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- Impact of the COVID-19 pandemic on monitoring people living with HIV in Dakar, Senegal;

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- Beneficial properties of olive tree leaves concerning personal care ingredients: Herbal tincture;

- Pemphigus and cancer: A single-center experience over 30 years in Morocco;

- Atopic dermatitis associated with tropical endemic limbo-conjunctivitis: Epidemiology, clinical phenotypes, and allergological investigations;

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- Evaluation of the therapeutic efficacy of topical 50% hydrogen peroxide vs. 100% trichloroacetic acid vs. 5% 5-fluorouracil in the treatment of warts;

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Original Article

Impact of the COVID-19 pandemic on monitoring people living with HIV in Dakar, Senegal

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ABSTRACT

Background: The COVID-19 pandemic has had a considerable impact on chronic disease monitoring. Previous work has asserted that people living with HIV (PLHIV) are at risk of developing COVID-19 and have difficulty accessing care and antiretroviral (ARV) treatment. The aim of this study was to determine the prevalence of HIV/COVID-19 co-infection and vaccination and to assess the impact of the pandemic on the follow-up of PLHIV and on their psychosocial and economic lives. **Materials and Methods:** This was a cross-sectional, multicenter study conducted from August 16, 2021, to October 10, 2021, at two dermatology departments of Dakar. We included all PLHIV followed at these two services during the study period. **Results:** We identified 57 cases of PLHIV. The hospital frequency was 6.44%, the mean age was 46, and the sex ratio was 0.54. The prevalence of COVID-19 infection was 14.1%. All cases had a mild clinical form of COVID-19, outpatient management, complete remission, and no deaths were noted during the follow-up. Viral load was available and undetectable in 25%. All patients co-infected with HIV/COVID-19 were on antiretroviral therapy. The prevalence of PLHIV vaccinated against COVID-19 was 31.6%. During the COVID-19 pandemic, 28.1% of cases missed their appointments. 96.5% of cases accessed to ARV treatment. However, 3.5% of PLHIV stopped their ARV treatment for reasons unrelated to the COVID-19 pandemic. Opportunistic infections were present in 31.6% of cases, with a significant impact on psychological (64.9%), social (45.6%), and economic (71.9%) well-being, as well as on quality of life in 59.6% of cases. **Conclusion:** The COVID-19 pandemic and its health measures have had a major impact on the follow-up and quality of life of people living with HIV. The reinforcement of therapeutic education, barrier measures, and COVID-19 vaccination seem to contribute to improving the quality of life of PLHIV.

Key words: HIV, COVID-19, Psychosocial impact

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major public health problem. In 2020, there was an estimated 37.6 million HIV-positive people in the world, 27.4 million of whom was estimated to have access to antiretroviral (ARV) treatment [1]. In Africa, there was an estimated 25.3 million people living with HIV (PLHIV) in 2020, 18.5 million (73.1%) of whom had access to ARV treatment. In Senegal, an estimated 39,400 people were living with HIV in 2020. The HIV epidemic was widespread, with low prevalence in the general population and high prevalence in certain localities and among the most vulnerable populations [2]. The advent of the COVID-19 pandemic led to considerable disruption of health services in many countries, with people restricted in their movements and care suspended. Elderly people and those with chronic illnesses such as HIV were exposed to severe manifestations of COVID-19 [3]. These resource-limited countries have inadequate healthcare infrastructures, which could increase the risk of COVID-19-related mortality [3,4]. The COVID-19 pandemic and its sanitary measures led to

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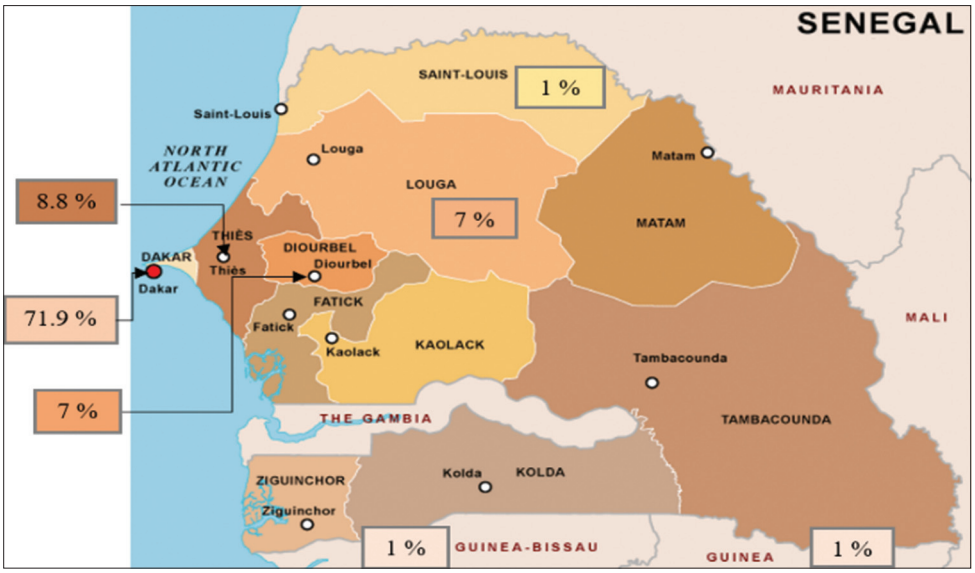

Figure 1: Distribution of the patients by geographic origin.

disruptions in health services, particularly in centers for monitoring and caring for people living with HIV. The consequences were a reduction or suspension of care and supply of antiretroviral drugs in some countries [5]. The pandemic also had a psychosocial and economic impact on patients' quality of life. The most commonly reported consequences were depression, reduced food security, and economic decline [6]. The aims of our study were to determine the prevalence of COVID-19 infection in PLHIV and to assess the psychological, social, and economic impact of COVID-19 on people living with HIV.

MATERIALS AND METHODS

This study was transversal and multicