fever was observed during hospitalization in 42 patients (68%), and 5 other patients reported febrile sensations before hospitalization. Dysphagia was reported in 3 cases. Skin rash is the most frequent clinical sign, found in 73–100% of cases. It usually begins on the face, trunk, and root of the limbs. The cutaneous signs are variable, often consisting of a morbilliform exanthema that is difficult to distinguish from a benign toxidermia with a maculopapular rash. The eruption generally affects more than 50% of the skin surface (Fig. 1). The maculopapular elements may merge to form infiltrated erythematous plaques sometimes with a purpuric evolution. The skin rash usually becomes generalized and evolves toward a severe exfoliative phase with significant desquamation, especially on the legs and feet. Other clinical aspects may also be observed, most often with a polymorphic eruption with atypical target lesions, vesiculobullous lesions, erosions, or lichenoid, pustular, urticarial, or eczematous elements. Desquamation marks the phase of symptom resolution (Fig. 2) [12]. In our series, a maculopapular rash was present in all our patients,

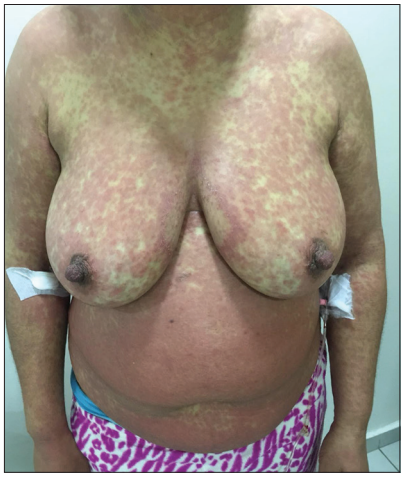


Figure 1: Morbilliform maculopapular rash in DRESS syndrome.

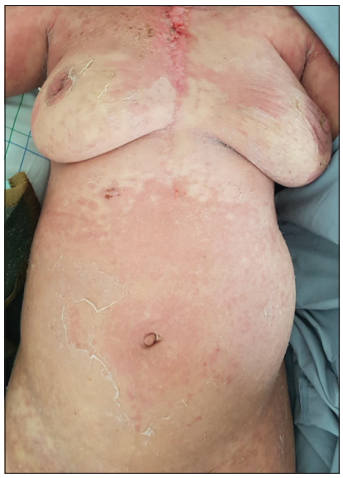


Figure 2: Large flap desquamation with erosions on the upper part of the trunk during DRESS syndrome.

with 78% having erythroderma. Purpura was found in 33.87% of the cases, and pustules were present in 7 patients. Facial edema, predominant in the periorbital region, is characteristic of DRESS syndrome. It is seen in 50–76% of cases [9]. It was present in 75% of our patients. Mucosal involvement is described as cheilitis, pharyngeal erythema, or even tonsillar hypertrophy manifested by odynophagia. Conjunctivitis is possible as well as oral or genital aphthous lesions. These

conditions may be seen in more than 50% of cases. Infiltration of the salivary glands leading to xerostomia may also be observed [13]. In our series, cheilitis was the most frequently observed sign (41.46%) (Fig. 3), followed by conjunctivitis (21.95%). Oral erosions were noted in two cases and genital erosions in two.

Hematological abnormalities are mainly characterized by hypereosinophilia, leukocytosis, hypereosinophilia, as well as the presence of hyperbasophilic lymphocytes. Hypereosinophilia is usually associated with organ involvement. In our series, leukocytosis was noted in 63% of our patients, hypereosinophilia was greater than 1500 in 75% of patients and between 900 and 1500 in 4 cases. The presence of atypical lymphocytes was noted in 27% of our cases. Other systemic involvements may also occur (lymph nodes, liver, lung, kidney, heart, neurological, digestive, endocrine), which contribute to the severity of the syndrome.

The histopathological features of DRESS syndrome are generally non-specific. In recent years, several commonly encountered histopathological patterns of DRESS syndrome have been identified, including spongiosis, interface dermatitis, vascular abnormalities, and superficial and perivascular infiltrate [14].

More than forty drugs have been reported to be associated with DRESS syndrome. In 2013, a prospective study by RegiSCAR on 117 patients reported that anti-epileptics, particularly carbamazepine, were the most commonly implicated drugs (37%), followed by allopurinol (18%). Other drugs traditionally associated with DRESS syndrome were much less common (Sulfasalazine in 8 cases, vancomycin in 7, minocycline in 6, dapsone in 3)[15]. In our study, the most commonly implicated drug was allopurinol (46.34%), followed by phenobarbital (22%), and sulfasalazine (17%). Carbamazepine was only implicated in four cases.

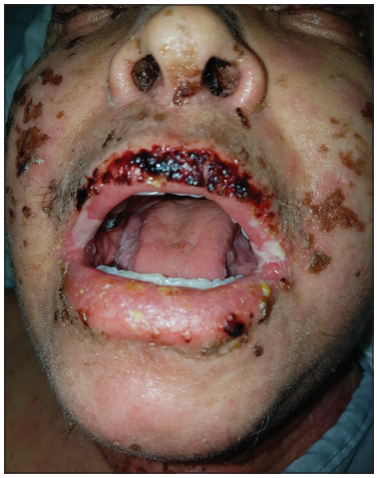


Figure 3: Erosive cheilitis in DRESS syndrome.

Regarding prognosis, DRESS syndrome is a potentially fatal severe drug reaction with a mortality rate of approx. 10% [4]. In our series, three deaths were noted, resulting in a rate of 7.3%. The course of DRESS syndrome is variable and unpredictable. A higher risk of severe systemic involvement was reported in DRESS syndrome induced by allopurinol and minocycline than by other medications [12]. However, organ damage may be highly severe in some patients, resulting in the permanent impairment of the function of the affected organs [13]. Liver transplants have been recommended for patients with severe liver injury. Patients with underlying chronic renal disease are subject to marked and permanent deterioration of renal function, sometimes requiring lifelong hemodialysis [16].

Thyroid disorders are the most commonly reported long-term sequela of DRESS syndrome, with a rate of 4.8%. These mainly include Graves' disease, Hashimoto's thyroiditis, and subacute lymphocytic thyroiditis. The reactivation of HHV-6 is also believed to play an important role in the development of these thyroiditis conditions [17].

In 2018, the reference center for toxic bullous dermatoses and severe drug-induced skin reactions (FISARD: French Investigators for Skin Adverse Reactions to Drugs) proposed a therapeutic scheme for the management of severe drug-induced skin reactions, including DRESS syndrome. The discontinuation of the implicated drug, hospitalization during the acute phase, and clinical and paraclinical evaluations are always necessary [18].

Following the initial assessment, patients may be classified according to the severity of the various systemic manifestations of DRESS syndrome into mild, moderate, or severe cases. Severe DRESS syndrome justifies urgent general corticosteroid therapy, the modalities of which (methylprednisolone bolus 500 mg/day for three days followed by oral prednisone 1 mg/kg, or prednisone 1 mg/kg from the outset) are not consensus-based. In the case of moderate-severity DRESS syndrome, a trial comparing the efficacy of local corticosteroid therapy with clobetasol propionate and general corticosteroid therapy at a dose of 0.5 mg/kg/day of prednisone is underway in France. Minor DRESS syndrome may be treated with local

corticosteroid therapy, such as clobetasol propionate at a dose of 30 g/day until the dermatological and systemic manifestations are controlled, followed by gradual tapering over 3 to 6 months [19].

Regardless of its modality (local or general), corticosteroid therapy should be prolonged (3 to 6 months) with slow tapering to prevent relapses. Other therapeutic modalities, such as antivirals and IVIG, are no longer recommended [20].

CONCLUSION

DRESS syndrome is a serious toxidermia that may be life-threatening and functionally dangerous. Currently, reliable diagnostic criteria are available to make the diagnosis as quick as possible. Treatment is mainly based on corticosteroid therapy in the presence of serious signs. Respecting the rules of prescription remains the most preferable way to prevent avoidable cases.

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Our Dermatology Online

Original Article

Clinical and onychoscopic evaluation of nail changes in psoriasis at a tertiary-care hospital: A cross-sectional study

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ABSTRACT

Background: Up to 30–50% of cases of psoriasis experience nail involvement, while 5–10% may have only isolated nail disease. Recently, the use of onychoscopy, a non-invasive technology, has emerged as a promising tool that may eliminate the necessity of a nail biopsy in most cases. **Objective:** The objective of this study was to assess the onychoscopic characteristics of the nail unit in individuals with nail psoriasis. **Materials and Methods:** The study recruited fifty patients with a clinical diagnosis of nail psoriasis. Each nail underwent onychoscopic assessment. The clinical degree of cutaneous and nail involvement was evaluated with the Psoriasis Area and Severity Index (PASI) and the Nail Psoriasis Severity Index (NAPSI), respectively. **Results:** The following findings were observed significantly more often on onychoscopy than with the naked eye: pitting ($p = 0.03$), leukonychia ($p = 0.04$), onycholysis ($p = 0.04$), and splinted hemorrhage ($p = 0.05$). The other novel findings included fuzzy lunula, which was only onychoscopically (8%), We also encountered 4% of cases of triangular onychomadesis and 6% of non-traumatic Median canaliform dystrophy of Heller. **Conclusion:** Our findings suggest that, even before clinical symptoms become obvious, onychoscopy may help with nail lesion diagnosis.

Key words: Onychoscopy; Nail Psoriasis; Psoriasis; Nail Pitting; Fuzzy Lunula; Triangular Onychomadesis

INTRODUCTION

Psoriasis is a chronic, papulosquamous disorder with an immune-mediated pathogenesis. The disease may involve not only the skin, yet also the nails and mucosa. The prevalence of psoriasis varies over the world, affecting between 0.5% and 2.5% of the global population [1,2]. In around 30–50% of cases, nail affliction is observed, with a lifetime prevalence between 80% and 90%. Nail involvement is widely prevalent in psoriatic arthropathy (PsA) and severe plaque psoriasis [3,4]. In fact, 5–10% of psoriatic individuals typically have isolated nail disease [5,6].

It is fairly simple to detect nail psoriasis when skin lesions are present. Although, due to its resemblance to other causes of dystrophic nails, including onychomycosis, lichen planus pityriasis rubra pilaris, alopecia areata, and traumatic onycholysis, there is a diagnostic conundrum in cases with solitary nail involvement [7]. Despite the high specificity of nail biopsies in diagnosing nail diseases, they have a low sensitivity and may proficiently diagnose nail psoriasis in only 50% of cases [3,8].

Dermoscopy is a quick, non-invasive, and *in vivo* technique with proven diagnostic value for pigmented skin and nail abnormalities. Dermoscopy is also one of the most effective methods for spotting early nail involvement. This property may eliminate the need for histopathological analysis in nail psoriasis diagnosis and treatment follow-up.

To date, only a handful of authors have attempted to examine the dermoscopic characteristics of nail

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psoriasis [9-12]. In this study, we intended to assess the value of onychoscopy in nail psoriasis. Our primary objective was to observe the onychoscopic findings in the nails of the psoriatic patient. The secondary objectives included assessing the prognostic significance of subclinical nail changes visualized on the onychoscope and correlating the severity of the disease with onychoscopic findings.

MATERIALS AND METHODS

This prospective and observational study was conducted at outpatient and inpatient dermatology departments over the course of one year after obtaining due approval from the institutional ethics committee (F.29.(Acad)SPMC/2021/3014). All participants gave written informed consent to be a part of the study. The study population included patients with a clinical diagnosis of psoriasis. In clinically ambiguous cases, histopathological analysis was performed to confirm the diagnosis. Only those cases who had psoriasis with nail lesions or isolated nail psoriasis were enrolled. Patients with a significant systemic illness or another concurrent dermatological or cutaneous disease were excluded. A thorough medical history was taken, and general physical examination and systemic and joint examinations were performed.

In addition to clinical and onychoscopic examinations, photographic documentation was completed on all 20 nails (10 fingers and 10 toenails) with a handheld dermatoscope (DermLite, 3rd generation; magnification: 10×) under the supervision of a senior faculty. Digital photographs were taken with a mobile camera with the same settings. The images were examined on the computer screen and, after thorough image analysis, onychoscopic findings were interpreted and noted.

Calculating the mean and standard deviations for the continuous variables served as descriptive statistics. Categorical variables were displayed as percentages and absolute numbers. In order to compare nominal categorical data between the groups, the chi-squared goodness-of-fit test was employed. The Pearson correlation coefficient was employed to calculate the correlation between the different variables.

Considering the prevalence of psoriasis in India at 2.8%, a clinical involvement of the nails in 60% of cases, a confidence level of 50%, and a 5% margin of error, a sample size of 31 was calculated [13,14]. However, we increased the sample size to 50 in view of potential subclinical nail involvement visualizable on the onychoscope.

Data was entered, checked, and analyzed with SPSS 22.0. The chi-squared test and Z scores were calculated wherever necessary. A p value < 0.05 was considered statistically significant.

The clinical degree of cutaneous and nail involvement was evaluated with the PASI and NAPSI, respectively.

RESULTS

In our study, a total of fifty patients with psoriasis were included, ranging from 14 years to 71 years. The majority of the psoriatic patients were between 20–29 years of age (26%), with a male-to-female ratio of 1.78:1. The mean age of our study subjects was 39.66 ± 19.06 years. The demographic data of the patients was tabulated in Table 1. In this study, 64% of the patients were diagnosed with chronic plaque psoriasis (CPP), followed by 14% of cases with palmoplantar psoriasis (PPP), 10% of cases with erythrodermic psoriasis (EP), 6% of cases with nail psoriasis (NP), 4% of cases with guttate psoriasis (GP), and 2% of cases with inverse psoriasis (IP).

Clinically, a majority of the cases had the involvement of ≤ 5 nails (38%), followed by the involvement of 6–10 nails (30%), and of 11–15 nails (26%) The average number of nails involved per case was 7.8 nails. Similarly, onychoscopically, a majority of the cases had the involvement of ≤ 5 nails (38%), followed by the involvement of 6–10 nails (30%), and of 11–15 nails (20%). The onychoscope had a higher proficiency in detecting a higher number of nails, yet the difference was statistically insignificant (0.71) (Table 2).

Table 1: Clinical and epidemiological data of the study participants

Parameter	Value
Mean age	39.66±19.06 yrs.
Sex	**Number of patients (%)**
Male	32 (64%)
Female	18 (36%)
Male-to-female ratio	1.78:1
Clinical diagnosis	**Number of patients (%)**
Chronic plaque psoriasis (CPP)	32 (64%)
Palmoplantar psoriasis (PPP)	7 (14%)
Erythrodermic psoriasis (EP)	5 (10%)
Nail psoriasis (NP)	3 (6%)
Guttate psoriasis (GP)	2 (4%)
Inverse psoriasis (IP)	1 (2%)

A majority of the patients (n = 28; 56%) had NAPSI scores ranging from 0 to 20, followed by 14% with scores of 21–40, 10% with scores of 41–60, 10% with scores of 61–80, 6% with scores of 81–100, and 4% with scores of 101–120.

In our study, the following nail matrix findings were seen: 68% had pitted nails, 44% had leukonychia, 48% had crumbling, 8% had onychomadesis, 8% had fuzzy lunula, 6% had median canaliform dystrophy, and 6% had trachyonychia. However, onychoscopically, a greater number of patients had nail matrix findings. Significant p-value results were found with the chi-squared test for pitting (p = 0.03) and leukonychia (p = 0.04), with onychoscopy being superior to clinical examination for the identification of these nail matrix findings (Table 3).

The following nail bed findings were seen clinically: 54% had onycholysis, 42% had SUHK, 20% had splinter hemorrhage (Figs. 1a and 1b), and 14% had oil drop signs (Figs. 1c, 1d, 2a, and 2b). On onychoscopy, significant p-value results were found with the chi-squared test for onycholysis (p = 0.04) and splinter hemorrhage (p = 0.05), with onychoscopy being superior to clinical examination for the identification of these nail bed findings (Table 4).

Overall, the mean NAPSI of the patients was 31.46. There was a strong positive correlation between NAPSI and duration of psoriasis. The correlation coefficient was 0.82, and the p value was < 0.0001 (highly significant correlation). There was also a moderate correlation between NAPSI and PASI. The correlation coefficient was 0.67, and the p value was < 0.0001 (highly significant correlation).

DISCUSSION

In our study, the mean age of the study subjects was 39.66 ± 19.06 years (ranging from 18 to 79 years), which was comparable to similar studies conducted across the globe. A study by Yadav et al. reported a mean age of 38.36 years [10]. Similar results were reported by Wanniang et al. (45.02 years) and Daulatabad et al. (36.3 years) [9,14], together with studies by van der Velden et al. (48 years), Marina et al. (51.89 years), Brazzelli et al. (52.53 years), and Hashimoto et al. (47.5 years) [15-18]. There was also a male preponderance in this study, with a male-to-female ratio of 1.78:1. Fairly similar results were reported by Chauhan et al., Hashimoto et al., and Yadav et al. [3,10,18].

Table 2: Number of nails involved clinically vs. dermatoscopically

Number of nails involved	Clinically	Percentage	Onychoscopically	Percentage	*p* value*
≤ 5	19	38%	19	38%	0.71
6–10	15	30%	15	30%	
11–15	13	26%	10	20%	
16–20	3	6%	6	12%	
Total	50	100%	50	100%	

*Chi-squared test

Table 3: Nail matrix in clinical vs. onychoscopic findings

Nail Matrix findings	Clinically		Onychoscopically		*p* value*
	Clinically	Percentage	Number of patients	Percentage	
Pitting	34	68%	43	86%	0.03
Leukonychia	22	44%	32	64%	0.04
Crumbling	24	48%	24	48%	-
Onychomadesis	4	8%	4	8%	-
Fuzzy lunula	0	0%	4	8%	-
Median canaliform dystrophy	3	6%	3	6%	-
Trachyonychia	3	6%	6	12%	0.29

*Chi-square test

Table 4: Nail bed in clinical vs. onychoscopic findings

Nail Bed findings	Clinically		Onychoscopically		*p* value*
	Clinically	Percentage	Number of patients	Percentage	
Onycholysis	25	50%	35	70%	0.04
Subungual hyperkeratosis	21	42%	21	42%	-
Splinter hemorrhage	10	20%	19	38%	0.05
Oil drop sign	7	14%	13	26%	0.13

*Chi-squared test

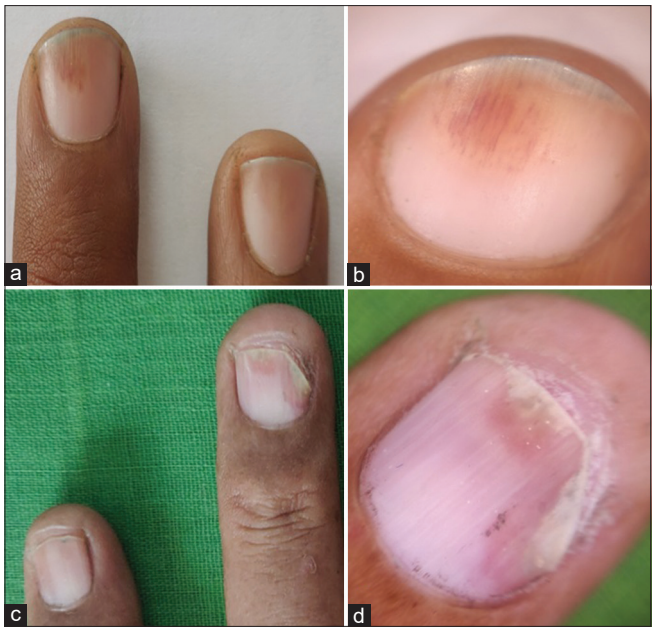

Figure 1: (a) Clinical image of splinter hemorrhage. (b) Dermatoscopic image of splinter hemorrhage with tortuous blood vessels and a diffuse, orangish-yellow background. (c) Clinical image of the oil drop sign. (d) Dermatoscopic image of the oil drop sign with leukonychia and a disrupted, onychocorenal band.

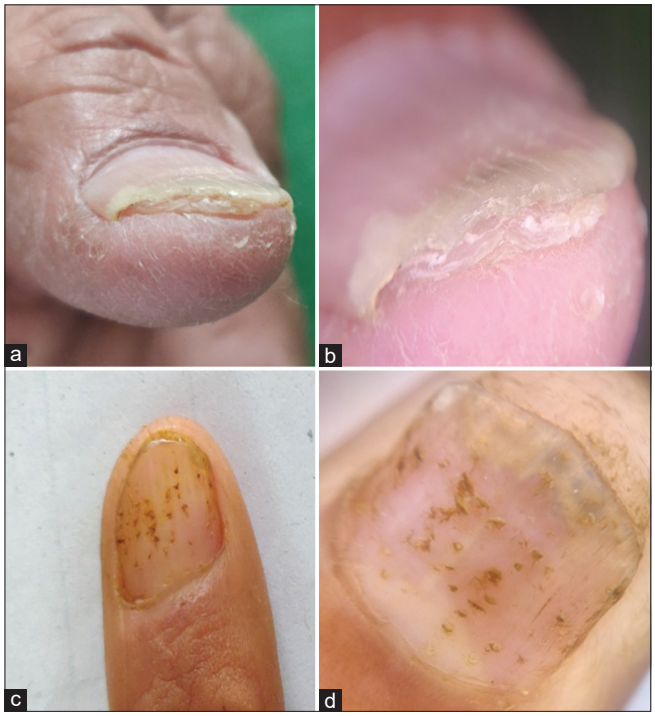

Figure 2: (a) Clinical image of subungual hyperkeratosis (SUHK). (b) Onychoscopic image of SUHK with white, superficial scales. (c) Clinical image of nail pitting. (d) Onychoscopic image showing coarse and deep nail pitting in a haphazard arrangement, nail plate scales, and onycholysis.

In our study, the most common nail finding was pitting (Figs. 2c and 2d), followed by onycholysis and crumbling. These results were consistent with previously conducted research [3,9,14]. However, red lunula, a relatively uncommon nail finding in psoriatic patients, was not observed in any of our cases. Our subjects' mean PASI score was 8.93 ± 5.04 (0–33), which was comparable to that observed by Chauhan et al. However, Wanniang et al., Brazzelli et al., Schons et al., and Daulatabad et al. observed a higher mean PASI [9,14,17,19]. The mean NAPSI was 31.46, which was comparable to similar studies [14,19,20]. NAPSI was also comparable in individuals with associated arthritis, and scores were greater in the fingernails than the toenails.

In this study, we also found a positive correlation between NAPSI and PASI scores, as well as between NAPSI and disease duration. This data was a strong indicator that nail involvement becomes more pronounced with increasing disease duration and severity. Although Rich et al. reported no significant correlation between NAPSI and PASI, both Chuhan et al. and Patsatsi et al. detected a significant correlation [3,21,22]. This was attributed to the fact that, while Chauhan et al. assessed the total NAPSI (0–160) the way that we did, Rich et al. used only the target NAPSI (0–8) [3,21]. As far as the correlation between disease duration and NAPSI was concerned, Daulatabad et al. found a significant correlation between the two variables. Wanniang et al. also reported a significantly positive correlation between dermatoscopic NAPSI and PASI scores [9,14].

On onychoscopic evaluation, pitting was the most common nail matrix finding, observed in 43 (86%) cases. There was a significantly higher prevalence of pitting on onychoscopy than clinically ($p = 0.03$). This finding was in agreement with observations made by Chauhan et al. Yadav et al., Yorulmaz et al., and Wanniang et al. [3,9,10,12].

Other findings, such as leukonychia ($p = 0.04$), onycholysis ($p = 0.05$), and splinter hemorrhage ($p = 0.04$), were also significantly higher on onychoscopy. Other onychoscopic findings of the nail matrix and nail bed findings were comparable to the naked eye examination.

Leukonychia and nail plate crumbling were the two most common nail findings, observed at a significantly higher rate on onychoscopy than clinically. These findings were also reported by Wanniang et al. and Yorulmaz et al [9,12].

A novel finding of this study was fuzzy lunula (Fig. 3a), which was observed only onychoscopically. Fuzzy lunula

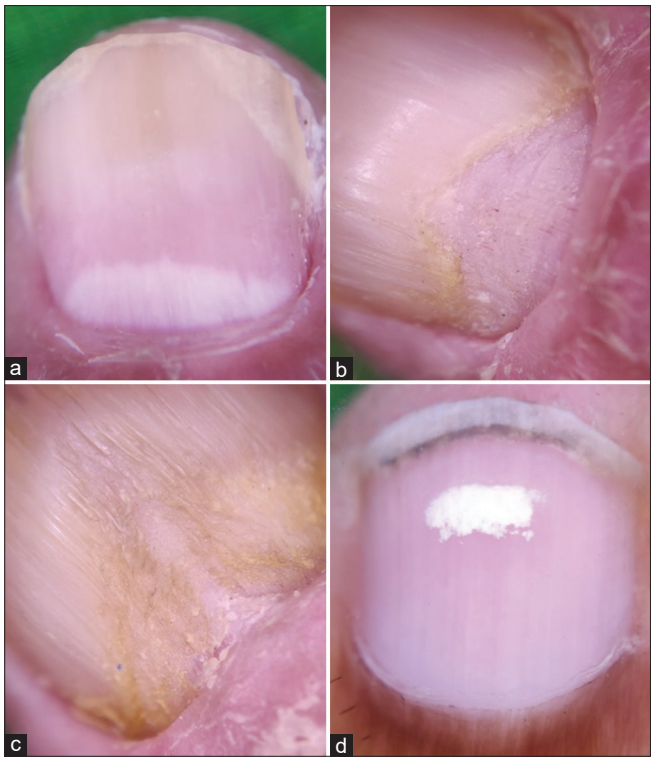

Figure 3: (a) Onychoscopic image showing fuzzy lunula. (b) Triangular proximal nail plate dystrophy with nail plate scales and cuticular destruction. (c) Medial canalicular dystrophy. (d) Leukonychia.

was seen in 4 (8%) cases. Fairly unprecedented in the literature, fuzzy lunula was a unique finding in this study, which had previously been reported only once, by Chauhan et al. [3]. Onychoscopically, the nail lesion appeared as a wide and crooked, white lunula.

We also encountered two cases of triangular onychomadesis and three of non-traumatic median canaliform dystrophy of Heller (Figs. 3b – 3d). To date, these findings have not been reported by any other study.

Our study was limited by a small sample size, a short study duration, and the absence of histopathological or radiological correlation. Additionally, the impact of the treatment on nail findings was not assessed.

CONCLUSION

In conclusion, the nails are indeed a window to the underling disorders of the body [23,24]. Dermoscopy serves as a bridge between histological and clinical examinations and aids in the identification of nail psoriasis well before the clinical indications of nail involvement are obvious. A possible early indicator of disease activity is the appearance of dermoscopic characteristics in apparently healthy nails. In patients with nail psoriasis, this study thoroughly detailed the dermoscopic characteristics of the nail matrix and nail bed. However, further controlled investigations need to be conducted on a larger sample size in order to proficiently determine the sensitivity and specificity of all dermoscopic features in order to standardize their diagnostic value.

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

Rickettsial diseases: A group of underdiagnosed fevers

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ABSTRACT

Background: Rickettsias are zoonoses transmitted to humans by arthropods. Their clinical manifestations vary. Prompt and effective treatment is recommended before biological confirmation. The aim of this study was to establish the epidemiological and clinical profiles of this group as well as its different extracutaneous manifestations. **Materials and Methods**: This retrospective study included patients with rickettsiosis who consulted between June 2016 and October 2022. **Results**: Twenty-nine patients, with a male predominance of 66%, aged between 2 and 74 years. A maculopapular rash was present in all cases. Symptomologies ranged from neurological and digestive to renal. All our patients underwent a rickettsia check-up and serology. Twenty-five patients presented a febrile cutaneous eruption forty-eight hours after the tick, leading to hospitalization and prompt treatment. Evolution was characterized by disinfiltration and positive improvement. **Conclusion:** Because rickettsial diseases have a wide geographical distribution, recognition of their symptoms is essential for prompt treatment.

Key words: Rickettsias; Eruption; Escharotic

INTRODUCTION

Tick-borne rickettsia is caused by Gram-negative bacteria belonging to the spotted fever group of the genus *Rickettsia* [1]. Among the oldest vector-borne diseases, these zoonotic diseases are the most common. The first clinical description of Rocky Mountain spotted fever (RMSF) in Idaho, U.S., was reported by Edward E. Maxey in 1899, and the first case of Mediterranean spotted fever (MSF) was reported by Conor and Brush in Tunisia in 1910 [2]. The disease affects people of all ages and mainly occurs in summer. The clinical presentation varies from mild to highly severe, with a mortality of 2–6% [3]. The signs are fever, headache, maculopapular rash, an escharotic spot, and localized adenopathy. Rickettsial diseases are also difficult to diagnose, as there are no rapid point-of-care tests to establish the diagnosis during acute infection, and the confirmation of the diagnosis, when sought, is usually retrospective using serological methods [3]. Treatment should be administered prior to biological confirmation for early and rapid improvement [4]. The objective of our study was to identify the epidemiological and clinical characteristics of our patients followed for rickettsial disease.

MATERIALS AND METHODS

In this prospective, retrospective, cross-sectional study, we collected all cases of rickettsiosis consulted at Hassan II Hospital of Dermatology and the emergency room between June 2016 and October 2022.

RESULTS

We collated 29 patients, with a male predominance of 66%, aged between 2 and 74 years. The legs and thighs were the most frequent topography of the escharotic spot (Fig. 1a); maculopapular rash was present in all our cases (Figs. 1b and 1c); purpura was present in 67%. The extracutaneous symptoms were rich and varied between neurological in 7 patients (headache, dizziness, behavioral, and consciousness disorders), digestive in

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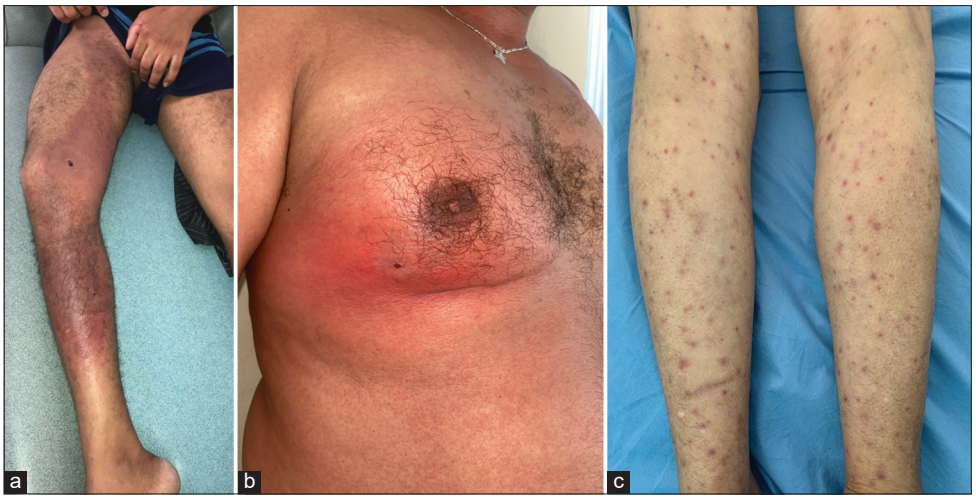

Figure 1: (a) Erythematous placard on the lower extremity.(b and c) Erythematous plaques centered by the escharotic spot.

5 (abdominal pain, nausea, and vomiting), and renal in 10. The average time to onset of the symptoms was 4 days. Six patients were admitted to the emergency room for a disorder of consciousness diagnosed late as secondary to rickettsiosis. Biological tests showed hyperleukocytosis with a neutrophil predominance and elevated CRP in all our patients. Serology for rickettsial disease was positive in twelve patients. Our patients described a typical cutaneous reaction composed of a febrile cutaneous and mucosal rash forty-eight hours after the tick bite (Fig. 2), particularly in one patient, who presented a declining infiltrated purpura on the limbs, diagnosed as vasculitis after a cutaneous biopsy. Doxycycline 200 mg/day was prescribed as a formal indication. A lumbar puncture and cerebral MRI of four patients revealed secondary cerebral MRI of rickettsial disease. There was also vasculitis and encephalitis. In the case of abdominal pain and lipasemia five times normal, an abdominal scan was performed, which showed pancreatitis at stage E, from where the indication of the addition of ciprofloxacin for seven days was given to the six patients. The evolution was marked by the disinfiltration of the rash and the healing of the escharotic ulceration, as well as the improvement of other cerebral and digestive conditions. However, one patient ultimately died. This was due to his late consultation and the late initiation of therapy.

DISCUSSION

Rickettsia, also known as spotted fever, is caused by *Rickettsia conorii* and is transmitted by the brown dog tick [5]. Cases occur during the summer months when ticks are most active [6].

Figure 2: A tick responsible for the bite.

The time from the moment of infection and the incubation period to the onset of the disease is six days on average. Often, patients present with a sudden increase in body temperature, flu-like syndrome (headache, chills, joint, and muscle pain), and scabs ("black spots") at the site of the tick bite [7]. These scabs are characteristic of the disease. These are red, inflamed papules, necrotic in the center, black, painless, more often located on the trunk, legs, or arms (in infants, they are more often found on the scalp in the occipital region). Sometimes, scabs may be absent. A generalized maculopapular rash (97%) affects the extremities and trunk. Other common clinical symptoms include myalgia, headache, conjunctivitis, hepatomegaly, and splenomegaly. Gastrointestinal symptoms may occur in approx. 30% of patients and are more common in children [8]. The severe form occurs in 5–6% of cases and is associated with disseminated vasculitis, renal, neurological,

and cardiovascular complications, and phlebitis. In a recent prospective study in Algeria, 49% of patients were hospitalized with severe forms. The overall mortality rates for patients hospitalized with severe neurologic signs and multiple lesions were 3.6% and 54.5% [9]. In order to include it in the differential diagnosis of undifferentiated fever, the clinical symptoms and epidemiological knowledge of rickettsia are required. Serology is the basis for diagnosis and indirect immunofluorescence (ELISA) is the serological method of choice [10]. If rickettsiosis is suspected, empirical treatment should be initiated prior to *in vitro* laboratory susceptibility and *in vivo* confirmation. Doxycycline is currently recommended for the treatment of rickettsiosis. For adults, doxycycline 200 mg for 2-to-5 days or within twenty-four hours of fever is most commonly used, yet doxycycline 200 mg once administered has been shown to be effective in some cases of rickets in the spotted fever group [11]. The treatment of severe forms of the disease involves an intravenous administration of 200 mg doxycycline per day, followed by oral administration of 200 mg doxycycline per day until complete recovery (10 days). For children and pregnant women, treatment with certain macrolides for 5 to 7 days is recommended. However, a single dose of doxycycline at 5 mg/kg/day is effective and does not cause the side effect of tooth discoloration. In individuals allergic to tetracycline, ciprofloxacin (1.5 g/day, orally administered for 5 days) or chloramphenicol (2 g/day, 7 to 10 days) is effective against rickettsia erythematosus [12]. Its prevention relies on early detection (within twenty hours) and the appropriate removal of ticks in order to avoid transmission. There are no vaccines available for the prevention of rickettsial diseases or antibiotic prophylaxis. We have outlined several points concerning this bacterial infection in our cases and the literature: it is a severe infection that is potentially fatal, and dermatologists should be aware of it so that they may initiate TRT without delay.

CONCLUSION

Rickettsial diseases are present worldwide and continue to emerge and re-emerge as leading causes of febrile illness. Early identification of clinical presentations will be helpful in prompt and 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 all patients.

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Our Dermatology Online

Brief Report

Cutaneous adverse reactions to antiepileptic drugs: 17 cases at the Dermatology Department of the Arrazi Hospital in Marrakech

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ABSTRACT

Background: Antiepileptics are among the drugs mainly implicated in cutaneous adverse drug reactions (CADRs). **Materials and Methods:** The aim of this case series was to study the epidemiological, clinical, evolutionary, and therapeutic profile of antiepileptic-drug-induced toxidermia and the most often incriminated antiepileptic drugs. **Results:** We collected seventeen cases of a CADR to antiepileptic drugs at the Dermatology Department of CHU Mohamed VI in Marrakech over a period of five years. The mean age was 42 years. The pattern of CADRs was as follows: DRESS syndrome in 52.9%, Stevens–Johnson syndrome in 23.5%, Lyell syndrome in 11.8%, and acute generalized exanthematous pustulosis and fixed bullous generalized drug eruption in 5.9% each. Carbamazepine was the most often incriminated antiepileptic drug. **Conclusion:** CADRs to antiepileptic drugs are dominated by DRESS syndrome. Through this study, we underline the potential of antiepileptic drugs to induce serious toxidermia and that, therefore, their prescription must be reasoned.

Key words: Cutaneous Adverse Reactions; Antiepileptics; Epidemiology; Prognosis; Pharmacovigilance

INTRODUCTION

Toxidermia is a group of cutaneous adverse reactions to drugs (CARDs) taken on medical prescription or self-medicated [1,2]. The severe and life-threatening conditions include anaphylaxis, acute generalized exanthematous pustulosis (AGEP), DRESS syndrome, Stevens–Johnson syndrome, and Lyell syndrome. These severe adverse reactions should be systematically reported to the pharmacovigilance authorities to allow for a better evaluation of the benefit-risk ratio of drugs. All drug classes may cause toxidermia, especially antibiotics, antiepileptics, and non-steroidal anti-inflammatory drugs. We conducted this case series to study the epidemiological, clinical, evolutionary, and therapeutic profile of toxidermia induced by antiepileptic drugs and to specify the most often incriminated antiepileptic drugs.

MATERIALS AND METHODS

The case series was conducted from January 2017 to December 2021 (for a period of five years) at a dermatology department in Marrakech on seventeen patients hospitalized for toxidermia to antiepileptics. Archival medical records were used to collect data. We began our study by elaborating on an exploitation form. The parameters submitted to the analysis were epidemiological, clinical, para-clinical, evolutionary, and therapeutic data. The results were recorded on a paper form, then entered into SPSS, version 20, and

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were given in the form of percentages and numbers for the qualitative variables and in the form of averages for the quantitative variables. They were presented with histograms and tables.

RESULTS

Characteristics of the Patients

During the study period, a total of 87 patients were hospitalized at the Dermatology Department for toxidermia induced by different drug classes. Seventeen cases of toxidermia to antiepileptic drugs were reported during this period. The average age of the patients was 42 years, with extremes of 16 and 70 years. The most represented age group was between 16 and 52 years. There was a female predominance (82.4%). Epilepsy was the main indication for antiepileptic drugs in our study (8 cases; 47.1%), followed by psychosis (2 cases; 11.8%), depression (1 case; 5.9%), and post-herpetic neuralgia (1 case; 5.9%). The reason for prescription was unknown in 5 cases (29.3%). A history of toxidermia was noted in 11.8% (2 cases) of the patients. Five cases of toxidermia to antiepileptic drugs were noted during the year 2021 when compared to the years 2017, 2019, and 2020; four cases were found in each year, and no cases in 2018 (Fig. 1).

Pattern of Cutaneous Adverse Reactions Induced by Antiepileptic Drugs (Carads)

A total of seventeen different CARADs were observed. The most commonly observed CARADs were DRESS syndrome (Figs. 2a and 2b), Stevens–Johnson syndrome, and toxic epidermal necrolysis (Figs. 3a and 3b) (Table 1).

Cutaneous or general signs of severity were present in all patients. Purpura was observed in 23.5% (4 cases), confluent erythema in 29.4% (5 cases), facial edema in 47.1% (8 cases), mucosal erosions in 58.8% (10 cases), a positive Nikolsky's sign in 29.4% (5 cases), bullae in 5 cases, fever in 13 cases (76.5%), adenopathy and hypotension in one case, and arthralgia and respiratory distress in 2 cases. Pruritus was present in 82.4% (14 cases). Neurological signs associated with cutaneous side effects were represented by drowsiness in 3 cases (17.6%) and behavioral disorders in only one case (5.9%).

Causative Drugs

The common causative antiepileptic drugs were carbamazepine (52.9%), sodium valproate (23.5%), lamotrigine (11.8%), and phenobarbital (11.8%) (Table 2). All patients had received their medication

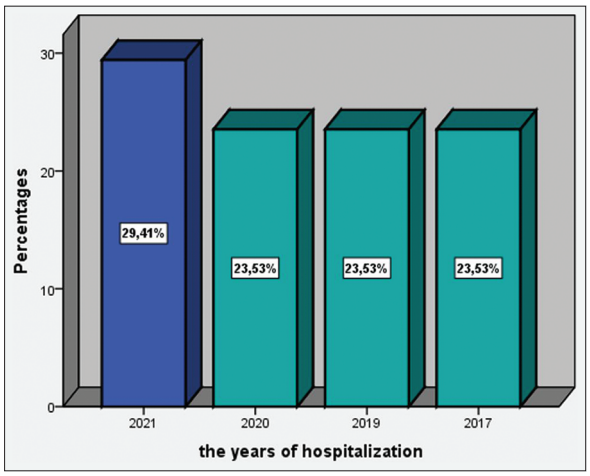

Figure 1: Distribution of toxidermia cases to antiepileptic drugs (%) during the five years of study at the Dermatology Department.

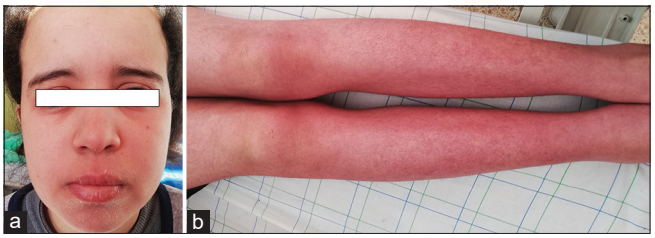

Figure 2: (a and b) Clinical photographs showing an extensive skin rash after the onset of carbamazepine for epilepsy. This patient had DRESS syndrome to carbamazepine.

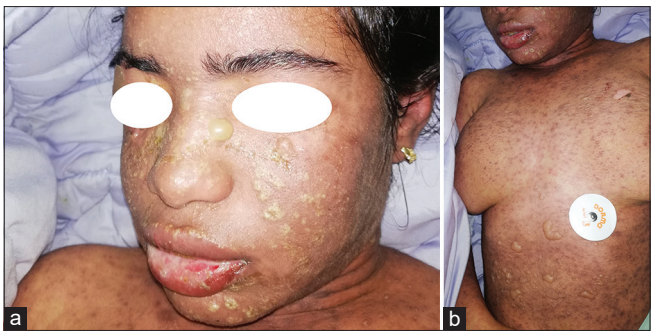

Figure 3: (a and b) Extensive macular and bullous lesions with a positive Nikolski sign and oropharyngeal involvement in toxic epidermal necrolysis induced by carbamazepine in the same patient.

Table 1: Distribution of cutaneous adverse reactions to antiepileptic drugs (CADRs) in our study

Type of CADR	Total cases (%)
DRESS syndrome	9 (52.9%)
Stevens–Johnson syndrome	4 (23.5%)
Toxic epidermal necrolysis	2 (11.8%)
Acute generalized exanthematous pustulosis	1 (5.9%)
Generalized fixed bullous erythema pigmentosa	1 (5.9%)

Table 2: Distribution of the most implicated antiepileptic drugs in our study

Antiepileptic Drug	Number	Percentage (%)	Valid percentage	Cumulative percentage
carbamazepine	9	52.9	52.9	52.9
lamotrigine	2	11.8	11.8	64.7
phenobarbital	2	11.8	11.8	76.5
sodium valproate	4	23.5	23.5	100.0
Total	17	100.0	100.0	

through a medical prescription and there were no cases of self-medication.

Biologically, a complete blood count was disturbed in 64.7% of the cases, with hypereosinophilia in 35.3%, neutrophilic leukocytosis in 11.8%, and leukopenia in 17.6%. Hydroelectrolytic disorders were noted in 17.6%, renal insufficiency in 5.9%, and hepatic cytolysis in 58.8%. Neurological explorations were indicated in 4 cases (23.5%).

Management of Cutaneous Adverse Reactions Induced by Antiepileptic Drugs (Carads)

CARADs required the withdrawal of the suspected drugs in all patients. An antiseptic was prescribed in 47.1%, dermocorticoids in 41.2%, bathing and emollient in 94.1%, and topical antibiotic in 11.8%. Six patients (35.3%) were treated with oral steroids, and fifteen patients (88.2%) were treated with antihistamines. The patients were given a drug card mentioning the name of the drug which had caused the reaction. The evolution was marked by healing in 15 cases (88.2%) and a transfer to the intensive care unit in 2 cases (11.8%).

DISCUSSION

Hypersensitivity to antiepileptic drugs was first reported in 1934 by Silber and Epstein [3,4]. A cutaneous adverse reaction to an antiepileptic drug occurs in 3% of individuals receiving anticonvulsants [3], and numerous sources indicate that antiepileptic drugs are among the most frequent triggers of serious cutaneous adverse reactions. Phenytoin, phenobarbital, carbamazepine, and lamotrigine are the anticonvulsants most frequently involved in toxidermia [3]. The female predominance in our series was consistent with the literature. The risk factors for toxidermia to anticonvulsants are a history of toxidermia to an antiepileptic drug, which was noted in our study in 11.8%, old age, female sex, ethnic origin, genetic predisposition (HLA), vitamin D deficiency, and the presence of comorbidities.

Toxidermia to antiepileptic drugs (AED) is varied, ranging from mild forms (rash and urticaria) to severe forms (DRESS syndrome, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis), with an estimated mortality rate of 10% [5-7]. According to a Korean study by Kyung [8] conducted over ten years (2008–2017) on adverse skin reactions to antiepileptic drugs, a total of 2942 cases were studied, among which 2702 (91.8%) had rash/urticaria, followed by 109 cases (3.7%) with DRESS syndrome, 106 cases (3.6%) with Stevens–Johnson syndrome, and 25 cases (0.85%) with Lyell syndrome; however, in our study, we noticed a predominance of cases of DRESS syndrome (52.9%), followed by Stevens–Johnson syndrome (23.5%), toxic epidermal necrolysis (11.8%), generalized acute exanthematous pustulosis (5.9%), and generalized bullous fixed erythema pigmentosum (5.9%); the absence of benign forms was explained by the nature of our study, which was only interested in severe toxidermia requiring hospitalization. In our study carbamazepine was the most often incriminated anticonvulsant (52.9%), followed by sodium valproate (23.5%), lamotrigine (11.8%), and phenobarbital (11.8%), while in a Korean study by Kyung et al, the most frequent antiepileptic drugs involved in mild and severe toxidermia were lamotrigine (699, 23.8%), valproic acid (677, 23%), carbamazepine (512, 17, 4%), oxcarbazepine (320, 10.9%), levetiracetam (181, 6.2%) and phenytoin (158, 5.4%). The same Korean study found that, in 241 cases of severe toxidermia (DRESS, SJS, and Lyell), the antiepileptic drugs involved were carbamazepine in 117 cases (48.8%), lamotrigine in 57 cases (23.8%), valproic acid in 20 cases (8.3%), phenytoin in 15 cases (6.3%), and oxcarbazepine in 10 cases (4.2%) [8]. According to the study by Kyung et al., DRESS syndrome was the most frequently reported adverse reaction, and carbamazepine was the most common antiepileptic drug in severe toxidermia and lamotrigine in general toxidermia [8].

Most of the allergic reactions induced by antiepileptic drugs are the result of delayed cell-mediated hypersensitivity with the probable involvement of HLA class I and sometimes class II. They are insidious and may appear up to several weeks after the beginning of a new treatment, which makes it particularly difficult to implicate a specific drug in multidrug patients. In this situation, the study of imputability scores makes it possible to formalize the evaluation of the causal link and is an aid for diagnosis and management [2,9].

Risk factors for antiepileptic-induced hypersensitivity include a genetic predisposition (HLA-B*15:02,

HLA-B*3101, HLA-B*44:03, and HLA-B*38:01), a history of an allergic reaction to other aromatic AEDs, the reactivation of latent viruses, such as human herpesvirus, Epstein–Barr virus, or *Cytomegalovirus*, infection with human immunodeficiency virus, the co-administration of antiviral drugs, liver disease, advanced age, and concomitant use of immunosuppressive agents [9-17].

The treatment of toxidermia induced by antiepileptic drugs has not yet been codified. The offending drug must be withdrawn if the patient cannot be monitored safely (cognitive problems, elderly, lack of a carer, etc.). Further use of the suspect drug should be contraindicated in severe toxidermia. Symptomatic treatment consisting of hydroelectrolytic control, nutritional support, local care of mucocutaneous lesions, and the prevention of superinfections is an essential part of treatment. The vital prognosis depends on the severity of the toxidermia, in severe forms in particular (DRESS, Stevens, and Lyell). In the literature, the mortality rate is estimated to be 25-30% for Lyell and 10% for DRESS. In our series, no death was found, yet we noted a transfer to the intensive care unit in 11.8% of the cases.

CONCLUSION

This study highlighted the potential of antiepileptic drugs in inducing serious toxidermia and, therefore, their inclusion must be reasoned. The prescription of anticonvulsants must take into consideration the potential risks for the patient versus the potential benefits. Symptoms that may indicate a reaction to the drug should be carefully discussed with the patient or their caregivers.

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

Thromboembolic disease in a patient treated with bleomycin for endemic Kaposi's disease at the Bamako Dermatology Hospital in Mali

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ABSTRACT

Herein, we report a case of thromboembolic disease occurring during endemic Kaposi's disease treated with bleomycin. Kaposi's disease is a vascular and fibroblastic disorder caused by human herpes virus type 8. The endemic form remains prevalent yet with a less severe prognosis. The first line of systemic treatment in our country is classically a monotherapy with bleomycin. This case of endemic Kaposi's disease was treated with bleomycin monotherapy that reportedly caused thromboembolic disease on two occasions after administration. This was one of the rarely reported effects of bleomycin in monochemotherapy, especially in the case of the treatment of endemic Kaposi's disease, considering the chronology of the appearance of this effect in your patient.

Key words: Bleomycin; Thromboembolic disease; Endemic Kaposi's disease

INTRODUCTION

Kaposi's disease is a vascular and fibroblastic disease caused by human herpes virus type 8 discovered in 1994 by Chang in the U.S. There are four clinical forms: the epidemic form, the endemic or African form, the classical or Mediterranean form, and the form related to iatrogenic immunosuppression. The endemic form remains prevalent yet with a less severe prognosis, and mainly affects the elderly with the elective involvement of the lower limbs [1].

The treatment of Kaposi's disease, depending on the size and number of lesions, combines the restoration of immunity (antiretrovirals), local treatments (surgery, radiotherapy), and general treatments (chemotherapy) in the case of extensive lesions [2].

Antineoplastic therapies (hormones, chemotherapy, or radiotherapy) may also increase the risk of thrombosis [3]. The first line of systemic treatment is usually a monotherapy with bleomycin, which is a cytotoxic antibiotic. The most important adverse effect of bleomycin is pulmonary fibrosis, which may be fatal in 1% of cases [2]. Thromboembolic events with bleomycin are usually reported in combination with other anticancer drugs yet are rarely reported alone. Herein, we report a case of thromboembolic disease occurring during endemic Kaposi's disease treated with bleomycin.

CASE REPORT

Endemic Kaposi's disease, which began seven years previously, was diagnosed in a 58-year-old cattle breeder

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from Kayes (region of Mali, 600 km from Bamako) with an altered general condition, a Karnofsky index of 50%, and a BMI of 17.72. The skin involvement was diffuse with ulcerated angiomatous nodules on the right plantar area (Figs. 1a and 1b). An X-ray of the foot revealed chronic osteitis related to Kaposi's disease. A pulmonary X-ray showed no particularity. We found no immunosuppression (no immunosuppressive treatments, negative HIV testing, normal blood sugar). CBC showed an anemia of 8 g/dL, normocytic hypochromic, with platelets at 197 G/l. A skin biopsy showed that the dermis was the site of a tumor proliferation taking a nodular aspect. It consisted of spindle cell patches alternating with a vascular proliferation. Vascular clefts with erythrodiapedesis were noted. The rest of the examination was normal. After correcting the anemia, which returned to 10.7 g/dL, treatment with bleomycin infusion of 15 mg every fifteen days was initiated on 09/06/2020. The evolution was marked 48 hours after the first administration by a painful, hot swelling of the right leg and a fever of 38.8°C. In front of this picture, erysipelas with ulcerated angiomatous nodules on the sole of the right foot and phlebitis were evoked. The patient received intravenous cefotaxime 3 g/d, and a workup was performed with the following particularities: D-dimer at 3343.63 ng/mL, PT at 60.60%, and Doppler echocardiography showing deep venous thrombosis in the affected limb involving the right femoro-tibio-peroneal trunk, and superficial thrombosis of the right leg. This clinical picture of thrombosis was treated with enoxaparin 8000 IU per day for six days and, then, relayed by warfarin 5 mg per day and elastic restraint with controls of the INR. Three weeks after clinical and biological improvement of the deep vein thrombosis, it was decided to continue with intramuscular bleomycin by the second dose of 15 mg (30/06/2020), which resulted in the same clinical picture within 48 hours as the first dose of bleomycin, this time accompanied by respiratory distress (pulmonary embolism), which rapidly led to the death of the patient (03/07/2020).

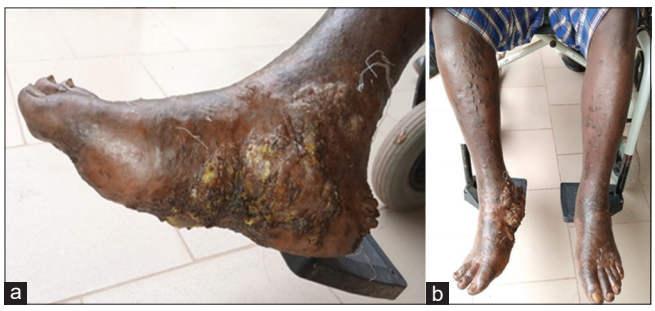

Figure 1: (a-b) Edema and angiomatous nodules, some of which were ulcerated and crusty on the lower limbs.

DISCUSSION

In view of the chronology of onset of thromboembolic disease in our patient and its occurrence on two occasions after the administration of 15 mg of bleomycin, we can say that this case was strongly suggestive of an adverse drug reaction. In a study by Yamamoto et al., the mean time between the administration of the treatment (bleomycin) and the appearance of the rash (flagellate erythema) varied from several hours to six months [4]. Although bleomycin has been cited to be a thrombogen in combination with other anticancer drugs, yet alone as monotherapy in the treatment of endemic Kaposi's disease, it has never been reported in the literature to our knowledge. The annual incidence of symptomatic venous thrombosis in these patients is on average 11%, yet this is largely underestimated [5]. Cancer increases the risk of thrombosis by a factor of four when compared to the general population and by a factor of six in the case of associated chemotherapy treatment [6,11]. This was the case in our patient with endemic Kaposi's disease treated with bleomycin. In addition, prolonged bed resting required prophylaxis of thromboembolic disease with low-dose acetylsalicylic acid (100 mg per day) during his hospitalization. Other risk factors, such as a platelet count greater than 350 G/L, a hemoglobin level below 10 g/dL, and the use of leukocyte growth factors or erythropoietin, were absent. Bleomycin, originally extracted from the fungus *Streptomyces verticillus* [7], is a molecule with both antibiotic and cytotoxic properties. Its oxidative power is indeed involved in the generation of DNA breaks, leading to cell death [8]. It is indicated in the treatment of various cancers: squamous cell carcinomas, malignant lymphomas, and germ cell tumors. More secondarily, it is employed as a topical treatment for keloid scars and plantar warts [9]. The mechanisms of thrombosis are multiple: an acquired deficiency in physiological inhibitors (antithrombin, proteins C and S), toxicity to normal cells (endothelium), and lysis of tumor cells. Its main side effects are the risk of pulmonary fibrosis, transient hyperthermic reactions shortly after injection, and skin manifestations, such as melanoderma, often predictive of pulmonary fibrosis [9]. In our case, we excluded prolonged bed resting as a possible cause of thromboembolic disease as the patient during hospitalization was on prophylaxis with acetylsalicylic acid 100 mg daily. Kaposi's disease was also excluded

because the patient had been living with his disease for seven years before coming to the clinic. Given the suggestive chronology, it seems reasonable to attribute this effect to bleomycin. The imputability score according to the French pharmacovigilance method was employed [10].

This original observation was, to our knowledge, the first published case of thromboembolic disease occurring during bleomycin monotherapy for endemic Kaposi's 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

Acute abdominal dermohypodermatitis associated with pregnancy: A new observation

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ABSTRACT

Erysipelas is an acute non-necrotizing bacterial dermohypodermatitis (DHD), most often (85%) affecting the lower limbs. The occurrence of dermohypodermatitis during pregnancy may jeopardize the maternal–fetal prognosis because of its severity and the obstetric complications. Early management and multidisciplinary follow-up may reduce the complications of these bacterial infections during pregnancy. Several risk factors are implicated in the risk of the occurrence of DHB. They are often encountered during pregnancy, such as lymphoedema, venous insufficiency, and varicose veins, which may explain the topography of the lesions in the lower limbs. In addition, pregnancy represents an additional risk factor due to the impairment of the immune system. Herein, we present the case of DHD in an unusual location in a pregnant female.

Key words: Dermohypodermatitis; Abdomen; Pregnancy

INTRODUCTION

Bacterial dermohypodermatitis (DHD) is a serious infection to appear during pregnancy, mainly due to group A beta-hemolytic streptococcus. This affection, located in the lower limbs in 85% of cases, is a serious and rare infection during pregnancy. Herein, we present the case of abdominal DHD occurring during pregnancy.

CASE REPORT

A 37-year-old women, multiparous, with no particular medical, presented with painful erythematous pain in the lower abdomen evolving at the beginning of the sixteenth month of pregnancy. The symptomatology initially concerned the iliac fossa with rapid extension to the hypogastric region. The interrogation did not report a similar episode or any notion of drug intake. On admission, a clinical examination found a patient in good general condition, with a fever at 38°C, a painful, hot, erythematous plaque, highly infiltrated at the level of the lower part of the abdomen, extending from the left iliac fossa to the hypogastric region, and inguinal intertrigo (Fig. 1a).

On biological assessment, the level of the C-reactive protein was elevated to 185 mg/L and the level of white blood cells was 24900/mm^3, with neutrophilic polynucleosis at 18970/mm^3. Fetal ultrasound showed no abnormalities. Faced with this atypical localization, a deep infectious focus was suspected. Abdominal ultrasound showed infiltration of subcutaneous tissue without an underlying collection.

The diagnosis of acute abdominal dermohypodermatitis was retained. The patient was initiated on intravenous antibiotic therapy based on amoxicillin-clavulanic acid with a good clinical evolution (Fig. 1b).

DISCUSSION

DHD is rarely described in pregnancy and constitutes a factor of obstetric morbidity. This affection is most

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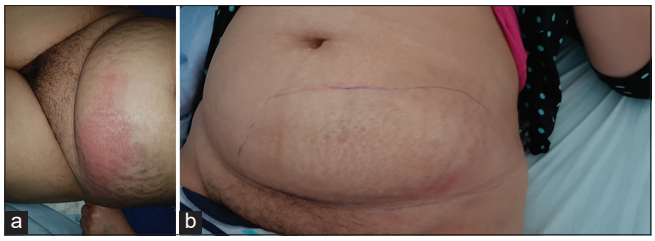

Figure 1: (a) Painful, hot, erythematous plaque in the left iliac fossa and the hypogastric region. (b) Complete improvement on day ten of treatment.

often located in the lower limbs and exceptionally at the abdominal level. This may be explained by risk factors also encountered during pregnancy, such as lymphedema, neglected wounds, and intertrigo inter-toes venous insufficiency, varicose veins, being overweight, and intertrigo [1]. In addition, pregnancy represents an additional risk factor due to the alteration of the immune and hormonal systems during the second and third trimesters and the postpartum period to obtain a sufficient level of neutralizing antibodies against exotoxins and surface proteins [2].

The search for a profound infectious focus in dermohypodermatitis of the abdomen is essential. Indeed, in the literature, three cases of DHD revealed abscesses secondary to the perforation of colon cancer, the perforation of a postoperative bladder, and the performation of the small bowel, respectively. While several cases of necrotizing fasciitis have been reported, secondary to several etiologies is most often neoplastic such as cancer of the cecum and sigmoid and rectum [3].

Management must be early in order to prevent maternal–fetal complications such as neonatal infections, prematurity, etc. [4]. Indeed, maternal inflammation has been shown to lead to exposure of the fetal brain to increased concentrations of this biogenic amine and to impaired growth of serotonergic axons through increased conversion of tryptophan to serotonin in the placenta.

In our patient, the dermatological signs were in the foreground, no local or deep portal of entry was discovered in our patient. Early medical management was established with good local and obstetrical evolution.

CONCLUSION

The particularity of our observation was in the rarity of DHB in the abdomen of a pregnant female. In this context, the early realization of a biological assessment and abdominal ultrasound in search of an infectious focus is of major interest. Medical treatment should be instituted with a delay with close maternal and fetal monitoring.

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

Metastatic tuberculous abscess caused by *Mycobacterium bovis* presenting as subcutaneous nodules in a woman with rheumatoid arthritis

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ABSTRACT

A metastatic tuberculous abscess is a rare condition that should be considered in the differential diagnoses of subcutaneous nodules in immunosuppressed patients. A 71-year-old woman with rheumatoid arthritis developed disseminated tuberculosis due to *Mycobacterium bovis*. After taking a vertebral biopsy, subcutaneous nodules appeared on the extremities. Initial histopathological and microbiological studies performed on the skin biopsy did not identify the mycobacterium. An aspirate obtained from a cold abscess was cultured and studied with a positive polymerase chain reaction; cultures grew *M. bovis* and treatment for disseminated tuberculosis was initiated. Two months later, the fevers recurred, and new skin nodules appeared. A repeated skin biopsy failed to identify the agent, yet it again grew from the material obtained from an aspirated abscess. Diagnostic tests should be exhausted in order to identify the organism successfully. This case suggested that recurrent hematogenous dissemination may originate after the manipulation of deep foci and present as a metastatic tuberculous abscess.

Key words: *Mycobacterium bovis*; Cutaneous tuberculosis; Vertebral tuberculosis; Metastatic tuberculous abscess; Immunosuppression

INTRODUCTION

Tuberculosis is an infection caused by a mycobacterium from the *Mycobacterium tuberculosis* complex; the most frequently identified agent is *M. tuberculosis*. Cutaneous tuberculosis is a rare manifestation, representing 1% to 1.5% of cases of extrapulmonary tuberculosis. Its etiological agents include *M. tuberculosis*, *M. bovis*, and the attenuated form of the Calmette–Guérin bacillus (BCG vaccine) [1].

Infection by *M. bovis* may be acquired through the inhalation or ingestion of contaminated products, especially unpasteurized dairy products. Hematogenous transmission may present with cervical lymphadenopathy, intestinal involvement, and skin manifestations [1]. A previous series from a Mexican referral center reported that up to 26.2% of cases of tuberculosis were due to *M. bovis*; 5.2% of the patients had bone, joint, skin, and soft tissue involvement [2].

CASE REPORT

A 71-year-old woman was admitted for a diagnostic workup due to a fever, weight loss, and lumbar pain. She had a history of rheumatoid arthritis treated with methotrexate (15 mg weekly) and prednisone (5 mg daily). An interferon-gamma release assay (IGRA) was negative, and no pulmonary infiltrates were identified. A PET CT scan revealed a hypermetabolic

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lytic lumbar vertebral lesion, from which a bone biopsy was obtained. A polymerase chain reaction (PCR, GeneXpert MTB/RIF) was positive and a tissue culture isolated *M. bovis*. Treatment began with rifampin, isoniazid, pyrazinamide, and ethambutol. One week after the bone biopsy, she developed multiple subcutaneous, asymptomatic, violaceous nodules, 1 cm in size, on the left arm and hand (Fig. 1). A skin biopsy revealed a granulomatous process with central necrosis, yet Ziehl–Neelsen staining did not find microorganisms (Fig 2a - 2d). Tissue culture and PCR tests yielded negative results. After two days, new fluctuant nodules appeared on the arms and legs (Fig. 3). One of these cold abscesses was drained, and the aspirate was sent again for culture and PCR. The GeneXpert MTB/RIF test was positive, and cultures grew *M. bovis*. The diagnosis of a metastatic tuberculous abscess (MTA) was established and the treatment was continued. Two months later, the fevers recurred, and new skin nodules appeared. A repeated skin biopsy and tissue culture failed to identify the agent, yet it grew from the purulent aspirated of the abscess. No antibiotic resistance was documented, and the treatment was continued. Over the following months, the patient developed neurologic symptoms attributed to central nervous system dissemination, and her overall condition worsened. Unfortunately, she died six months after the initial diagnosis.

DISCUSSION

MTA, also known as tuberculous gumma, is due to the hematogenous spread of the mycobacterium from an endogenous infectious source. It represents between 1% and 2% of all forms of cutaneous tuberculosis. In the absence of regional lymphadenopathy, single or multiple asymptomatic subcutaneous nodules represent the most common cutaneous finding. The term *cold abscess* describes a fluctuating nodule with no increase in local temperature [3]. Histopathologically, MTA presents a suppurative granulomatous dermatitis with central caseous necrosis [4].

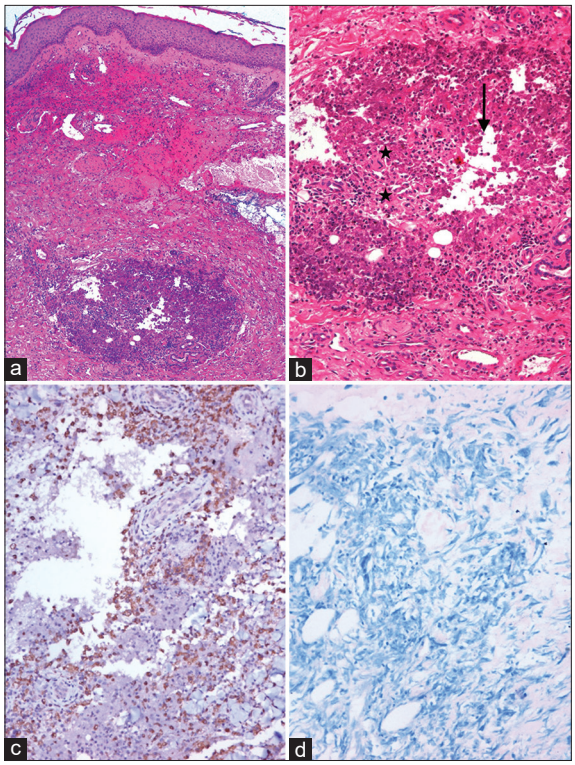

Figure 2: a) Extravasated erythrocytes observed in the superficial dermis and granuloma in the deep dermis (H&E; 4×). b) The granuloma consisting of epithelioid macrophages (*) and showing necrosis in its central portion (arrow) (H&E; 10×). c) Immunohistochemistry for CD68 showing the presence of abundant histiocytes in the lesion. d) Directed search for acid-fast bacilli by Ziehl–Neelsen staining returning negative.

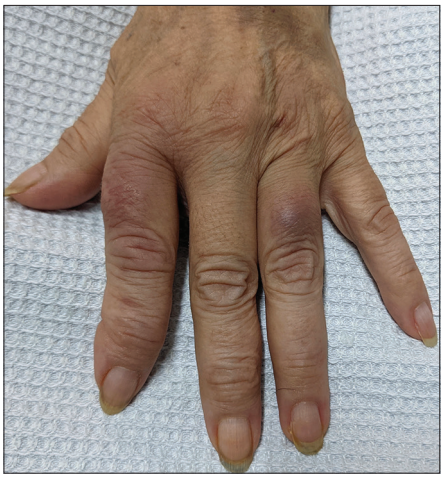

Figure 1: Subcutaneous erythematous and violaceous nodules on the back of the left hand.

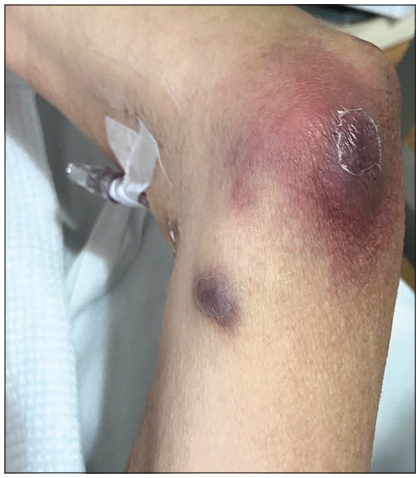

Figure 3: Presence of gumma in the upper left extremity.

Although infrequent, MTA commonly occurs in the setting of immunosuppression. Most descriptions involve individuals living with HIV, yet there are some reports in which immunosuppression was due to medical treatment, such as in rheumatoid arthritis [5] and systemic lupus erythematosus [6]. MTA development associated with osteomyelitis is rare, yet reports describe cases caused by *M. tuberculosis* [7]. The reviewed literature did not reveal cases of MTA accompanied by osteomyelitis due to *M. bovis*.

A relevant finding in our case was the development of MTA after taking a bone biopsy, which suggests that the procedure could have prompted the hematogenous spread. Documenting MTA should always drive physicians to search for an internal infectious source.

The prevalence of *M. bovis* in humans is underestimated or ignored in most developing countries, such as Mexico and Latin America [1]. Jaka Moreno et al. described five cases of lupus vulgaris in the setting of infection by *M. bovis* [8].

The gold standard for diagnosis is the isolation of the mycobacterium in tissue samples. However, the sensitivity of culture and special stains for extrapulmonary forms is lower when compared to pulmonary tuberculosis, which makes the diagnosis difficult. PCR has increased sensitivity (24.5–100%) and specificity (73.7–100%) for the diagnosis of cutaneous tuberculosis. Cutaneous tuberculosis constitutes a diagnostic challenge given the low sensitivity of the laboratory and histopathological tests and the paucibacillary nature. Based on previous studies, it has been shown that DNA polymerase chain reaction (PCR) has greater sensitivity for the diagnosis of cutaneous tuberculosis (24.%) than culture (16%) [9]. Both tests could have a higher diagnostic performance in multibacillary samples, such as abscesses, when compared to samples obtained from skin tissue, which are typically paucibacillary [10].

Treatment should be directed according to a sensitivity study, yet it generally consists of a scheme based on rifampin, isoniazid, pyrazinamide, and ethambutol [3].

CONCLUSION

MTA is one of the least common skin manifestations of cutaneous tuberculosis and should be considered in the differential diagnosis when immunosuppressed patients develop subcutaneous nodules and cold abscesses. The possibility that taking a bone biopsy initiated a hematogenous spread cannot be excluded in our case. Likewise, despite adequate treatment and mycobacterial susceptibility, recurrent MTA may develop in immunosuppressed hosts.

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

Bullous pemphigoid secondary to an orf nodule: A still unrecognized complication

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ABSTRACT

Orf is a rare viral zoonosis due to *Parapoxvirus* infection. Transmission to humans occurs through contact with infected goats and sheep. It may be complicated by fever, lymphangitis, lymphadenopathy, bacterial infection, and erythema multiforme. Only several cases of autoimmune bullous dermatoses have been described. Bullous pemphigoid secondary to an orf was found in ten patients. Herein, we report one case of a human orf complicated by bullous pemphigoid. This is an occasional complication following an orf. Knowledge of co-occurrence allows for the better management of the affected patient. This case is reported for its rare association.

Key words: Bullous Pemphigoid; Orf; Orf-Induced Immunobullous Disease

INTRODUCTION

An orf nodule is a rare viral zoonosis caused by *Parapoxvirus* infection. Human transmission may occur by contact with sheep or goats themselves suffering from contagious ecthyma. Diagnosis is often clinical and manifests as a single or multiple lesions on a finger or hand.

Several complications may occur following an orf: fever, lymphangitis, lymphadenopathy, and bacterial infection [1]. Post-orf autoimmune bullous dermatoses are much rarer, with only eleven cases reported in the literature: ten cases of bullous pemphigoid and one case of pemphigoid with mucosal involvement and the presence of anti-laminin-332 antibodies [2]. We describe the eleventh case of bullous pemphigoid secondary to an orf, which is considered a highly rare complication.

CASE REPORT

A 56-year-old Moroccan male with a history of type 2 diabetes, on metformin for two years, presented eight days after Eid al-Adha (a Muslim religious sacrifice) with a nodule on the right middle finger gradually increasing in size. In view of the lesion and the context of occurrence (handling of sheep during Eid al-Adha), the diagnosis was in favor of an orf. The patient received a topical antibiotic with a complete regression of the lesion in five weeks. Three weeks after the appearance of the orf nodule, he consulted for a diffuse, pruriginous, bullous eruption, initially located on the right arm, then generalizing to the trunk, abdomen, and all four limbs. A dermatological examination revealed an erythematous, ulcerated nodule, well-limited, firm, deeply infiltrated, measuring 2 cm in size, and located on the right middle finger (Fig. 1). Multiple tense blisters with a clear content on non-inflamed skin affecting the four limbs, abdomen, and back (Fig. 2a). Multiple erythematous papules were on the four limbs and abdomen (Fig. 2b). Some erosions were on the limbs and abdomen (Fig. 2c). The Nikolsky sign was negative.

He did not present any lesions on the mucous membranes or scalp. The rest of the examination was normal.

Dermoscopy of the nodule on the hand revealed an erythematous lesion with yellowish scales, especially on the periphery, red areas without a structure, glomerular

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vascularization on the periphery, and whitish structures (Fig. 3).

A skin biopsy revealed a subepidermal bulla with a mixed inflammatory infiltrate in the dermis. Direct immunofluorescence revealed a deposition of C3 linearly along the basal membrane. Indirect immunofluorescence revealed the presence of anti-basal membrane antibodies positive at 40. The rest of the biological assessment was unremarkable.

The diagnosis of pemphigoid complicating an orf nodule was retained. The patient received topical steroids (clobetasol propionate) for several weeks with a complete regression of the lesions three weeks later. He did not present any bullous eruptions after one year of follow-up.

DISCUSSION

Orf, or ecthyma contagiosum, is a zoonosis caused by a DNA virus from the *Parapoxvirus* family. It is a rare and often misunderstood pathology that affects sheep and goats. The population at risk includes shepherds, butchers, farmers, wool shearers, and veterinarians.

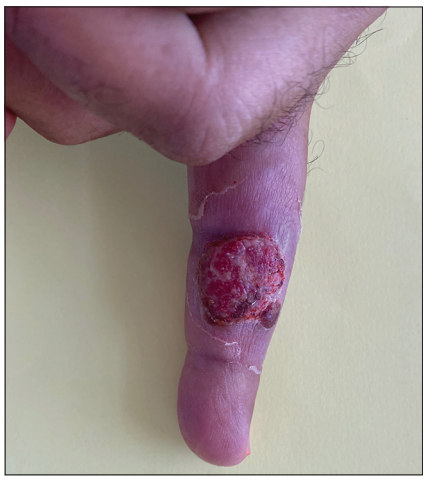

Figure 1: Orf nodule: an erythematous, ulcerated nodule on the right middle finger.

It is transmitted to humans through direct contact with infected animals, or indirectly through contaminated offal or knives, which was the mode of transmission in our patient. No human-to-human transmission of *Parapoxvirus* infection has been reported [3]. The most frequently observed complications are fever, lymphangitis, lymphadenopathy, and bacterial infection. Cases of erythema multiforme complicating an orf nodule have also been described in the literature, despite it being a highly rare complication [4,5].

Alian et al. reported a case of erythema multiforme associated with a pemphigoid-like eruption [6]. Post-orf autoimmune bullous dermatoses are much rarer, with only eleven cases reported in the literature [2]. The first cases of bullous pemphigoid secondary to an orf nodule were described in 1995 by Murphy et al., who reported five cases occurring after two-to-three weeks [7]. In our case, the bullous lesions appeared around three weeks after the appearance of the orf nodule, which was consistent with the literature (2–4 weeks) [2,7].

Avci et al. also reported the relationship between orf infection and bullous pemphigoid [8].

The clinical, histopathological, immunofluorescence results, as well as the improvement under topical steroids and the absence of a relapse, confirmed the diagnosis of orf-induced bullous pemphigoid.

The relationship between orf and bullous pemphigoid has not yet been fully elucidated [9].

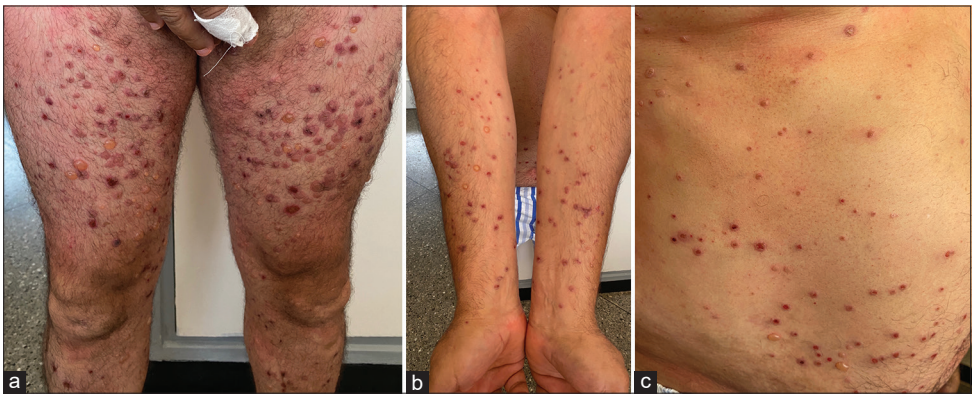

Figure 2:(a) Multiple, tense blisters with a clear content on the tights. (b) Erythematous papules with some blisters on the arms. (c) Erosions on the abdomen.

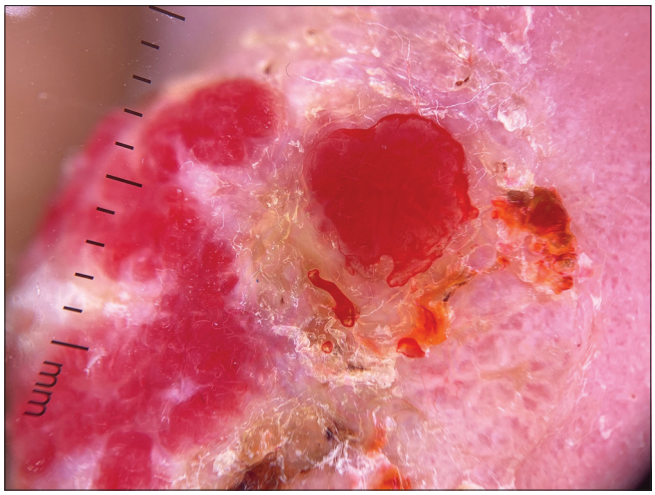

Figure 3: Dermoscopy of the orf nodule: an erythematous lesion with yellowish scales, red areas without a structure, and glomerular vascularization on the periphery.

The pathophysiological mechanism of autoimmune diseases secondary to an orf may include viral mimicry of host proteins or the destruction of basement membrane proteins by the virus.

The physiopathological mechanism of autoimmunity induced by orf virus is poorly understood, hence the interest in reporting other cases of this complication.

Further case reports regarding this clinical condition are needed.

The patient was treated with a topical steroid giving a complete improvement.

In cases described in the literature, their patients were also treated by topical steroids, yet some patients received prednisone, azathioprine, dapsone, colchicine, or cyclosporine.

CONCLUSION

Herein, we have reported a case of bullous pemphigoid secondary to an orf nodule, which is a highly rare complication. The relationship between the two diseases has not been elucidated completely. Further case reports regarding this clinical condition are needed.

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

Comedonal variant of chronic cutaneous lupus erythematosus on the nose

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ABSTRACT

A thirty-year-old patient presented with an erythematous papule on the left nostril evolving for ten months. A clinical examination revealed an infiltrated, erythematous, well-limited plaque with a raised border, covered with multiple open and closed comedones. On dermoscopy, there was an erythematous background with some fine telangiectasias and horny plugs at the follicular orifices. A skin biopsy was performed, revealing orthokeratotic hyperkeratosis sinking into the follicular orifices dilated by sebum clumps with basal vacuolation associated with a subepidermal and periadnexal/perivascular lymphocyte band infiltrate. Direct immunofluorescence staining for immunoglobulin M was positive. The diagnosis of lupus comedones was retained, and the patient was put on topical tacrolimus 0.1% twice a day. A systemic damage assessment was negative. Our case highlighted, the importance of recognizing this rare variant of cutaneous lupus, confused with acne vulgaris, hence the delayed diagnosis, which may also be an early sign of a concomitant systemic involvement.

Key words: Acne; Chronic Cutaneous Lupus Erythematosus; Comedonal Variant; Discoid Lupus Erythematosus

INTRODUCTION

Chronic cutaneous lupus erythematosus most commonly presents as a discoid form consisting of scaly, erythematous plaques covered with fine telangiectasias surrounding central atrophy. Comedonal lupus is an extremely rare variant of chronic cutaneous lupus with a misleading acneiform appearance. Herein, we report a rare case of comedonal lupus on the left nostril and present its characteristics.

CASE REPORT

A thirty-year-old patient with no medical history presented with a firm, erythematous papule on the left nostril evolving for ten months, progressively increasing in size.

A clinical examination revealed an infiltrated erythematous plaque, 1 cm in diameter, well-limited with a raised border, and covered with multiple open and closed comedones, especially on the periphery (Figs. 1a and 1b). On dermoscopy, there was an erythematous background with some fine telangiectasias and horny plugs at the follicular orifices.

A skin biopsy with an anatomo-pathological examination was performed, finding orthokeratotic hyperkeratosis sinking into the follicular orifices dilated by sebum clumps. There was also vacuolation of the basement membrane with significant lymphocyte infiltrate in subepidermal and periadnexal/perivascular bands (Fig. 2). The dermis was the seat of discrete deposits of mucin of Alcian blue color. Direct immunofluorescence staining for immunoglobulin M was positive.

The diagnosis of lupus comedonal was retained, and the patient was put on topical tacrolimus 0.1% twice a day combined with rigorous photoprotection. A systemic damage assessment was negative.

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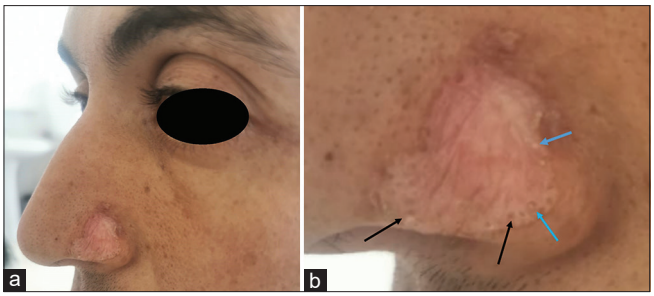

Figure 1: (a) Infiltrated, erythematous plaque, well-limited with a raised border and covered with multiple open and closed comedones, especially on the periphery. (b) Multiple open (*black arrows*) and closed (*blue arrows*) comedones, especially on the periphery.

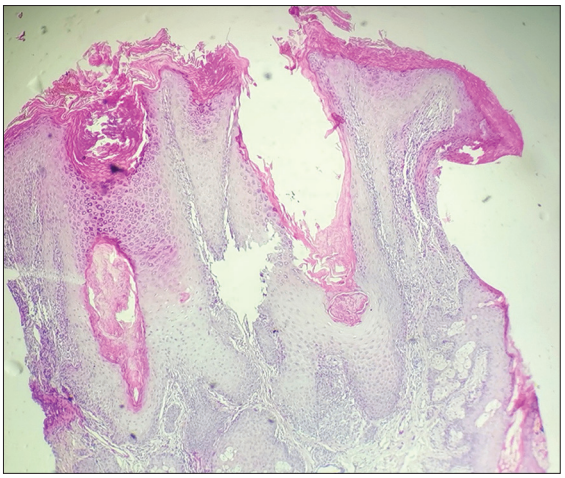

Figure 2: Large follicular openings dilated by clumps of sebum, interface dermatitis, and dermal mucinosis (H&E).

DISCUSSION

Comedonal lupus is a rare and, probably, an underestimated variant of chronic cutaneous lupus erythematosus. Clinically, it appears in the form of comedones on an erythematous plaque, mainly in seborrheic areas [1]. Its etiology remains unknown. Actinic lesions allow modifications of the collagen of normal skin, which modifies its structure and, thus, promotes the retention of sebum. This leads to the training of actors, as in Favre–Racouchot disease. The other postulated theory is that follicular plugging promotes comedogenesis [2].

Dermoscopy may be of great help in revealing black openings in pseudo-comedones and images of pseudo-grains of milium testifying to the folliculotropic character.

The differential diagnosis is inflammatory acne, milium spots, Favre–Racouchot disease, and comedonal hamartoma [3]. If there are no comedones, there is an acneiform scar pattern. In this entity, the lesions are characterized by the presence of ice-pick scars secondary to the destruction of the hair follicle and the sebaceous glands by the inflammatory infiltrate [4].

A histopathological study confirms the diagnosis and finds predominant interface dermatitis with the degeneration of the basal layer and thickening of the basal membrane, associated with follicular plugs and comedones, as described in our patient. Direct immunofluorescence may aid in the diagnosis if the histological results are inconclusive, in which a deposition of IgM, IgG, and C3 is observed at the dermal–epidermal junction [2,5].

The therapeutic options vary, although the treatment of choice is hydroxychloroquine (200 mg twice a day). In our case, it was not administered in front of a single small lesion. As an alternative, a topical corticosteroid or topical tacrolimus is offered [6].

The prognosis of comedonal lupus is uncertain and, although few cases have been described in the literature, a risk of progression to SLE was observed in four of them [7]. Early diagnosis and long-term follow-up are of great importance because of the risk of progression to systemic involvement.

CONCLUSION

This clinical case illustrates the need to broaden the differential diagnosis of atypical acneiform and comedonal lesions. Lupus comedones should be considered especially in an itchy, localized lesion that does not improve with conventional treatment for acne vulgaris and should be investigated for systemic involvement.

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

Control of ochre dermatitis with aminaphtone in an adolescent

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ABSTRACT

The aim of this manuscript is to report the case of a 22-year-old adolescent who presented with brownish patches on the skin of her lower legs persistent since the age of eleven years. She was treated by a dermatologist since the age of twelve years with a clinical diagnosis of ochre dermatitis confirmed by a biopsy. The patient was treated for two years without a success and was sent to a vascular surgeon at fourteen years of age. The diagnosis was confirmed, and the venous duplex scan discarded the possibility of a macrocirculation abnormality. The patient was treated with aminaphtone with the normalization of the skin for two years, after which the patches returned and were controlled again with the same medication. As ochre dermatitis may be associated with capillary fragility, the use of aminaphtone is a therapeutic option.

Key words: Ochre Dermatitis; Hyperpigmentation; Capillary Fragility; Aminaphtone; Adolescent

INTRODUCTION

Chronic venous disease progresses with important changes to the skin, such as edema, dermatofibrosis, hyperpigmentation, and ulcers [1]. Stasis dermatitis is a common occurrence in these patients. However, the condition occurs at an advanced age and is caused by venous hypertension resulting from a backflow due to incompetent venous valves, destroyed valves, or an obstruction in the venous system [2].

Dermatofibrosis is another finding in chronic venous disease, in which various histological abnormalities are found. Septal fibrosis, lipomembranous fat necrosis, prominent vascular changes due to stasis, and erythrocyte extravasation are in the histopathological definition of dermatofibrosis. Iron deposition in the subcutaneous tissue is a tactile finding of this chronic condition [3,4].

In some patients, ochre dermatitis is not associated with chronic venous disease or abnormal venous macrocirculation, which is detectable with venous Doppler [5]. Authors of a study involving children (< 18 years of age) found no inflammatory process or hyperpigmentation [4], suggesting that causes other than chronic venous disease may be responsible for ochre dermatitis in patients with no other evident clinical abnormalities.

The aim of this manuscript was to report a case of ochre dermatitis in an adolescent, in whom a good temporary resolution was achieved with the use of aminaphtone. The condition returned after two

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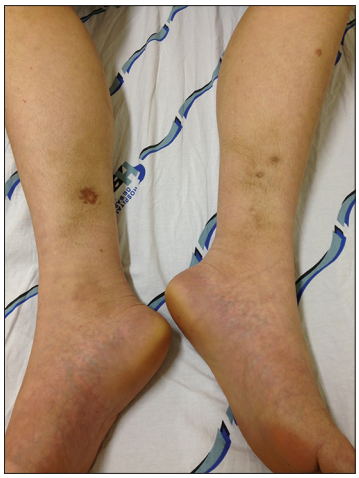

Figure 1: Distal third of the leg showing the biopsy site and areas of hyperpigmentation.

years, which was once again controlled with this medication.

CASE REPORT

A twelve-year-old female patient sought dermatological treatment for brownish patches on her lower limbs. A skin biopsy revealed ochre dermatitis (Fig. 1). At fourteen years of age, the patient was sent to a vascular surgeon, who confirmed the diagnosis of ochre dermatitis. The patient was asymptomatic. Deep and superficial venous duplex scans were performed, which revealed no abnormalities in the venous system. Aminaphtone was prescribed, which led to the cessation of new patches and the continual fading of the existing patches until their complete disappearance. At 16, 19, and 22 years of age, the patient returned reporting that the brownish patches returned and also complained of social discomfort due to the unpleasant esthetic appearance of the hyperpigmentation. Aminaphtone was prescribed the second time and control of the patches was achieved. This study received approval from the Human Research Ethics Committee of the São José do Rio Preto School of Medicine, SP, Brazil #3.764.416.

DISCUSSION

The paper reports control of ochre dermatitis in an adolescent and the long-term evolution of the treatment. Ochre dermatitis is associated with chronic venous hypertension, yet there is a report of an association with probable capillary fragility [3]. The most striking occurrence in the present case was the emergence of ochre dermatitis in a patient beginning at twenty-two years of age.

The patient began treatment with a dermatologist, yet without a satisfactory result, and at twelve years of age, was sent to the vascular surgery service of the university. During the initial clinical evaluation, the occurrence of ochre dermatitis was confirmed, along with some isolated telangiectasias, fitting C1 of the CEAP classification. Venous Doppler revealed no abnormalities in the superficial or deep venous system, discarding the possibility of chronic venous hypertension. This finding lent support to the hypothesis of capillary fragility as the cause of the initial purpura that progressed to hyperpigmentation.

Another aspect to consider in the present case is the more appropriate diagnosis between ochre dermatitis and stasis dermatitis. There was no venous hypertension in the present case to suggest stasis dermatitis. This is important because there are reports of ochre dermatitis in patients with and without evidence of chronic venous hypertension. Therefore, capillary fragility may be an aggravating factor in patients with chronic venous hypertension, and studies suggest that the presence of iron ions may be an aggravating agent of the inflammatory process.

With regard to the treatment of stasis dermatitis, there are some reports on therapeutic options, yet with no emphasis on the physiopathological hypothesis of capillary fragility. The use of aminaphtone has recently been described as a therapeutic option in cases of ochre dermatitis and small hemorrhages [6]. In the present study, hyperpigmentation was controlled with the use of aminaphtone for three to four years, followed by a recurrence, which suggests that yet treatment is not curative and only achieves temporary control. A further prescription of the drug enabled control of the new patches. Thus, aminaphtone was useful for treatment and may be administered again in cases of recurrence.

Aminaphtone was prescribed at a dose of 75 mg twice a day for two months, during which there was no emergence of new purpura, and there was a progressive reduction in pigmentation until complete elimination. Thus, there was a slow resolution of hyperpigmentation, with fading of 30% to 40% after two or three months, and a complete disappearance over time.

CONCLUSION

Ochre dermatitis may be associated with capillary fragility, and the use of aminaphtone is a therapeutic option in such cases.

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 skin aplasia associated with unilateral focal dermal hypoplasia

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ABSTRACT

Congenital skin aplasia (CCA) is a rare congenital anomaly involving variable layers of the skin, most commonly affecting the scalp yet may be seen on the trunk and limbs as well. It is most often seen as solitary lesions or as part of a heterogeneous group of syndromes, such as Goltz syndrome and focal dermal hypoplasia. Herein, we report a newborn of one day of life, who presented multiple, well-limited, reddish-orange, ulcerated patches with irregular contours and a clean surface, as well as hyperpigmented atrophic macules with a linear distribution along the Blaschko's lines along the left hemisphere. We observed syndactyly of the left second and third toes with hypoplasia of the left great lip. Goltz syndrome is a rare congenital skin characterized by a unique clinical presentation, which is unilateral focal dermal hypoplasia (FDH). Looking for other associated features is important. The recognition of these characteristic features will permit early appropriate genetic counseling and treatment.

Key words: Congenital skin aplasia; Syndrome; Unilateral focal dermal hypoplasia

INTRODUCTION

Congenital skin aplasia (CCA) is a rare congenital anomaly involving variable layers of the skin, most commonly affecting the scalp yet may be seen on the trunk and limbs as well [1,2]. CCA is most often seen as solitary lesions or as part of a heterogeneous group of syndromes, such as Goltz syndrome and focal dermal hypoplasia.

CASE REPORT

This was a newborn of one day of life from the non-consanguineous marriage of a 29-year-old mother. Well-monitored pregnancy was carried to term with a vaginal delivery. No specific medication, smoking, alcoholism, or toxin intake were present. No similar case in the siblings and no notion of autoimmune bullous dermatosis in the family was present as well.

Our opinion was sought for the congenital absence of skin on the left hemisphere. A general examination found a pink-toned and responsive newborn, HD, and respiratorily stable.

A dermatological examination revealed multiple, well-limited, reddish-orange, ulcerated patches with irregular contours and a clean surface (Figs. 1 and 2), as well as hyperpigmented atrophic macules with a linear distribution along the Blaschko's lines along the left half of the body (Figs. 3a and 3b).

The rest of the examination revealed syndactyly of the left second and third toes with hypoplasia of the left great lip. Trans-fontanelle and cardiac ultrasound returned without any particularities. Biological tests were normal. The diagnosis of focal dermal hypoplasia was retained.

DISCUSSION

Cordon first described CCA in 1767 and, since then, over 500 cases have been reported [2].

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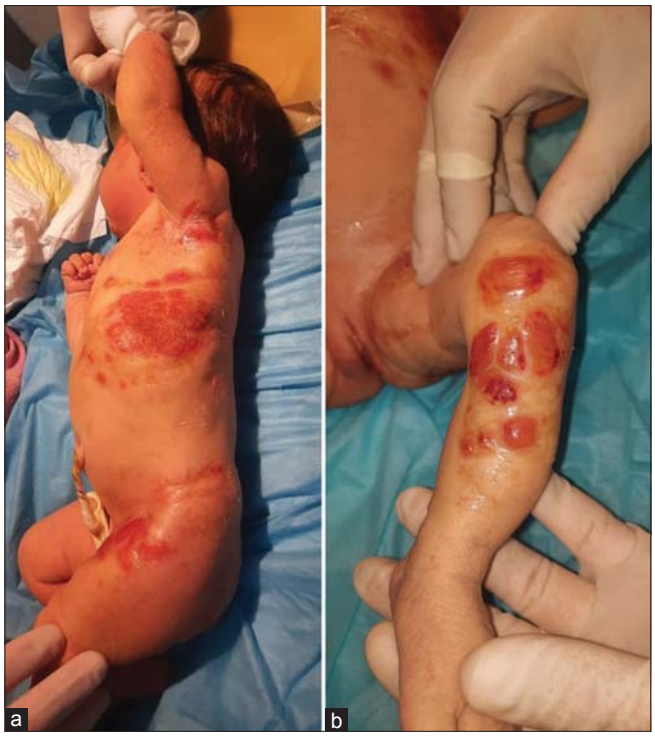

Figure 1: (a and b) Congenital patchy skin aplasia on the left half of the body.

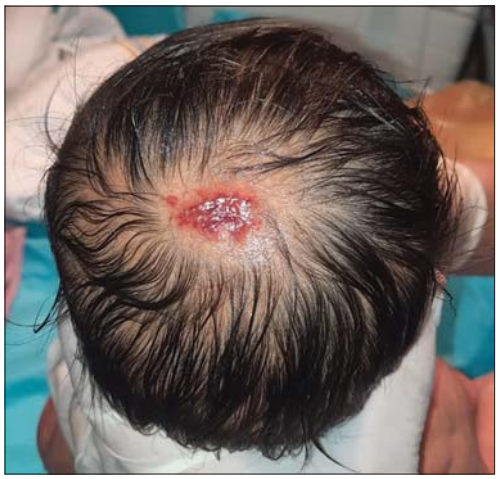

Figure 2: Congenital patchy skin aplasia on the scalp.

Eighty percent of cases of CCA occur on the scalp, while rarely being associated with a malformation syndrome. Some cases have been reported in the literature associated with trisomy 13, Wolf–Hirschhorn syndrome, ectodermal dysplasia, and Goltz syndrome (focal dermal hypoplasia).

According to the literature, more than 250 cases of unilateral focal dermal hypoplasia (FDH) have been reported worldwide [3]. Among these reports, only nine cases had unilateral or nearly unilateral FDH. Our case was one of the few cases of HPF with unilateral manifestations associated with congenital skin aplasia.

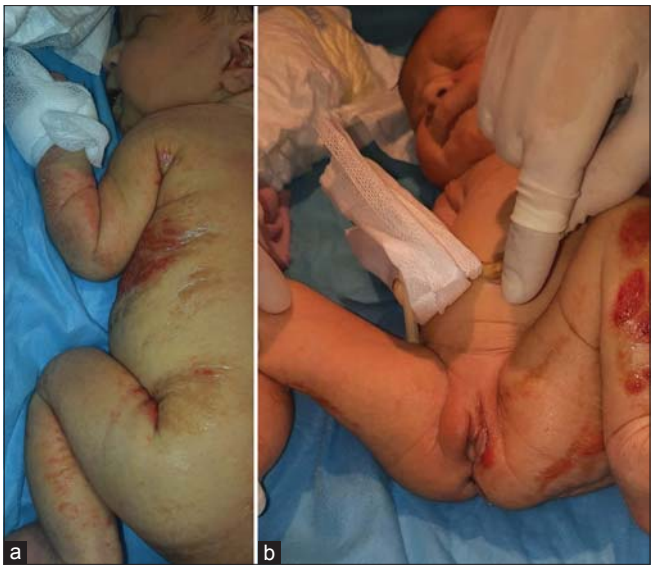

Figure 3: (a and b) Hyperpigmented atrophic macules with a linear distribution following a Blaschko's lines distribution along the left half of the body.

While HPF is an X-linked disease, as expected, 9 of 10 patients with unilateral HPF were female. However, only one male patient was reported with unilateral HPF. The right side of the body was predominantly affected in 70% of the patients, in contrast to our case, in which the left side was affected.

All patients had the classic presentation of pigmented atrophic skin, which follows Blaschko's lines associated with lesions of congenital cutaneous aplasia in hemicorporeal plaques. However, half of the patients (including our case) did not have fat herniation represented by fat nodules in the dermis, nor did they have scalp or dental involvement.

Musculoskeletal abnormalities were involved in 70% of the cases reported. Our case presented syndactyly of the second and third toe [4]. Ocular and nail involvement has been described in about 30% of the patients. It is somewhat surprising that internal organ involvement is mentioned in only one case report, published in 1984.

The diagnosis of unilateral focal dermal hypoplasia was usually based on the clinical skin presentation and associated symptoms. However, molecular genetic testing may be employed to confirm the diagnosis in cases where the clinic is inconclusive.

CONCLUSION

In conclusion, Goltz syndrome is a rare congenital skin characterized by a unique clinical presentation, which is FDH unilateral focal dermal hypoplasia.

Looking for other associated features is important. The close examination of the extremities is recommended. The recognition of these characteristic features will permit early treatment.

Consent

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

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

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Our Dermatology Online

Case Report

Multiple non-familial trichoepitheliomas: A rare case and a review of the literature

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ABSTRACT

Trichoepitheliomas are benign tumors of follicular origin often appearing in childhood or early adolescence. They present as small, firm papulonodular lesions of normal skin color or translucent. The lesions gradually increase in size and then stabilize. They sit electively on the face, mainly on the nasolabial folds, forehead, chin, and cheeks, and sometimes on the scalp and neck. Trichoepitheliomas may be divided into three subgroups: multiple familial trichoepitheliomas, solitary non-hereditary trichoepitheliomas, and desmoplastic trichoepitheliomas. Non-familial multiple trichoepitheliomas are rarely described. Herein, we report the case of a twelve-year-old child whose clinical history and clinicopathologic correlation allowed us to retain the diagnosis of multiple non-familial trichoepitheliomas.

Key words: Trichoepitheliomas; Sporadic; Genodermatosis; Cyld Gene; Anatomopathology

INTRODUCTION

Trichoepitheliomas (TE) are benign tumors of follicular origin. They were first described by Brooke in England in 1892 as "cystic adenoid epithelioma" and, in the U.S., by Fordyce as "multiple benign cystic epithelioma" [1,2]. These are papules, measuring several millimeters, mainly located on the face, scalp, and neck, appearing in childhood and increasing in number with age. They may be isolated or multiple and occur sporadically or in families [3]. Although rare, the malignant transformation of TE into trichoblastic carcinoma or basal cell carcinoma has been described [4]. Herein, we report a case of multiple non-familial TE in a twelve-year-old child.

CASE REPORT

This was a twelve-year-old male child, with no particular pathological history and no notion of consanguinity, who presented with asymptomatic skin lesions on the face evolving for the previous one year, gradually increasing in size and number, without any similar case in the family or other associated cutaneous and extra-cutaneous signs.

A general examination found a patient who was hemodynamically and respiratory stable. A dermatological examination revealed translucent, flattened, and globular papules, 2 to 4 mm in size, pink, fleshy, and painless, sitting on healthy skin, electively on the face (nose, nasolabial folds, eyelids, cheeks, forehead, and chin) (Figs 1a and 1b). The rest of the dermatological and somatic examinations was unremarkable.

A histopathological study of the papules confirmed the diagnosis of TE by showing a well-limited, benign tumoral proliferation localized in the reticular dermis, comprising lobules and islands of basaloid cells arranged in anastomosed spans and developing around horny cysts (Fig. 2). The diagnosis of multiple non-familial

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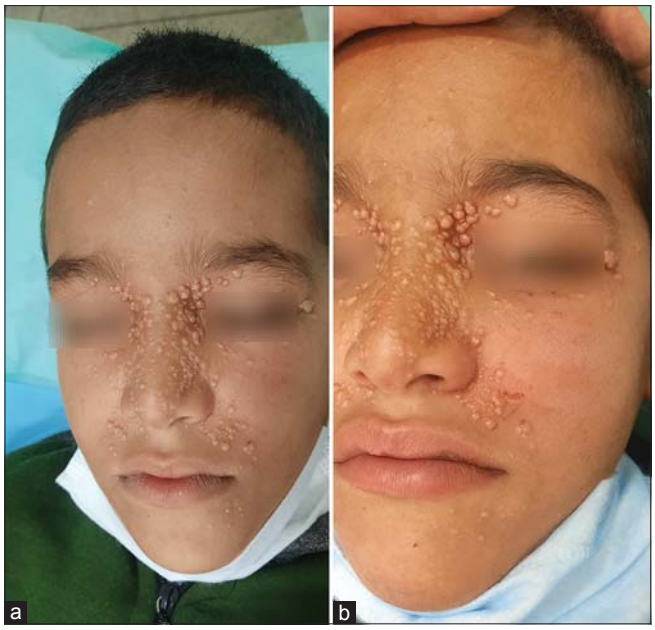

Figure 1: (a-b) Translucent, flattened, globular papules, 2 to 4 mm, pink and fleshy, located on the healthy skin of the face.

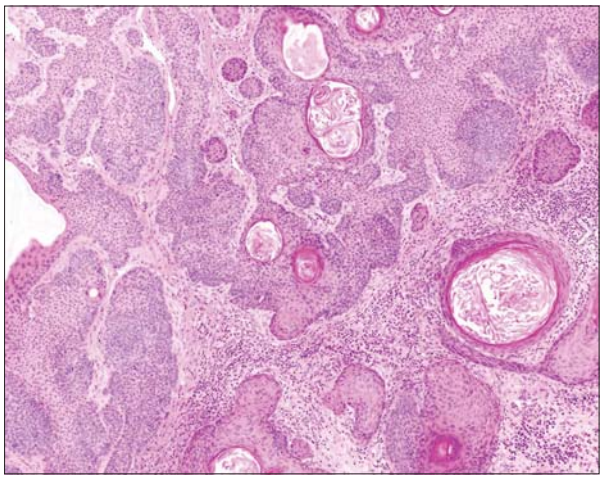

Figure 2: Horny cysts of trichoepithelioma on the face (H&E, 100×).

TE was retained, given the absence of similar cases in the family and the clinical and histological aspects. We offered CO_2 laser with regular clinical monitoring, having informed the parents about the risk of malignant transformation of the disease.

DISCUSSION

Trichoepitheliomas are benign hamartomas of pilosebaceous follicles often appearing in childhood or early adolescence [5]. The various synonyms of TE are trichoepithelioma papulosum multiplex, cystic adenoid epithelioma, cystic adenoid acanthoma, multiple benign cystic epithelioma, Brooke's tumor, and Brooke Fordyce's trichoepithelioma [6]. Clinically, TE presents as small, firm, papulonodular lesions of normal or translucent color, sometimes covered with telangiectasias. The lesions gradually increase in size and then stabilize. They sit electively on the face, mainly on the nasolabial folds, forehead, chin, and cheeks, and sometimes on the scalp and neck [7]. Their prevalence is unknown. However, a dermatopathology laboratory in the U.S. found 2.14 to 2.75 cases of TE out of 9,000 biopsies per year [8].

TE may be divided into three subgroups: multiple familial TE, solitary non-hereditary TE, and desmoplastic TE. Non-familial multiple TE is rarely described, Sehrawat et al. published the first case in 2016 [9]. Our case had multiple TEs with no similar family history.

Multiple familial trichoepitheliomas (MFT) is an autosomal dominant hereditary genodermatosis associated with mutations in chromosome 9p21 or the cylindromatosis (CYLD) tumor suppressor gene, located on chromosome 16q12-113 [10,11]. The CYLD gene encodes a protein of 956 amino acids with a molecular weight of 120 kDa belonging to the family of deubiquitinases. In the normal state, the CYLD protein acts primarily as an inhibitor of nuclear factor B in the TNF signaling pathway. In the majority of cases, the mutations lead to the formation of an abnormal truncated protein, leading to an increase in NF-kB activity induced by TNF and a defect in apoptosis at the origin of tumor proliferation [12,13]. MFT may be seen in Brooke–Spiegler syndrome, in which inherited adnexal tumors are combined, including multiple trichoepitheliomas, cylindromas, and spiradenomas [5]. Moreover, it may also be seen in other syndromes, such as Rombo syndrome (vermicular atrophoderma, milia, trichoepithelioma, hypotrichosis, basal cell carcinomas, and hypohidrosis) and Bazex syndrome (follicular atrophoderma, trichoepithelioma, hypotrichosis, basal cell carcinomas, and hypohidrosis) [14]. MFT has also been found to be associated with multiple renal and pulmonary cysts, basal cell adenoma of the parotid gland, ovarian cancer, breast cancer, steatocystomas, alopecia, and myasthenia gravis [15].

The differential diagnosis of TE includes the juvenile colloid milium, cylindroma, syringoma, milium, eccrine poroma, eccrine nevus, nevus comedonicus, multiple trichoblastoma, sebaceous adenoma, trichofolliculoma, basal cell carcinoma, and molluscum contagiosum [14]. A histological examination of TE confirms the diagnosis. It shows a well-defined lesion comprising

epithelial bands and small cords of basophilic cells, often centered or terminated by horny cysts forming the characteristic "tadpole tail" appearance. The basaloid cells may assume a palisade arrangement around the periphery of the lobules and islets. The perilesional stroma is dense and fibrous [16].

Multiple non-familial TE is rare and the diagnosis is usually reached by clinicopathologic correlation in the absence of a family history of similar cases and, if necessary, a genetic study. Our original case was the fourth case of multiple non-familial TE reported in the literature. For the three other cases, one presented multiple, non-segmental, unilateral, grouped papules on the trunk [8], one had extensive and disfiguring TE on the face [9], and one had multiple segmental TE along Blaschko lines on the right shoulder [17].

The evolution of non-familial multiple TE is marked by the multiplication of lesions. The damage is essentially aesthetic, as was the case of our patient. However, rare cases of associated malignant tumors have been described (basal cell carcinoma, trichoblastic carcinoma), justifying regular monitoring [18,19].

Therapeutic methods are based on surgical excision or destructive methods (cryotherapy, electrocoagulation, CO^2 laser, or Er: YAG laser), yet the latter does not prevent the occurrence of new lesions [20,21].

Topical sirolimus at 1%, imiquimod at 5%, and tretinoin at 1% are also used. In an eleven-year-old girl with multiple TEs, the application of imiquimod initially alone, then in combination with tretinoin, resulted in an 80% improvement in the lesions after three years [22,23].

A better knowledge of the pathophysiological mechanisms of the CYLD protein, in particular, concerning its inhibitory activity on nuclear factor B induced by TNF may lead to the consideration of other therapeutic alternatives, such as NF-B antagonists (aspirin or non-steroidal anti-inflammatory drugs) and anti-TNF (adalimumab). Yet, as the lesions are asymptomatic and have an extremely low malignant potential, treatment is usually not necessary unless there is disfigurement [7,24].

CONCLUSION

Herein, we have reported a rare case of sporadic multiple TE with no family history. To our knowledge, our case represented the fourth case described to date in the literature.

Consent

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

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

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Our Dermatology Online

Review Article

Advances in targeted strategies for managing neurofibromatosis type 1-related tumors

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ABSTRACT

Neurofibromas are the most common and disfiguring feature of neurofibromatosis type 1 (NF1). The treatment options for NF1 have been limited to surgical removal, yet in some cases, the growth pattern of neurofibroma may make its complete resection unpractical. Practitioners are attempting to determine the treatment options for NF1-related tumors that may shrink tumor size, which may cause local organ compression or even decrease the potential long-term risk of undergoing malignant transformation. Several clinical trials evaluating targeted therapeutics reported to have achieved promising results, including Raf inhibitors (sorafenib), MEK inhibitors (selumetinib and trametinib), mammalian target of rapamycin (mTOR) inhibitors (rapamycin), and those targeting the tumor environment (imatinib mesylate and pirfenidone). In 2018, due to high efficacy and low side effects of selumetinib symptomatically and progressively for inoperable plexiform neurofibromas, it was granted orphan drug designation by the FDA and the European Medicine Agency. In this review, we discuss the most common types of NF1-related tumors and the possible mechanisms of tumorigenesis, including the contributions of different signaling pathways and the tumor microenvironment for its management. We also focus on the recent notable advances in the development of therapeutic strategies for NF1-related tumors, including the compounds that have completed their clinical trials and the promising drugs still in clinical trials that have not shown their outcomes to provide perspective to researchers for future studies.

Key words: Neurofibromatosis; Neurofibromas; Therapeutics; Inhibitors

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant and multisystem disorder that affects approx. 1 in 2500–3000 individuals worldwide [1]. The defining manifestation of NF1 is the presence of neurofibroma with a considerable variation in clinical features such as pigmentary abnormalities, skin freckling, Lisch nodules, and behavioral abnormalities [2], even among monozygotic twins. In addition, there are few correlations between genotype and phenotype, with much depending on stochastic events [3].

Recent decades have revealed the pathogenesis of NF1, which is frequently caused by the mutation of the NF1 gene, a tumor suppressor gene that resides on chromosome 17 and encodes Ras-GTPase activating a protein known as neurofibromin. It is a 2818-amino acid cytoplasmic protein that negatively regulates the Ras cascade by accelerating the conversion of Ras from the active to inactive form [4]. With its decrease, Ras signaling pathways sustain hyperactivity, subsequently leading to uncontrolled cell proliferation and differentiation. Recently, research on developing compounds aimed at the mechanism of tumorigenesis has become a hotspot. Inhibitors targeting the pathogenesis of neurofibroma showed promising clinical improvement in some clinical trials [5,6]. New therapies for NF1related tumors may be divided into those targeting the

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tumor microenvironment and those targeting the Ras pathways within NF1deficient tumor cells. Herein, we will focus on the pathogenesis of NF1-related neurofibromas, discuss the preclinical and clinical research accumulated over the past several years, and provide more therapeutic options for clinicians to treat NF1-related tumors.

NEUROFIBROMAS

Neurofibromas are histologically benign tumors consisting of Schwann cells, fibroblasts, mast cells, macrophages, lymphocytes, and other elements of the nerve. All neurofibromas have certain histological and cellular characteristics [7]. Two subtypes—cutaneous neurofibromas (CNFs) and plexiform neurofibromas (PNFs)—are often seen.

CNFs are tumors with the highest prevalence and almost all patients with NF1 will experience cutaneous tumors. They originate from small peripheral nerve branches and are always limited to the skin. CNFs are histologically benign tumors and have no possibility of progression to a malignant form [8]. However, they may manifest as thousands of nodules, and the number increases with increasing age. Although they are not life-threatening, they may have a significant influence on physical appearance and mental health of the patient [9].

Approx. 20–50% of patients with NF1 will develop PNFs, which may be present in various regions of the body and all stages of life. PNFs develop from cranial and large-peripheral nerve sheaths and may easily invade the adjacent tissues and occasionally result in lifelong disfigurement, pain, and mortality [10]. Furthermore, around 7–12% of patients with PNF have a lifetime risk of developing malignant peripheral nerve sheath tumors (MPNSTs) [11].

MPNSTs are highly rare soft-tissue sarcomas, with an incidence of 0.001% in the general population, yet its incidence is higher in NF1. MPNSTs arise from peripheral nerve cells and develop from PNFs or secondary to radiation therapy [12]. Their specific histogenesis is unclear. The aggressive growth pattern and chances of early metastasis make MPNSTs a significant threat to the patient's life and contribute significantly to NF1 mortality [11].

PATHOGENESIS OF NEUROFIBROMAS

The Role of the Tumor Microenvironment in NF1-related Tumors

Currently, solid tumors are regarded increasingly often as complex organs, and researchers are paying more attention to the tumor environment, which is critical for tumor progression, metastasis, and drug resistance. Neurofibromin-deficient Schwann cells are identified as the primary neoplastic cells in NF1, while studies on murine models and patients have demonstrated that the loss of the NF1 gene in Schwann cells is insufficient for neurofibroma formation. Non-tumorigenic cells such as mast cells and hematopoietic effector cells, which are known to permeate in neurofibromas, also play an important role in tumor development and progression [13,14]. Interactions between tumorigenic cells and their surrounding microenvironment are critical for tumor progression as tumorigenic cells in neurofibromas hardly arise and grow in isolation.

Role of Ras Signaling in NF1-related Tumors

Neurofibromin acts as a Ras-GTPase activating protein that accelerates the intrinsic hydrolysis of Ras from active GTP-bound to inactive GDP-bound conformation. In NF1-related tumors, biallelic NF1 inactivity causes a complete loss of the functional activity of neurofibroma. With a complete loss of function of neurofibromin, Ras signaling sustains hyperactivity and results in the activity of diverse protein signaling networks, including Ras-MAPK and Ras/PI3K/AKT/mTOR pathway [15,16] (Fig. 1).

TREATMENT

At the early stage, clinical trials were aimed at mast cell function and angiogenesis, which were thought to be integral for the progression of neurofibromas in NF1. With further understanding of the pathogenesis of NF1-related tumors, more therapeutic trials attempted to focus on targeting the neoplastic Schwann cell and the tumor microenvironment [17].

In 2002, Packer et al. summarized the agents employed to treat NF1, including the antihistamine agent ketotifen fumarate, retinoic acid, interferon-alpha, thalidomide, and farnesyl protein transferase inhibitor [17]. According to that report, ketotifen fumarate and farnesyl protein transferase inhibitor

are well tolerated. However, no patients experienced shrinkage of tumors, and the results were in accord with the subsequent clinical trials, which blocked their further application [18]. Later, a study on a NF1-deficient mouse model demonstrated that ketotifen fumarate indeed decreased mast cell infiltration, yet had no impact on mast cell numbers, degranulation, and tumor behavior [19]. The other three agents revealed symptomatic improvement and tumor shrinkage in several patients (Table 1). A phase 1 and 2 clinical trial of PEGylated interferon alpha-2b demonstrated partial responses (≥ 20% decrease from the baseline) in several patients, and time to progression (TTP) prolonged significantly to 29.4 months vs. 11.8 for the placebo group [20,21].

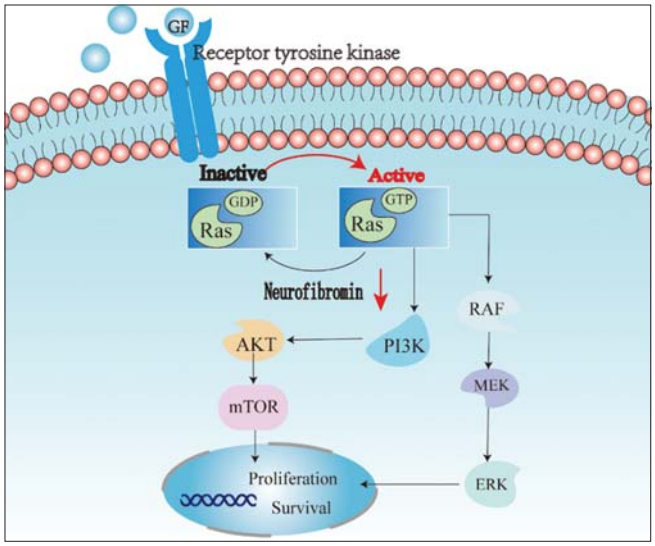

Figure 1: RAS signaling may be activated by the combination of growth factors and receptor tyrosine kinase. Neurofibromin accelerates the transformation of RAS from GTP-bound (active) to GDP-bound (inactive). In NF1-related tumors, the mutations of the NF1 gene result in an aberrant function of neurofibromin and increase the activity of Ras/Raf/MEK/ERK and Ras/PI3K/AKT/mTOR pathways, ultimately activating the RAS signaling pathways, which results in cell proliferation and survival.

Those agents only showed low responses in several patients, which encouraged researchers to explore more effective agents. We will further discuss the efforts made in targeting the tumor environment and the signaling pathways in NF1-related tumors (Tables 2 and 3).

Efforts Targeting the Tumor Environment

Pirfenidone

Several studies implied that fibroblasts play an important role in the pathogenesis of NF1-related tumors [22]. A phase 2 clinical trial of pirfenidone, a broad-spectrum oral antifibrotic drug that modulates the expression of growth factors and cytokines relevant to fibrosis, was performed [23]. In this open-label pilot trial, pirfenidone at a total daily dose of 2400 mg proved to be effective in adult patients, which suggests that it deserves further investigation. However, in a phase 1/2 clinical trial of pirfenidone in children with NF1, neither tumor shrinkage nor significantly prolonged TTP were achieved, which was in contrast to the former trial [24].

Imatinib mesylate

Recent studies have revealed that a haploinsufficiency of NF1 and c-kit signaling in the hematopoietic system is required and sufficient for tumor progression [25]. Imatinib mesylate is a multitargeted c-kit, PDGFR, and c-ABL inhibitor and has been approved by the FDA for some tumors. It is the first medical treatment for PNFs targeting the stem cell factor/c-kit axis. A preclinical study demonstrated that imatinib mesylate not only reduced cell viability *in vitro* yet also inhibited cell proliferation and decreased tumor volume in xenograft models [26]. Yang et al. treated a cohort of adult $Nf1^{flox/-}$;Krox20cre mice with imatinib, and the treatment group revealed regularly patterned Schwann cells, free of mast cell infiltrate, and reduced tumor volume [13].

Table 1: A summary and supplement of trials from Packer's literature [17]

Drug	Target	Symptomatic Improvement	Tumor Response
Ketotifen fumarate	Mast cell	Improved itching, pain and tenderness	No shrinkage of the tumor.
Retinoic acid or interferon alpha	Differentiation and angiogenesis	Eight cases (three: retinoic acid, five: interferon)	No imaging responses. Two retinoic acid and two interferon patients had a 10–20% reduction in area.
Thalidomide	Angiogenesis	7/12 (58%)	Four patients showed minor responses.
Tipifarnib	RAS	Significantly improved	No significant responses or prolonged TTP.
Pegylated interferon alpha-2b	Immune modulator and angiogenesis	11/16 (69%)	Phase 1: One (5.9%) partial response. Phase 2: Four (5%) imaging responses. Prolonged TTP.

Based on this efficacy, clinicians treated a three-year-old girl with 350 mg/m^2 imatinib mesylate. After three months of treatment, a remarkable 70% reduction in tumor volume was observed, resolving the tumor-induced airway compression [13]. Khelifa et al. reported a case of a 42-year-old female with a 34-year history of NF1 and cutaneous vasculopathy that improved after treatment with imatinib [27].

Robertson et al. reported an open-label phase 2 trial of imatinib at 220 mg/m^2 twice a day for pediatric patients and 400 mg for adults for at least six months in PNFs. In this trial, 23 patients completed the study and were evaluated. Six patients had a partial response, while the remaining thirteen patients withdrew prematurely. There was no significant difference between pediatric and adult patients [28].

The most common adverse effects included skin rash and edema. Other adverse effects such as reversible neutropenia and elevated aminotransferase were also noted in several patients. The patients in this study revealed poor compliance, which may be related to the biology of PNFs and the initial dosing of the drug [28].

Furthermore, a preclinical trial reported that nilotinib, a tyrosine kinase inhibitor, has several advantages and is more potent than imatinib in treating PNFs *in vitro* and *in vivo* [29].

Table 2: Main results of clinical trials for NF1-related tumors

Drugs	Target	Phase 1/2
Sorafenib	Raf, VEGFR, PDGFR, c-kit	Not well tolerated, no tumor shrinkage. Plus Dacarbazine: Improved efficacies and toxicities [42].
Selumetinib	MEK1/2	Mild adverse effects. 17 (71%) showed partial responses. 35 (70%) showed partial responses, 28 showed durable responses with a significant symptom improvement [5,6].
Trametinib	MEK1/2	No severe adverse effects. 12 (46%) showed partial responses [48].
Rapamycin	mTOR	Stratum 2: No response. Stratum 1: No partial response. Poor improvement [33,34].
Imatinib	c-kit, PDGFR, and c-ABL	Six (26%) showed partial responses. Reversible side effects [28].
Pirfenidone	Tumor-associated fibroblasts	Well tolerated. No objective response in children. Two (8%) showed partial responses, five (21%) showed minor responses in adults [23]. No response in children [24].

Efforts in Targeting the Ras Signaling Pathway

The MAPK/ERK pathway has been one of the most important pathways for developing novel antitumor drugs. Initially, several drug discovery programs focused on farnesyltransferase inhibitors, which may prevent Ras locating to the membrane. Unfortunately, the disappointing clinical data prevented further investigation [18]. Currently, several compounds targeting the substrates of Ras are under clinical investigation and have made notable achievements.

Rapamycin

Rapamycin is an allosteric inhibitor of mTOR complex 1 and has been approved as an anti-rejection medication for transplantation [30]. Preclinical studies in patient-derived xenografts and genetically engineered mouse models demonstrated that rapamycin significantly inhibited the activity of mTOR and tumor growth [31,32].

Based on these findings, Weiss et al. conducted a 2-strata phase 2 clinical trial in NF1-associated non-progressive PNFs (stratum 2) and progressive PNFs (stratum 1), respectively [33,34]. In stratum 2, after six courses, no patients experienced disease improvement. However, the mean emotional and school domain scores revealed a significant increase [34]. The results differed from the preclinical trials. However, a lack of PN shrinkage was consistent with a preclinical study in which the administration of mTOR inhibitor, everolimus, did not cause a significant decrease in tumor volume [35]. This trial demonstrated that rapamycin could not cause tumor shrinkage in non-

Table 3: Clinical trials remaining to publish their outcomes

Drugs	Target	Tumor	Phase	Status	ClinicalTrials.gov Identifier
Mirdametinib	MEK	PNFs	2	Recruiting	NCT03962543
Binimetinib	MEK	PNFs	2	Recruiting	NCT03231306
PLX3397	CSF1R	PNFs	1/2	Recruiting	NCT02390752
Selumetinib	MEK	PNFs in adults	2	Recruiting	NCT02407405
Selumetinib	MEK	CNFs	2	Recruiting	NCT02839720
Everolimus	mTOR	CNFs	2	Completed	NCT02332902
Rapamycin	mTOR	CNFs	1	Completed	NCT01031901
Ranibizumab	VEGF	CNFs	1	Completed	NCT00657202
Imiquimod	Immune system	CNFs	1	Completed	NCT00865644

progressive PNFs, and further investigation of the efficacy on TTP was evaluated in stratum 1.

In stratum 1, after treatment, the subjects showed a partial response, with a maximum decrease of 17%. However, the estimated median TTP of the patients (15.4 months) was significantly longer than that of the placebo group (11.9 months) [33]. In addition, the study revealed some improvement in pain intensity. There were also cases reporting alleviated pain in patients with severe PN after receiving rapamycin [36].

Overall, the efficacy of rapamycin in reducing tumor volume was not especially satisfactory, yet considering the shortage of effective treatment options, rapamycin may be considered for selected patients. Further studies are required to identify subsets of PNFs that might be more likely to respond to rapamycin therapy and to explore combination therapies that may improve its efficacy.

Sorafenib

Sorafenib is a dual-action inhibitor that has been approved by the FDA for patients with advanced renal cell carcinoma or unresectable hepatocellular carcinoma [37]. Not only does it inhibit Raf kinase, yet also inhibits several receptor tyrosine kinases involved in neovascularization and proliferation, including VEGFR, PDGFR, and c-kit [38]. Sorafenib revealed a broad-spectrum antitumor activity in preclinical and clinical trials against numerous solid tumors. Similar results were obtained in clinical trials of progressive low-grade gliomas revealing high activation of MAPK pathways [39].

Little is known about NF1-related tumors, thus to explore the further application of sorafenib, Ambrosini et al. assumed that MPNSTs would be susceptible to this compound and conducted a preclinical trial with series of sarcoma cell lines. As a result, by suppressing the level of p-MEK and p-ERK, inhibiting cyclin D1 and pRb phosphorylation, sorafenib inhibited the growth of MPNST at low concentrations [40]. An *in vivo* study also illustrated that sorafenib significantly decreased MPNST volume by volumetric MRI with mild adverse reactions [35].

However, a phase 1 trial of the drug on children with PNFs demonstrated that, after an average of seven cycles, no tumor shrinkage was observed in nine patients enrolled in the study [41]. Considering the low single-agent response rates of sorafenib, D'Adamo et al. attempted sorafenib 400 mg oral twice daily plus dacarbazine 1000 mg/m^2 intravenously, which achieved a modest clinical improvement with an eighteen-week disease control rate of 46%. However, combination therapy may increase the potential for significant toxicity [42].

Selumetinib

Initially, because of the lack of selective and potent Ras, Raf, and ERK inhibitors for most tumors, research on MEK inhibitors developed rapidly. Selumetinib is a second-generation MEK1/2 inhibitor. Mechanistically, with a non-competitive activity to ATP, MEK inhibitors bind to the binding site in MEK1/2, locking MEK1/2 into an inactive conformation, and thus prevent molecular interactions required for catalysis and ERK activation, consequently inhibiting cell proliferation and differentiation [43]. Selumetinib has shown promising potency and extensive antitumor activity in preclinical and clinical trials such as in glioma, gastrointestinal malignancies, thyroid cancers, NSCLCs, and melanomas. In preclinical models, MEK inhibitors have also been proven to be effective for PNFs. Walter et al. treated several genetically engineered mice with a highly specific MEK inhibitor PD0325901. At the end of the study, 80% of the mice experienced a striking reduction in neurofibroma volumes [44]. Then, Dombi et al. reported that selumetinib targeting MEK1/2 at a dose of 10 mg/kg twice daily on an intermittent dosing was also effective on a mouse model. At the end of the study, 12 out of 18 mice (67%) experienced a decrease in neurofibroma volume when compared to the baseline [5].

Based on these preclinical outcomes, Dombi et al. performed a phase 1 trial to test the clinical efficacy and safety of selumetinib in pediatric patients with inoperable, measurable plexiform neurofibromas [5]. In this trial, twenty-four children were treated with selumetinib at three dose levels—20 mg/m^2, 25 mg/m^2, and 30 mg/m^2—twice daily on a continuous dosing schedule (cycles: 6–56). All patients experienced a decrease in tumor volume (average: 31%), and 17/24 (71%) patients had partial responses. Moreover, not only decreases in volume were achieved, yet also a significant symptomatic improvement was observed, such as in disfigurement, pain, and functional impairment. The most common side effects were mild, and some patients also experienced dose-limiting toxicities, including 4/12 patients in the 20 mg group, 3/6 patients in the 25 mg group, and 4/6 patients in the 30 mg group, yet all were resolvable [5].

Recently, a phase 2 trial of selumetinib for PNFs also showed a clinically meaningful improvement, with 35 patients (70%) having a confirmed partial response, among which 28 experienced a durable response (≥ 1 year). However, six patients suffered tumor progression and five patients discontinued the drug because of selumetinib-related toxicities [6]. A single-institution study confirmed that selumetinib was effective and safe for NF1-related PNFs, with all patients experiencing a sustained clinical improvement except one [45]. The exact efficacy in adult patients remains unclear, hence further investigation needs to be conducted.

Trametinib

Trametinib is a novel and highly specific allosteric MEK inhibitor. As monotherapy or combined therapy, it has been approved for numerous tumors harboring mutations in members of the MAPK pathway [46]. In 2019, Vaassen et al. reported an eleven-year-old girl suffering from a huge PNF that caused an extreme deformity, which benefited from trametinib therapy [47]. In that study, after six months of trametinib 0.5 mg twice daily, there was a 22% decrease in tumor volume, which made surgery possible.

McCowage et al. conducted a phase 1/2 single-arm multicohort trial that evaluated trametinib at 0.025–0.040 mg/kg/day in pediatric patients with unresectable NF1associated PNFs [48]. Twenty-six patients were recruited to the trial, and after a median duration of 61 weeks, twelve patients (46%) experienced a partial response, and no patients experienced severe adverse effects. The trial is still ongoing, yet reports have already demonstrated tolerability and clinical benefits in a cohort of children with plexiform neurofibromas.

Perreault et al. also presented a protocol for a phase 2 study investigating singleagent trametinib at a fixed dose of 0.025 mg/kg (≥ 6 years old) or 0.032 mg/kg (< 6 yrs. old) for eighteen cycles to evaluate the efficacy and safety in patients with pediatric low-grade gliomas and neurofibromas [49]. In this study, the authors expected to recruit a total of 150 patients, which included 46 patients with plexiform neurofibroma. At the end of the trial, they will evaluate not only standard response rates yet also progression-free survival, overall survival, and quality of life during treatment.

CONCLUSION

Despite neurofibromatosis-1 being a type of familial disease, a half of the reported cases are yet due to *de novo* mutation on chromosome primarily derived paternally, which may decrease quality of life and average life expectancy of the victim. Traditional therapeutic regimes for NF1-related tumors are limited to surgical removal or physical destruction, which by the involvement of adjacent tissues, particularly the nerve and vasculature, may complicate the procedure with ensuing frequently neoplasm recurrence that creates the urgency to explore new therapeutic methods of treating NF1-related tumors radically.

At the very beginning, experts focused on agents targeting the tumor microenvironment, such as pirfenidone and imatinib, yet there were low responses in patients with NF1. More efforts were made to explore small molecule compounds targeting RAS signaling pathways. By using these compounds, not only clinical symptoms were improved, yet also the shrinkage of tumors was achieved. Focusing on the development of precision oncology and the increased investigation of pathogenesis and molecular landscape of NF1-related tumors, more agents targeting MAPK/ERK and mTOR pathways are under investigation, with some having achieved inspiring outcomes.

As there is remarkable clinical efficacy of selumetinib in numerous other non-cutaneous tumors and some NF1-associated tumors, it may be considered for the tumor shrinkage of NF1 to not only shrink the volume, yet also improve other symptoms that may increase the quality of life of the patient. It has been proven to be effective against melanomas in some literature as well. Hence, more effort needs to be exerted to explore the specific mechanism of its action. We cannot ignore the fact that it may be considered for NF1 cases with large tumor sizes with an aim of, first, decreasing its size and volume then, subsequently, excising it. Furthermore, ERK1/2 inhibitors have recently produced inspiring results in preclinical research, especially in those tumors with acquired resistance to MEK inhibitors. Yet, they have been implicated less for NF1related tumors, hence more clinical research may be performed regarding its efficacy. Several systemic trials are currently being conducted to evaluate the efficacy of targeted therapeutics for cutaneous neurofibromas and many of them are still under investigation (Table 3). Only one phase 2 open-label, single-arm trial of everolimus (ClinicalTrials.gov; identifier: NCT02332902) revealed

a significant reduction in lesion surface volume and PNF, yet no serious adverse events were accounted [50]. Hence, more clinical trials should be conducted with such agents to further study its outcomes with a lifetime observation if possible.

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Histopathological Image

Tumoral infrapatellar calcinosis

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Tumor calcinosis is a rare pathology characterized by circumscribed calcifications in the periarticular connective tissue. They are composed mainly of crystals of hydroxyapatite and amorphous calcium phosphate [1]. This term has usually been employed to describe metastatic periarticular calcification secondary to renal failure, hyperparathyroidism, hypervitaminosis D, and milk-alkali syndrome [2].

Herein, we present the case of a 58-year-old female who consulted for a tumor in the lower anterior region of the knee, subcutaneous, of months of evolution, bothering the flexion of the joint. She suffered from multiple sclerosis with a favorable evolution without medication and osteoporosis with multiple vertebral fractures. Treatment consisted of risedronate and calcifediol. On physical examination, a nodule of about 2–3 cm, infrapatellar, subcutaneous, mobile, not attached to deep planes, with a hard consistency was observed. With the diagnosis of a probable epidermal inclusion cyst, surgical excision was indicated, and the sample was sent for a histopathological study. The histological sections examined (Figs. 1a and 1b) corresponded to soft tissue, consisting of subcutaneous tissue and connective tissue, showing multiple calcified nodular formations associated with a histiocytic reaction with multinucleated giant cells.

The histological picture was compatible with a cutaneous calcium deposit (calcinosis cutis), and the preferential involvement at the level of periarticular soft tissue could correspond to tumoral calcinosis. With this diagnosis, the patient was referred to internal medicine, where they assessed the extent of the disease and adjusted the treatment.

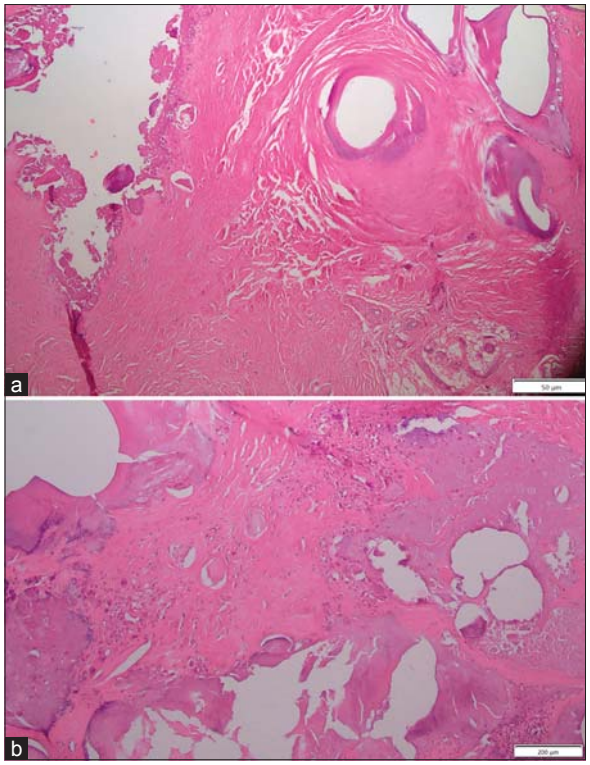

Figure 1: (a) Subcutaneous and connective tissue revealing multiple calcified nodular formations (H&E, 20×). (b) Calcified nodular formations associated with a histiocytic reaction with multinucleated giant cells (H&E, 20×).

Histologically, these lesions are identical regardless of etiology, which explains why periarticular calcifications are often referred to as *tumoral calcinosis*. Surgical resection is the usual treatment, yet recurrences are

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frequent after incomplete excisions or in cases with osteoblastic activity [3].

Consent

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

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Our Dermatology Online

Study Letter

Skin cancers in kidney transplant patients: Experience of the Dermatology Department of the Ibn Sina University Hospital in Rabat, Morocco

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Sir,

Adult renal transplantation has become the treatment of choice for end-stage renal disease as it improves the quality of life of the patient as well as their life expectancy [1,2].

Chronic and potent systemic immunosuppression, which has ensured prolonged survival for most organ transplant patients, has given rise to a new set of challenges for patients and providers, manifested by an alarming increase in the incidence of skin infections and neoplasia, responsible for 12% and 16% of deaths, respectively, in patients with a functional graft, hence the need for systematic and regular dermatology follow-up of this population [3].

In order to conduct our retro-prospective study, we established the following objectives:
- To search for the different skin cancers following renal transplantation;
- To evaluate their frequency;
- To compare them with the data in the literature.

We collected all renal transplant patients who consulted in dermatology for a case of skin manifestations or were in the framework of the systematic biannual follow-up of renal transplant patients.

All patients were subjected to a detailed interrogation:
- Age at the time of transplantation and current age;
- Sex;
- Data related to the transplant (date, place);
- Causal diseases;
- Type of donor;
- Number and reason for transplantation;
- Modalities and type of immunosuppression.

A complete dermatological examination was performed to detect the different tumor manifestations.

One hundred forty-four patients were collected. The mean age at transplantation was 41.93 years (extremes: 14 and 82 years). There was a male predominance (male-to-female ratio: 1.21).

Fifty-four percent of our patients had phototype IV, 30% had phototype III, 12% had phototype II, and two patients had phototype V.

One hundred forty-one of our patients were under polychemotherapy and three were under monochemotherapy.

The first transplant was performed in France in 1981 and it was only in 1998 that renal transplantation was started at the Ibn Sina University Hospital. Sixty-seven percent were transplanted in Rabat.

Seventy-two percent of the patients presented with cutaneous and mucosal manifestations with a median delay of twelve months (1 week to 148 months).

During the study period, five skin cancers were identified in five patients. Table 1 summarizes the clinical characteristics of the five patients who developed a malignant tumor during the study period.

How to cite this article: Ammar N, Meziane M, Ismaili N, Benzekri L, Senouci K. Skin cancers in kidney transplant patients: Experience of the Dermatology Department of the Ibn Sina University Hospital in Rabat, Morocco. Our Dermatol Online. 2023;14(3):321-322.

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Table 1: Clinical characteristics of kidney transplant patients who developed a skin cancer during the observation period

	Sex	Age at Cancer Onset	Duration of Immunosuppression before Cancer Onset	Type of Cancer
Patient 1	Male	42 years	4 years	Bowen's disease
Patient 2	Male	52 years	1 year	Squamous cell carcinoma
Patient 3	Male	51 years	17 years	Basal cell carcinoma
Patient 4	male	51 years	19 years	CD30+ anaplastic large cell lymphoma
Patient 5	Female	58 years	2 years	Kaposi's sarcoma

Renal transplantation remains the only radical treatment for chronic end-stage renal disease. However, as in the case of any treatment, renal transplantation has its drawbacks, risks, and constraints [4]. Indeed, organ transplantation is necessarily accompanied by immunosuppressive treatment, which may be responsible for short- and long-term adverse effects. The risk of cancer in transplanted patients is at least three times higher than in the general population, yet varies greatly with the type of cancer, which also determines the latency (from several months to, sometimes, twenty years). It is estimated that 17% of patients develop cancer after transplantation, including 9% of cutaneous squamous cell carcinomas and 7% of basal cell carcinomas. The cumulative incidence of all cancers combined is 13%, 33%, and 47% at 10, 20, and 30 years, respectively [5]. Other tumors have been reported, such as Kaposi's disease, the frequency of which is 500 times higher than in the general population. Rarely, lymphomas, melanomas, sarcomas, and Merkel tumors have been reported [6].

Several factors are incriminated: immune status, duration and intensity of immunosuppression, sun exposure, genetic susceptibility, and pre-existing HPV lesions [7].

The average time to the onset of skin tumors was nine years. Only five of our patients presented tumor lesions. This was probably due to insufficient follow-up after transplantation in our series.

The main finding of our study was the low cumulative incidence of skin cancers (2.7%), particularly carcinomas, which, subject to the limited duration of the observation period, was lower than the incidences found in other cohorts of transplant patients.

Despite these limitations, the types of cancers developed during our observation period corresponded to those most frequently reported in transplant patients.

Patients should be informed about the risk of developing skin tumors and should be encouraged to consult regularly, thus enabling the dermatologist to detect lesions at an early stage.

A skin examination for the early detection of lesions should be performed regularly at a rate of once per year in the absence of complications or even more often in the case of pre-existing cancerous lesions.

Statement of Human and Animal Rights

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

Statement of Informed Consent

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

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Our Dermatology Online

Case Letter

Success of punch elevation combined with CO_2 laser and trichloroacetic acid touches in a depressed-scar nose

Sokaina Chhiti, Hanane Baybay, Fatima Zahra Hashas, Zakia Douhi, Meryem Soughi, Sara Elloudi, Fatima Zahra Mernissi

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Sir,

The revision of a depressed scar is more difficult because it does not follow the line of relaxed skin tension. Several measures have been proposed for the recovery of this type of scar, yet they have a number of limitations, complications, and disadvantages. The combination of punch elevation, fractionated carbon dioxide laser, and trichloroacetic acid (TCA) touches offer satisfactory results.

This was a twenty-year-old female of phototype III, with no medical history, who consulted for a scar at the tip of the nose that had been evolving for the previous four months following the manipulation of a button. A clinical examination revealed the presence of two contiguous, 2.5 mm, irregular, depressed, and atrophic scars of normal skin color at the tip of the nose (Fig. 1a), for which the patient initially benefited from punch elevation of 3 and 4 mm (Fig. 1b) performed under local anesthesia with well-coded, post-surgical scar support based on the placement of Steri-Strips, the twice-daily application of fusidic acid, preventive valaciclovir, and a healing cream. A significant improvement was observed in the depressed scar during the 24-month post-operative follow-up without complications or pigmentation disorders (Fig. 1c).

Johnson stated the punch elevation method for the remedy and repair of deep pimples and scars with Steri-Strips and other strategies [1]. This approach is undertaken for scars 3 mm in diameter or larger with true shade matching and directly walls [2]. It involves the use of a punch barely larger than the scar to be handled, besides that the scar that is being punched is not always disposed of. The cylinder of tissue is incised down to the extent of the subcutaneous fat. The incised scar is authorized to flow till it is far with the encompassing pores and skin. If it does not thrust upward easily, it may be launched at the level of the fat with an excision, as was the case of our patient. The cylinder of tissue may be kept in place by means of the patient's serum and rest as if it was a graft, by a surgical tape [2,3], or by stitches.

Some scars will heal at the same level of the skin surface and some will be raised [3], hence the value of combining other resurfacing techniques to treat superficial irregularities, dermal fillers to replace lost volume in large atrophic areas, and surgical procedures, such as punched excision and remodeling, such as fractional CO_2 laser, which allows more precise control of ablation, especially for certain deeper scars requiring several passages [4,5].

The deep penetration of high-concentration TCA focal peel has produced extraordinary clinical effects and rare complications. Similarly, to a 3–5-day shorter recuperation time than with laser resurfacing, there was no need for preconditioning or anesthesia as only a small vicinity of pores and skin became unsatisfactory. Moreover, the simplicity of the method, similarly to the excessive charge of satisfaction said with the aid of sufferers and its low cost, confirms that the use of a concentration of more than 70% of TCA is a safe and powerful method for the treatment of atrophic scars [6].

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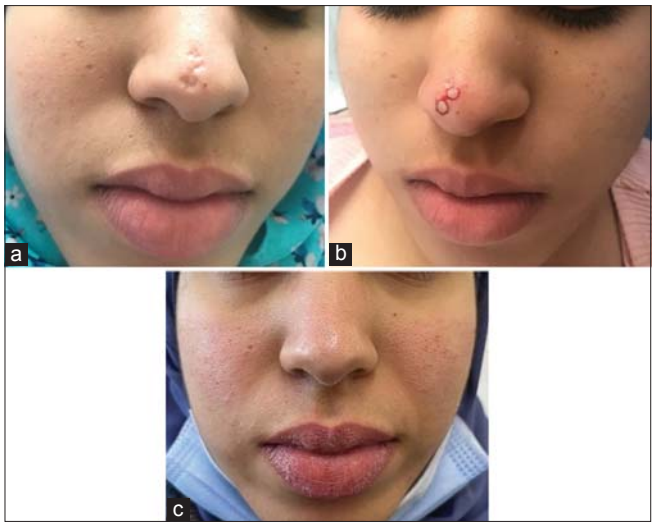

Figure 1: (a) The two depressed scars at the tip of the nose. (b) Punch elevation of 3 and 4 mm. (c) Control one year after laser and TCA touching.

Our case illustrated the amazing success of a simple and rapid procedure based on punch elevation in combination with 100% TCA touches and fractional CO_2 laser in the management of depressed nasal scarring in a young female.

Fractional CO_2 laser treatment in combination with punch elevation and TCA touching improves the results of treating depressed facial scars. This combination offers the benefit of increased patient satisfaction without increased side effects.

Consent

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

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

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Our Dermatology Online

Case Letter

Sulfasalazine-induced lichen planus in a patient with ulcerative colitis

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Sir,

A 76-year-old female with ulcerative colitis was treated with sulfasalazine. Six years after the initiation of sulfasalazine, she developed a pruritic eruption and was referred to our department. A physical examination revealed small, round, brownish, erythematous plaques with scales on the trunk and extremities. Small, scaly erythemas and plaques were distributed on and around old surgical scars due to osteomyelitis (Fig. 1). Neither mucosal nor nail lesions were observed. A laboratory examination revealed normal blood cell counts with a normal eosinophil percentage, as well as normal liver and kidney function. Antinuclear antibody was positive (1:320, homogenous and speckled), yet ani-HCV antibody, anti-thyroglobulin antibody, anti-microsome antibody, anti-SS-A antibody, and anti-SS-B antibody were negative or within normal ranges. The drug transformation test with sulfasalazine was negative. A histopathological examination revealed mild acanthosis of the epidermis, individual cell keratinization of the epidermal cells, vacuolar degeneration in the basement membrane, and infiltration of mononuclear cells in the epidermis and upper dermis (Fig. 2a). Immunohistochemistry revealed that the infiltrating mononuclear cells were positive for both CD4 and CD8 (Figs. 2b and 2c). The cutaneous lesions completely disappeared with the use of topical corticosteroid ointment and the discontinuance of sulfasalazine after two years (Fig. 3).

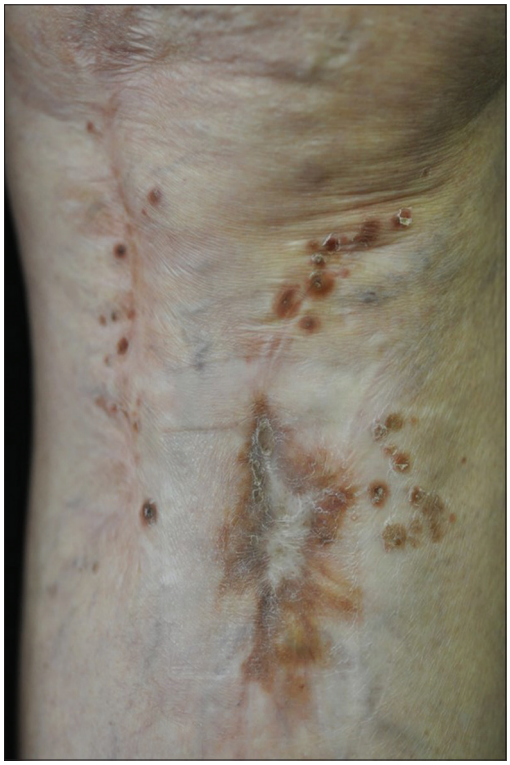

Figure 1: Multiple, round, brownish, scaly erythemas and plaques on and around the surgical scars on the lower leg.

The patient developed lichenoid eruptions on the trunk and extremities, with a unique distribution of the keratotic erythemas on and around old surgical scars, which was considered a physical trauma of Köbner phenomenon [1]. The discontinuation of sulfasalazine and topical corticosteroid therapy resulted in the complete disappearance of cutaneous eruptions, thus we diagnosed the case as sulfasalazine-induced lichen planus.

Sulfasalazine has immunosuppressive, immunomodulatory, and anti-inflammatory effects and is commonly used in the treatment of rheumatoid arthritis and ulcerative colitis [2]. In the dermatological field, sulfasalazine is occasionally employed off-label for numerous autoimmune and inflammatory disorders [2]. Previous studies have shown the efficacy of sulfasalazine in the treatment of generalized lichen

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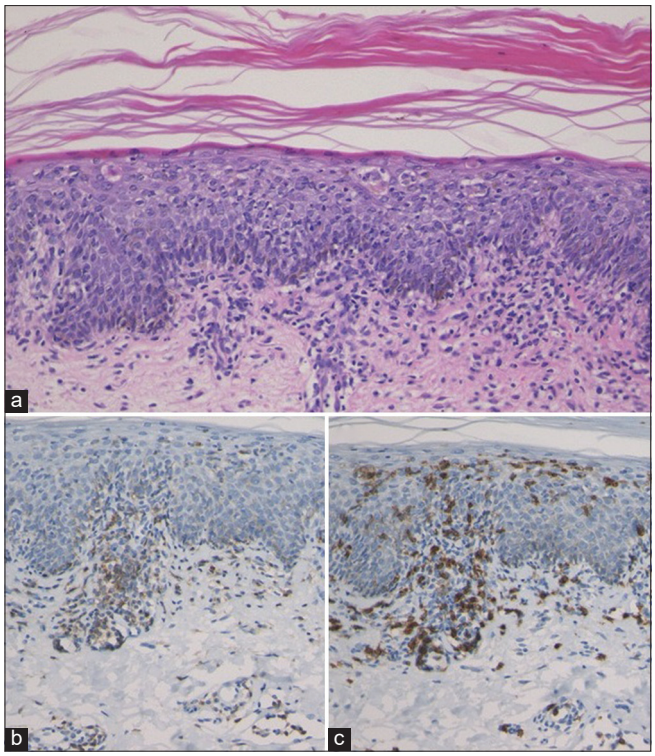

Figure 2: a) Histopathology showing mild acanthosis of the epidermis, individual cell keratinization of the epidermal cells, vacuolar degeneration in the basement membrane, and infiltration of mononuclear cells in the epidermis and upper dermis, which were immunoreactive for b) CD4 and c) CD8.

planus in a randomized double-blind clinical trial. A group on oral sulfasalazine (initial dose of 1 g/day, increasing 0.5 g every three days up to 2.5 g/day) showed a greater clinical improvement (80.7%) when compared to a placebo group (7.6%) [3].

After six weeks, the group treated with sulfasalazine showed an improvement at 82.6%, whereas an improvement was observed in 9.6% of the placebo patients. Although not in a placebo-controlled trial, sulfasalazine resulted in a complete resolution ($n = 13$) or partial response ($n = 7$) in twenty patients with cutaneous lichen planus. Although the mechanism is unknown, it is speculated to be caused by the inhibition of the expression of several cytokines and adhesion molecules by sulfasalazine [4]. Although sulfasalazine is a possible therapeutic candidate for refractory lichen planus, reports of sulfasalazine-induced lichen planus are rare. In previous reports, lichen planus have been induced during sulfasalazine treatment in patients with rheumatoid arthritis [5,6]. Concurrent lichen planus and ulcerative colitis have rarely been observed [7]. However, to our knowledge, this is the first case of sulfasalazine-induced lichen planus in a patient with ulcerative colitis.

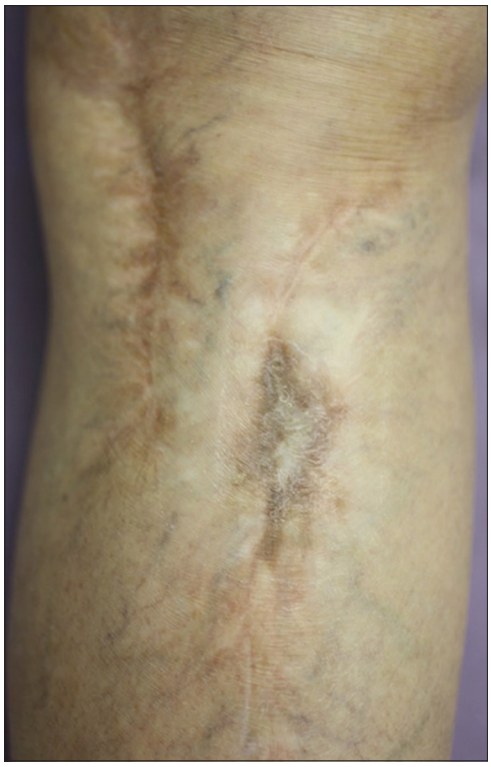

Figure 3: Complete improvement of the skin lesions.

Consent

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

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Case Letter

A strange umbilical rash in a newly diagnosed HIV-positive male: A new clinical description of *Trichosporon spp.* dermatosis

Ryme Dassouli[1], Zakia Douhi[1], Kenza Tahiri Joutei[1], Hanane BayBay[1], Sara Elloudi[1], Khaoula Abdellaoui[2], Laila Tahiri[2], Hinde El Fatemi[2], Fatima Zahra Mernissi[1]

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Sir,

Trichosporon is a basidiomycete yeast of tropical origin that is also opportunistic in the immunocompromised. It is characterized by irregular nodules attached to the hair known as *white piedra*. *Trichosporon spp.* have been reported as the second most common agent of disseminated, potentially fatal fungemia [1]. Nevertheless, no pure cutaneous manifestation has been reported. Herein, we report a single case of *Trichosporon spp.* causing an umbilical papulonodular rash in a newly diagnosed HIV-positive individual.

A 25-year-old patient, with a history of homosexuality and unprotected sexual intercourse, presented with a one-week-old, asymptomatic, reddish rash associated with umbilicated, papular lesions of the trunk and lower back, which were pruritic and concomitant in appearance. A dermatological examination revealed scattered, copper-red papules on the face, trunk, and limbs, palmo-plantar, papular lesions surrounded by a thin, circular, whitish collar, with large papules and nodules with an umbilicated center, pruritic and eroded, located in the sacral region and pre-pectoral area (Figs. 1a and 1b). Dermoscopy revealed a star-like appearance with erythema in the center, whitish lines in a radial arrangement surrounded by a crown of vessels in points (Fig. 2). A mucosal examination revealed a syphilitic chancre on the glans. The lymph nodes were free. The rest of the examination was unremarkable. HIV and syphilitic serology were positive, with a VDRL titer of 1/64. The lumbar puncture was sterile. A biopsy of the umbilical lesions was performed, which revealed sheets of inflammatory cells consisting essentially of macrophages forming nodules around the vascular structures of the superficial and deep dermis. Microscopic yeasts were present in the macrophagic cytoplasm. A mycological study on the collected tissue revealed the presence of *Trichosporon spp*. The diagnosis of an opportunistic infection with *Trichosporon spp.* in an HIV-positive and syphilitic individual in the second bloom phase was accepted. The patient was treated with late penicillin for syphilis, and antiretroviral treatment was recommended after a normal pre-treatment workup. Three weeks later, the syphilis disappeared and the nodular lesions subsided. Dermoscopy of the lesions revealed the disappearance of the star-like appearance with the presence of vessels in points and the attenuation of the erythema.

Trichosporon are natural soil inhabitants as well as components of the human skin and nail flora, which, in tropical climates, may cause benign, superficial hair lesions (*piedra blancs*), characterized by the presence of irregular nodules on the affected hair [2]. These nodules are loosely attached to the hair shaft, have a soft texture, and may be white or light brown [3].

David et al. reported a case of lichenoid lesions of the trunk in an HIV-positive patient, in whom histological and mycological studies revealed the coexistence of *Trichosporon* and *Histoplasma capsulatum* during systemic fungemia [4].

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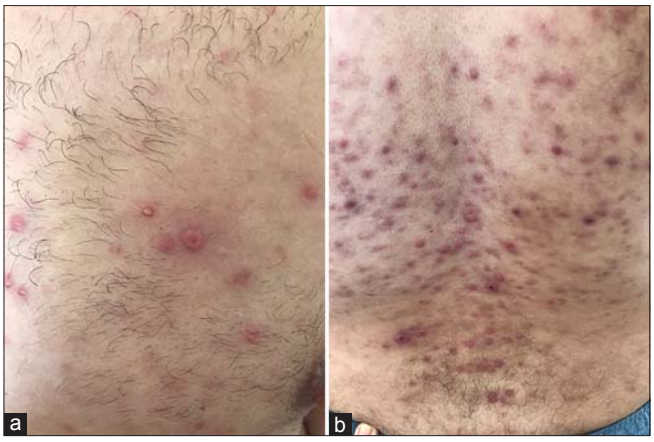

Figure 1: (a and b) Umbilical, papulonodular lesions of the trunk.

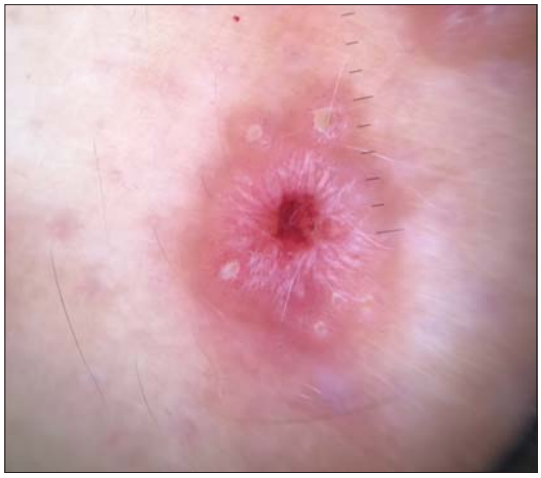

Figure 2: Dermoscopy showing a star-like appearance with erythema in the center, whitish lines in a radial arrangement that were surrounded by a crown of vessels in points.

In our case, the association of a syphilitic chancre and asymptomatic coppery papular lesions of the body with nail-like palmar lesions surrounded by Biett's collarette represented the typical aspect of syphilis in coexistence with primary syphilis, frequently encountered in seropositive individuals. HIV serology was, then, requested together with syphilitic serology to confirm the diagnosis of syphilis, which returned positive. Moreover, the papulo-nodular lesions of the trunk and lower back had a different appearance, with an umbilical and pruritic character. Two hypotheses were evoked: syphilis with an atypical clinical presentation in a seropositive individual or a cutaneous fungal co-infection such as histoplasmosis, cryptococcosis, or penicilliosis. Histology revealed yeasts in the papillary and reticular dermis surrounded by inflammatory cells, and further mycological analysis confirmed the presence of *Trichosporon spp*.

The clinical form of this fungus in our patient indicated a good therapeutic response to Penicillin G. However, previous studies have demonstrated positive antifungal activity with azoles and amphotericin B treatment for *Trichosporon* infection [5]. Other forms of treatment, such as the resection of the infected tissue, are associated with greater improvement [5,6].

Herein, we have reported an original case of opportunistic fungal dermatosis in an HIV-positive individual with a good therapeutic response to penicillin. Indeed, a *Trichosporon* infection should not be excluded in front of umbilical eruptions in an immunocompromised patient. Although not reported in the literature, the efficacy of penicillin against this mycosis remains to be demonstrated.

Consent

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

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

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Our Dermatology Online

Case Letter

Central centrifugal cicatricial alopecia: A call for additional literature in the pediatric population

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Sir,

Central centrifugal cicatricial alopecia (CCCA), formerly known as *follicular degeneration syndrome* or *hot comb alopecia*, is a lymphocytic scarring alopecia seen more commonly in females of African descent [1]. However, emerging literature suggests a prevalence in adolescent Black and Asian populations [2,3].

The variability in the presentation of CCCA requires a high index of suspicion in the pediatric population. Classically, patients in the adult population present with hair loss to the vertex of the scalp, which spreads laterally and forward. However, other presentations vary from hair breakage to the vertex of the scalp with the later addition of papules and pustules to a patchy alopecia involving the vertex and the parietal and occipital scalp [1,2]. Clinical mimickers may, therefore, include tinea capitis, traction alopecia, androgenetic areata, and alopecia areata [4]. This letter aims to highlight the importance of entertaining it as a differential diagnosis in this population.

Scarring alopecia is rare in the pediatric population, likely due to a low index of suspicion and late presentation [5]. There is a paucity of literature on the demographics, clinical presentation, prevalence, and treatment outcomes for scarring alopecia in the pediatric population. This deficit extends to medical education, as these authors have observed that entire book chapters geared toward primary physician education of scarring alopecia omit the differential diagnosis of CCCA [6].

The common modalities employed to diagnose CCCA include dermoscopy and histopathology, with the finding of peripilar, grayish-white halos surrounding the emergence of 1–2 hair follicles in the former being highly sensitive and specific for the diagnosis of CCCA [4]. Because both CCCA and tinea capitis may present with pruritus, scaling, and hair breakage, a potassium hydroxide (KOH) preparation or fungal culture may be warranted to exclude the latter [4]. Timely diagnostic intervention is critical as the hair follicles slowly burn out [3,5,7]. In a study by Imhof et al., the average time from symptom onset to the diagnosis of scarring alopecia in a pediatric population was 17.1 months, and the concurrent psychiatric co-morbidities included anxiety (22.2%) and depression (22.2%) [7]. This finding reinforces the importance of having a low diagnostic threshold to decrease overall morbidity. Psychologic burden and quality of life are reportedly more severely impaired in patients with scarring alopecia [7]. This is likely a result of the poorer responses to therapy and the associated symptomatology, such as pain, burning, and pruritus [4,7]. Successful treatment of CCCA generally requires combination and systemic therapies, such as topical and intralesional corticosteroids, topical minoxidil, oral tetracyclines, hydroxychloroquine, and oral retinoids [7]. However, further data is needed to outline the most efficacious treatment modalities for the pediatric population.

In conclusion, a deficit of literature surrounding pediatric scarring alopecia, particularly CCCA, exists in online medical databases. More studies need to be conducted to determine the epidemiology, clinical

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presentations, treatment outcomes, and comorbidities in the pediatric population.

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 Letter

The mystery of diaper rash

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Sir,

Human scabies is an ectoparasitosis caused by *Sarcoptes scabiei*. Its diagnosis is generally easy in the presence of acute generalized family pruritus with nocturnal exacerbation. Nevertheless, atypical presentations may confuse the clinician [1].

Scabies is a frequent, highly pruritic, and contagious dermatosis. The disease is favored by promiscuity, lack of hygiene, and poverty. It affects males and females of all ages, ethnicities, and socioeconomic levels [1,2].

The clinical signs are typically vesicles, grooves, or nodules on preferential sites: interdigital spaces, anterior surface of the wrists, elbows, axillary hollows, umbilicus, buttocks, mammary areola, and external genitalia. Pruritus is often intense, generalized, and nocturnal [1].

The reference diagnosis is based on direct parasitological examination, which allows *Sarcoptes* to be visualized under the microscope. However, this examination cannot be performed in routine practice [1].

Herein, we report a clinico-dermoscopic description of atypical scabies.

A 69-year-old patient, with a history of hepatitis B, consulted for intergluteal pruritus evolving for two months. He was treated with a topical antimycotic and dermocorticoid without improvement. The clinical examination revealed several erythematous nodules, rounded, well-limited with regular contours, of firm consistency, mobile to the superficial and deep planes, resting on an erythematous placard excoriated at the intergluteal level (Fig. 1a).

A dermoscopic examination revealed scabious furrows, a positive delta sign with an erythematous background, and some fine whitish scales (Fig. 1b).

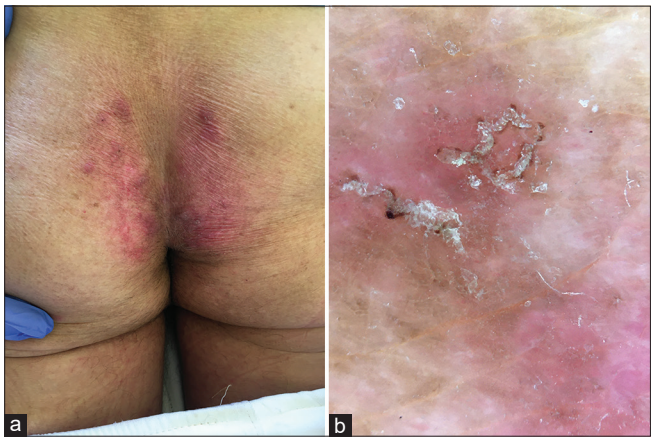

Figure 1: (a) Intergluteal erythema with nodules. (b) Dermoscopy revealing the delta sign and scabious furrows.

The patient was treated with Ascabiol with a good evolution, regression of the pruritus, and subsidence of the nodules.

The diagnosis is, therefore, based on the clinical examination in typical forms, confirmed by the dermoscope, which makes it possible to obtain diagnostic certainty and even redirect the diagnosis [3,4], as in the case of our patient.

Scabies is a frequent dermatosis of obvious diagnosis. Atypical forms with particular localizations should not be ignored.

Consent

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

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Case Letter

Dermatophytid in tinea capitis: A phenomenon to keep in mind

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Sir,

Tinea capitis is a fungal infection of the scalp occurring most often in preadolescent children [1]. Its clinical presentation is typically single or multiple hair loss lesions, which may be accompanied by inflammation, scaling, and pustules. The most common trichoscopic features in tinea capitis are comma hair (disintegrated, cracked, and bent due to the presence of fungal hyphae in the hair shaft), corkscrew hair (a variant of comma hair and a marker of endothrix), black dots (broken, dystrophic hair), Morse code-like hair (intermittent, horizontal, white streaks, barcode-like hair), zig-zag hair (unusual bends caused by the invasion of hair shafts), bent hairs (bending of the hair shaft with homogeneous thickness and pigmentation), block hair (very short hair with transverse horizontal distal end), I-hair (blocky hairs with an accentuated dark distal end), and peripillary scaling [2]. Thorough history taking (including the history of contact with animals), physical examination, dermoscopy, and mycological examination are necessary for the diagnosis. Treatment requires an oral antifungal, such as itraconazole or terbinafine.

Id reactions are a type of secondary immunological reaction that results from a variety of stimuli, including infectious and inflammatory skin diseases. A dermatophytic reaction is defined as an id reaction caused by dermatophytosis [3]. Dermatophytid reactions may occur in numerous different clinical manifestations, from mild to severe reactions. They are characterized by symmetrical, widespread, eczematous lesions (scaly patches, plaques, and papules) beginning on the scalp, face, and neck, and sometimes spreading to the trunk and extremities [3]. Lesions may also

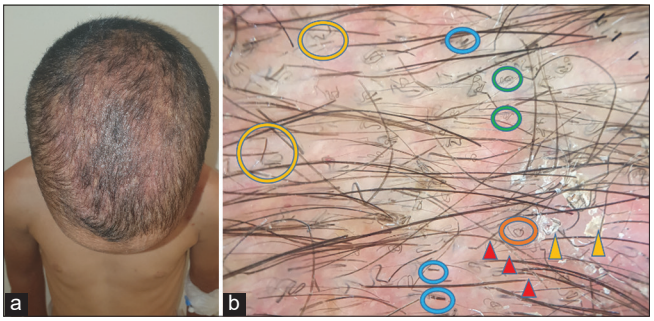

Figure 1: Clinical and dermoscopic features of tinea capitis: a) erythematous pseudoalopecic plaques with yellow crusts involving the frontal and parietal areas of the scalp; b) erythematous background, whitish peri-and inter-pillar scales (yellow arrows), broken hair (blue circle), corkscrew hair (green circle), zig-zag hair (yellow circle), Morse code-like hair (red arrows), hair in arrobas (orange circle).

appear on the palmar surfaces and interdigital spaces as papules, vesicles, bullae, or pustules [4]. Other rare dermatophytic manifestations reported in the literature are migrating thrombophlebitis, erysipelas-like dermatitis, erythema nodosum, erythema annulare centrifugum, and angioedema-like reaction [3,5]. Dermatophytosis may occur before or after the initiation of systemic antifungal therapy and must be differentiated from drug-induced allergic reactions. If this phenomenon is not recognized, the patient may be misdiagnosed, undergo unnecessary tests, and receive incorrect treatment. Antifungal therapy should be continued throughout the course of dermatophytosis to clear the infection and subsequently resolve the eruption. General or topical steroids may also be used in combination if the dermatophytic reaction is extremely widespread [6,7].

We herein set out the case of a ten-year-old boy who presented with a two-month history of multiple mildly

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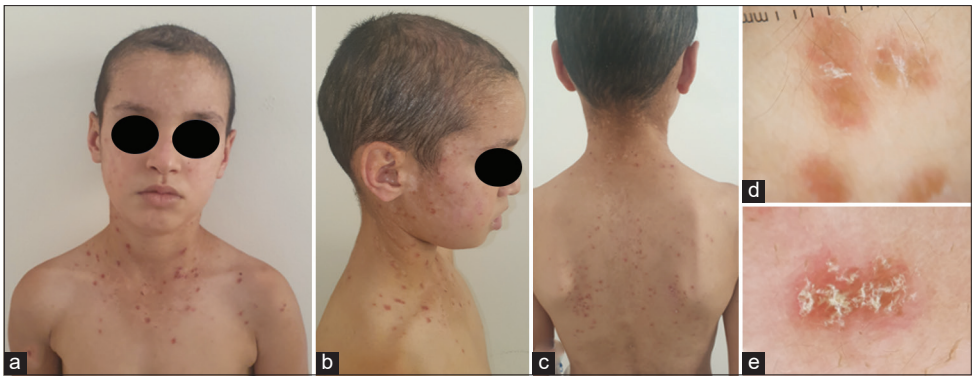

Figure 2: Clinical and dermoscopic features of dermatophytids: a-c) multiple papules, erythematous, mildly scaly on the face and neck, spreading to the trunk; d-e) structureless, erythematous, and orangish areas and white scales.

itchy, erythematous, and scaly lesions on the scalp, face, neck, and truck. His medical history was unremarkable and no other family member was suffering from a similar disease; however, a history of animal contact was present. Through a physical examination, we observed an extensive, erythematous, and slightly scaly plaque involving the frontal and parietal area of the scalp. The hairs present were easily pluckable and matted. The trichoscopic findings were erythema, whitish peri- and inter-pillar scales, broken hair, corkscrew hair, zig-zag hair, Morse code-like hair, hair in arrobas (Figs. 1a and 1b).

We also observed multiple papules, erythematous, mild scaly on the face and neck, spreading to the trunk. A dermoscopic evaluation revealed structureless, erythematous, orangish areas and white scales (Figs. 2a – 2e). The posterior cervical lymph nodes were enlarged and palpable. A potassium hydroxide (KOH) preparation made from scalp and hair scrapings showed fungal hyphae.

The diagnosis of tinea capitis associated with a dermatophytid reaction was established and the patient was treated successfully with oral and topical griseofulvin for eight weeks in association with symptomatic measures for the dermatophytid. There was complete clearance of lesions and hair regrowth.

Consent

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

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

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Our Dermatology Online

Case Letter

Annular and ulcerative lichen planus induced by nivolumab therapy

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Sir,

Lichen planus (LP) or lichenoid dermatitis are often observed in patients treated with immune checkpoint inhibitors (ICIs). Herein, we report a case presenting with rare forms of ulcerative as well as annular LP during nivolumab therapy.

A 73-year-old male began nivolumab (240 mg every two weeks) therapy for unresectable oropharyngeal cancer. One year later, after the twenty-fourth administration of nivolumab, itchy eruption appeared and gradually worsened, and he was referred to our department. A physical examination revealed several well-circumscribed, annular plaques with slightly elevated borders on the dorsum of the hands and forearms (Fig. 1a). Additionally, several keratotic plaques and ulcerated plaques were observed on the upper and lower extremities (Fig. 1b). A biopsy specimen taken from the annular plaque revealed wedge-shaped epidermal acanthosis with focal hyperkeratosis, interface changes with mononuclear cell infiltration of the basement membrane of the epidermis, individual cell keratinization, and cellular infiltration in the upper dermis (Fig. 2a). Another biopsy specimen, taken from the ulcerated plaque, revealed a lack of epidermis and a dense infiltration of mononuclear cells in the upper-to-mid-dermis (Fig. 2b). Infiltrative mononuclear cells were mainly composed of CD8-positive T-cells in both specimens (Figs. 3a and 3b). Nivolumab was continued further for five months; however, due to the tumor growth, the chemotherapy was switched to paclitaxel and cetuximab combination therapy. Thereafter, the skin lesions gradually disappeared after treatment with topical corticosteroid ointment within four months.

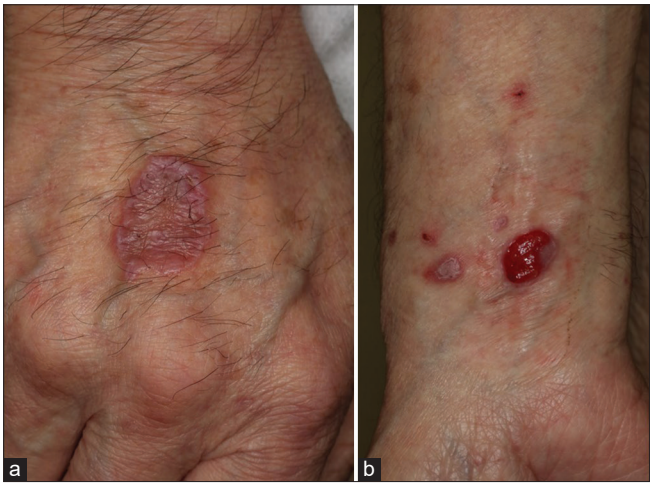

Figure 1: Clinical appearance of a) the annular plaque on the dorsum of the hand, b) and plaque and ulcerative lesions on the flexor aspect of the forearm (arrow).

LP or LP-like eruptions frequently occur on the trunk and extremities, with a mean time of 6 to 12 weeks after the initiation of ICI therapy [1]. By contrast, our case developed LP nearly one year after therapy initiation. Our case may indicate that LP or LP-like lesions may occur even at a late phase of ICI treatment. In a cohort study at a single institution, lichenoid reactions were observed in 14 of 82 patients (17%) with metastatic melanoma who received anti-PD-1 therapy [2]. Lichen mucosa and nail LP have sometimes been reported. Rare phenotypes, such as annular, hypertrophic, erosive, and bullous LP, have been observed; however, ulcerative LP is extremely rare in ICI therapy [3].

The main pathogenesis of LP is epidermal basal layer damage caused by autoreactive cytotoxic CD8+ T-cells mediated by interferon-γ (IFN-γ). In murine *in vivo* models of LP, abundant expression of PD-L1 in

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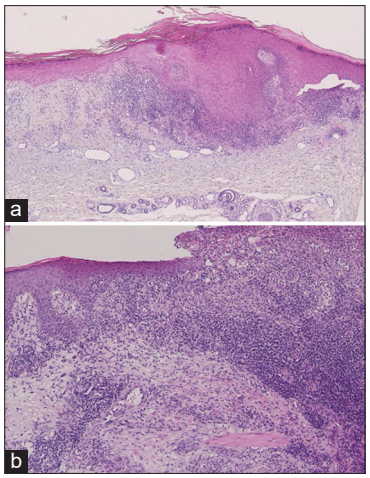

Figure 2: a) Histopathological examination of the annular plaque showing wedge-shaped acanthosis of the epidermis, individual cell keratinization, and interface change of the epidermis with mononuclear cell infiltration. b) Histopathological examination of the ulcerative lesion showing a lack of epidermis and a dense infiltration of mononuclear cells in the upper-to-mid-dermis.

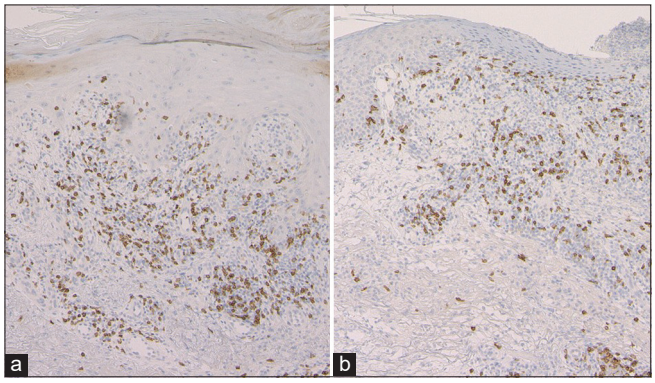

Figure 3: CD8-positive T-cells infiltrating within and below the epidermis of a) the annular plaque and b) the ulcerative lesions.

keratinocytes plays a protective role against cytotoxic CD8+ T-cells [4], which suggests that the blockade of the PD-1/PD-L1 pathway may induce epidermal damage by cytotoxic T-cells. *In vitro* studies have shown an increased production of IFN-γ from peripheral blood mononuclear cells in patients who developed oral LP after anti-PD-1 antibody administration [5]. Other studies showed elevated mRNA levels of IFN-γ and granzyme B after nivolumab treatment [6], suggesting that such molecules induce interface changes and epidermal damage. Ulcerative changes in the present case may have been attributable to extensive epidermal damage caused by CD8+ T-cells, mediated by IFN-γ, granzyme, and other molecules activated by PD-1 inhibition.

Consent

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

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Our Dermatology Online

Case Letter

Fingernail psoriasis versus onychomycosis: The value of dermoscopy

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Sir,

Onychomycosis is the most common nail infective disorder, affecting the toenails more frequently than the fingernails, with the most causative fungal agents being dermatophytes, such as *Trichophyton rubrum* and *Candida albicans*, respectively [1,2]. Psoriasis is a frequently encountered skin disease with nail involvement occurring in 80% of the patients, among which 5–10% may have isolated nail disease. It has been suggested that fungal nail infection is more frequent in patients with nail psoriasis, yet results in the literature remain controversial [1,3]. The differential diagnosis may be a significant challenge due to numerous identical clinical signs, the high prevalence, and the possible coexistence of the two diseases. Dermoscopy has proven to be a good asset in helping to make the distinction and properly treat patients, especially atypical refractory cases [4]. Herein, we report the case of a young female patient with an association of fingernail onychomycosis and psoriasis.

A 23-year-old female patient presented with a history of diffuse fingernail lesions evolving for two years and treated as onychomycosis after the identification of *T. rubrum* in the culture of a nail sample. The patient received terbinafine at a dose of 250 mg per day for six months with no improvement. A clinical examination revealed diffuse onycholysis of the fingernails surrounded by salmon patches defining the oil drop sign and diffuse subungual hyperkeratosis (Fig. 1). Dermoscopy showed yellowish onycholysis with a jagged edge and spiky structures associated with a ruin appearance of the distal free edge characteristic of fungal origin, yet also an oil drop sign with a salmon border around the edge of the same fingernail, highly suggestive of psoriasis (Fig. 2). An examination of the right index finger revealed onycholysis with a sinuous edge, no strikes, and diffuse salmon-pink patches, concluding to an association of nail psoriasis with onychomycosis. This could eventually explain the occurrence of *T. rubrum* infection in the fingernails, which is usually found in the toenails, as nail psoriasis may contribute to the development of atypical fungal infection. An examination of the rest of the body revealed an erythematous, squamous plaque in the occipital area that the patient had never noticed, confirming the diagnosis of associated psoriasis. Treatment with antifungal oral

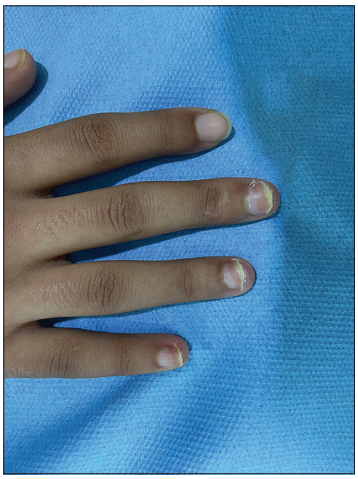

Figure 1: Diffuse onycholysis of the fingernails surrounded by salmon patches defining the oil drop sign and diffuse subungual hyperkeratosis.

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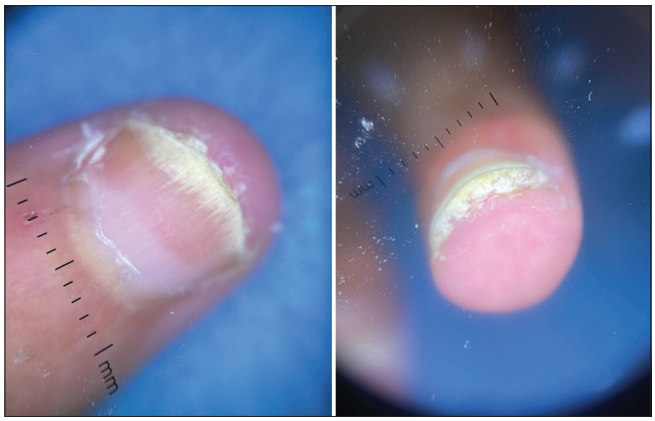

Figure 2: Dermoscopy revealing yellowish onycholysis, a jagged edge, and spiky structures, an oil drop sign with a salmon border around the edge of the same fingernail (left); distal free edge dermoscopy showing a ruin appearance (right).

therapy was continued along with the application of topical steroids.

Consent

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Our Dermatology Online

Case Letter

What does a clown's nose reveal?

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Sir,

Numerous diseases may cause a reddish swelling on the tip of the nose yet do not produce a lump. A clown's nose (CN) is a condition characterized by a rapidly growing mass resembling a clown's false red nose, which invariably suggests the presence of usually secondary and rarely primary malignancy. This localization requires careful excision with impeccable preoperative, intraoperative, and postoperative scar planning in order to obtain an acceptable aesthetic result. Herein, we report the case of a patient with a clown's nose appearance revealing a giant primary cutaneous squamous cell carcinoma.

A 65-year-old patient with no pathological history consulted for an enlargement of the nose present for a year. An examination revealed a red, fixed mass of 4 cm, surmounted by scales at the level of the nose in endonasal extension (Fig. 1a). On dermoscopy, an erythematous background, tree-trunk vessels, scales, and keratin were present (Fig. 1b). An initial skin biopsy revealed granulomatous dermatitis with reactive lymphocytic infiltrate. In view of the endonasal component and the clinical appearance, a second biopsy was performed, suggesting nasal T-cell lymphoma, granulomatous rosacea, and mucocutaneous leishmaniasis, the results of which were in favor of squamous cell carcinoma (SCC). An extension assessment comprising ultrasound of the lymph nodes and cerebral, thoracic, and abdominal scans were unremarkable, and the patient benefited from an enlarged excision with healthy margins associated with scar support based on local care (Fig. 2), antibiotic therapy orally, and healing cream until healing. Then, adjuvant radiotherapy sessions were performed to allow the reconstruction procedure, yet the patient refused the procedure.

A clown's nose (CN) is usually due to pulmonary, metastatic breast cancer or other diseases, rarely due to primary neoplasms such as squamous cell and basal cell carcinoma [1]. Several articles describe what may be defined as a CN [2,3]. Generally, the CN is due to a cutaneous metastasis of a known lung or breast cancer, of which only a histological examination makes it possible to distinguish these secondary malignancies from primary cutaneous squamous cell or basal cell carcinomas.

In only one article, the cause was a basal cell carcinoma [4] and, in another, a squamous cell carcinoma [5]. Our patient was the second case in which an SCC was involved. SCC usually affects elderly patients with a personal history of excessive sun exposure and fair skin types, as was the case of our patient.

Recently, Zhao et al. divided the CN into three groups: metastatic solid tumors, genetic diseases, and diseases involving the nasal tip. The clown's nose appearance is an indirect sign of the development of neoplasia [1].

Tumor-related tissue reactions leading to the formation of epithelioid cell granulomas have been known for almost seventy years. Such reactions may occur in the lymph nodes draining an area harboring a malignant tumor, in the tumor itself, and even in non-regional tissues [6]. They occur in 4.4% of carcinomas. Most likely, they are due to antigenic factors derived from tumor cells, causing an immunological hypersensitivity reaction leading to the formation of epithelioid cell granulomas [7]. It may be a good prognostic marker of the antitumor response against metastatic extension. In our case, the first biopsy showed a granulomatous reaction with a negative extension assessment.

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Figure 1: (a) Giant tumor on the nose topped with scales (b) Dermoscopy showing fundus erythematous, keratin, tree-trunk vessels.

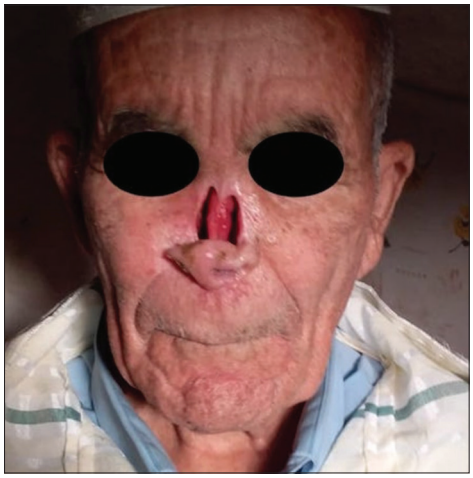

Figure 2: Clinical aspect after surgical excision.

Finally, a multidisciplinary approach involving dermatologists, maxillofacial/plastic surgeons, oncologists, and radiotherapists is also recommended for minor cutaneous malignancies in order to obtain optimal and aesthetic results.

Consent

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

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

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Our Dermatology Online

Case Letter

Lyell's syndrome: Exceptional dermatosis in an infant

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Sir,

Lyell's syndrome is a serious, acute, life-threatening condition, rare in the pediatric population [1], characterized by skin detachment of more than 30% of the body surface area, with at least two mucous membranes involved [1,2]. It is considered a hypersensitivity reaction to numerous types of drugs, primarily anticonvulsants, antibiotics, and nonsteroidal anti-inflammatory drugs [2]. Infections particularly with *Mycoplasma pneumoniae* may also act as potential co-factors in the pediatric population [2,3]. The diagnosis is often clinical [1]. A skin biopsy is not always required in young children or if the diagnosis is obvious and encounters complete epidermal necrosis [3]. Treatment is based on the immediate discontinuation of the offending drug, prompt admission to the intensive care unit, and local care [3]. Specific treatment in children is controversial, with a lack of clinical trials, and includes systemic corticosteroids and intravenous immunoglobulin [1,3,4]. Short-term sequelae are often related to mucosal involvement dominated by synechiae [4]. Long-term complications may occur, mainly ocular, such as dry eye syndrome, genitourinary, pulmonary, and renal. Thus, long-term monitoring must be instituted [5]. Finally, raising public awareness and educating the public about the harmful effects of self-medication may help decrease the occurrence of severe cutaneous drug reactions in children [6].

Herein, we report the case of a nine-month-old infant followed for epilepsy secondary to congenital hydrocephalus. Five days before the admission, he presented a pruritic cutaneous eruption with the appearance of liquid lesions 48 hours later on the lower limbs and the face, following treatment with sodium valproate and carbamazepine with a delay of one month for the former and fifteen days for the latter. A general examination revealed an apyretic infant. A dermatological examination revealed multiple vesicular bullae and blisters on the legs, thighs, and cheeks with a positive Nikolsky sign and maculo-papular exanthema on the rest of the body (Fig. 1a). The skin area affected was

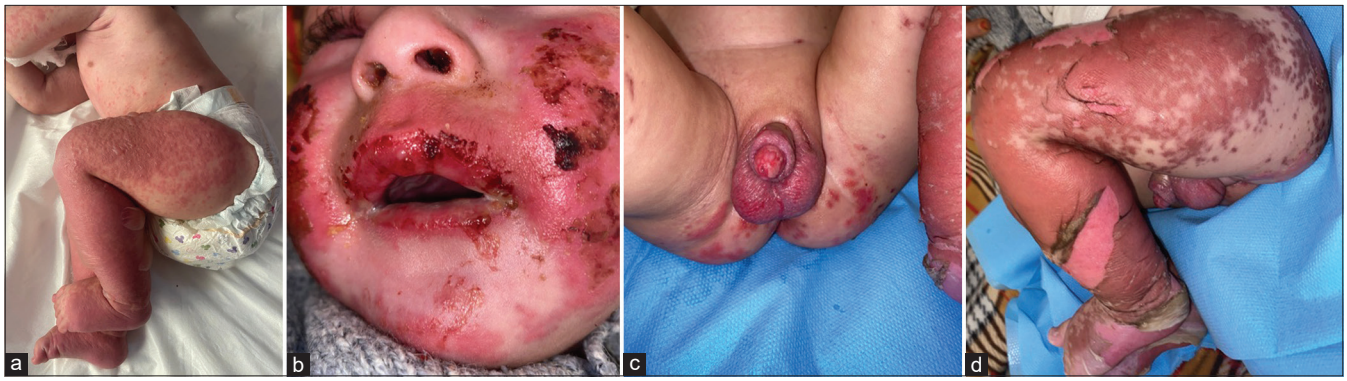

Figure 1: (a) Maculo-papular exanthema with multiple vesicular bullae and blisters on the legs and thighs. (b-c) Severe mucosal damage. (d) Skin detachment with a wet linen appearance.

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initially estimated to be 25%. The ocular, oral, nasal, and genital mucosa were affected as well (Figs. 1a - 1c). After hospitalization, a biological checkup revealed creatine phosphokinase (CPK) three times the normal value, CPK mb five times the normal value, with C-reactive protein (CRP) at 33 mg/L and negative procalcitonin. A skin biopsy was not taken. Both drugs were stopped immediately and replaced by levetiracetam and clobazam. On the next day, the skin surface area was extended to 35% with a wet linen appearance (Fig. 1d). The diagnosis of Lyell's syndrome was retained. The infant was put on rehydration, josamycin, local care, dermocorticoids for the skin lesions, a healing cream for the mucous lesions, and an antihistamine. A pharmacological investigation revealed the imputability of carbamazepine treatment. The evolution was favorable, with regression of the lesions without the appearance of short-term complications such as synechiae.

Consent

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Our Dermatology Online

Case Letter

Actinic keratosis of the eyelid: What management to avoid degeneration?

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Sir,

Actinic keratoses (AKs) appear on sun-exposed skin areas and are considered one of the clinical signs of cutaneous photoaging. They often present as multiple lesions that are rarely unique [1]. They are associated with considerable morbidity which may be decreased if detected and treated early. It has been shown that the risk of developing non-melanoma skin cancer is increased more than sixfold in patients with AK [2]. Dermoscopy is a rapid, non-invasive method that helps in the early diagnosis of AK, which may show erythema forming a reddish-pink vascular pseudo-network surrounding the hair follicles described as the strawberry-like pattern, yellowish-white scales, fine, wavy vessels surrounding the follicles, and follicular openings filled with keratotic plugs [3]. To treat AK and avoid the risk of degeneration, a variety of surgical and non-surgical treatments, such as cryotherapy, topical chemotherapy, chemical peels, laser therapy, and photodynamic therapy may be offered [4]. Some locations represent a therapeutic challenge, particularly in the eyelids. Indeed, on the one hand, surgical treatment, which is recognized for its effectiveness, must be performed with particular care and may be responsible for a functional alteration, ectropion with a constant risk of recurrence [1]. On the other hand, non-surgical treatments, which are often employed by dermatologists, have also shown their efficacy, yet with the possibility of side effects, such as skin erythema, superficial punctate keratitis, and conjunctival hyperemia, often leading patients to stop the treatment [2]. Generally, a large excision with reconstruction remains the method of choice to treat AK of the eyelid and to avoid an evolution toward a squamous cell carcinoma. Non-surgical treatments have also shown satisfactory results. Studies regarding the efficacy and safety of different treatments of AK are needed to determine the optimal treatment of AK in the eyelid and periocular region in order to prevent heavy functional and aesthetic ocular consequences [1]. Herein, we report the case of a patient who presented an AK of the eyelid with a dramatic evolution.

A seventy-year-old female patient, without any pathological history, presented with an erythematous lesion of the upper right eyelid evolving for one year. The patient consulted the dermatologist, who performed a skin biopsy in favor of actinic keratosis. She was treated with cryotherapy with burning and irritation at the palpebral level, which led the patient to stop the sessions. Six months later, she noted an increase in the size of the lesion with redness and tearing of the eye motivating her consultation with the ophthalmologist, who put the patient under several topical treatments without improvement, then the patient was referred to us for further management. An examination revealed an erythematous plaque on the upper right eyelid with a crusty ulceration in the center (Fig. 1). We noted an infiltration associated with erythema at the level of the free edge of the upper eyelid, the lower eyelid, and the internal cantus of the eye. Dermoscopy revealed irregular, linear vascularization with hairpin vessels, scales, and keratin (Fig. 2). The patient reported ocular discomfort with pruritus and lacrimation. The rest of the examination was normal. A biopsy was performed on our patient and found an invasive, poorly differentiated, non-keratinizing squamous

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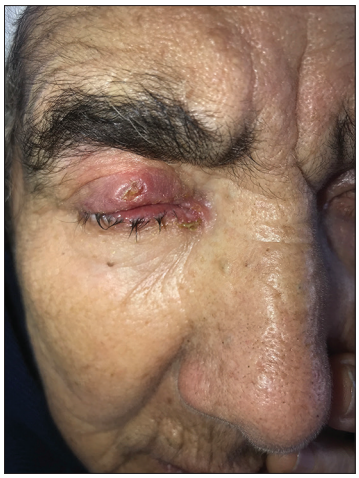

Figure 1: Clinical picture: erythematous plaque on the upper right eyelid with a crusty ulceration in the center.

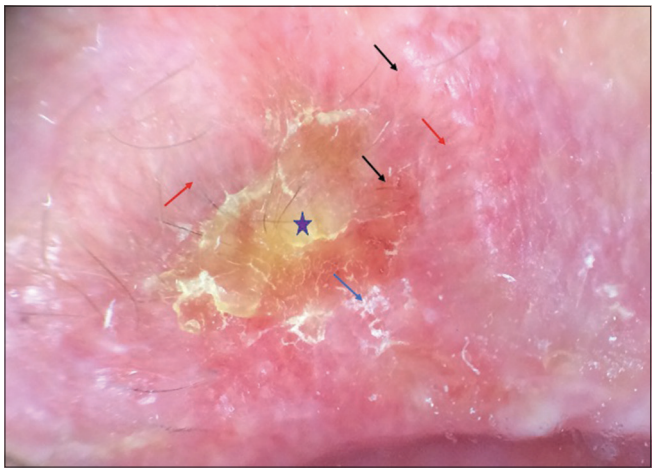

Figure 2: Dermoscopic picture: irregular, linear vascularization (black arrows) with hairpin vessels (red arrows), scales (blue arrow), and keratin (purple asterisk).

cell carcinoma. A locoregional and distant extension assessment was normal and we referred the patient to the ophthalmologist, who performed the exenteration of the eye.

Consent

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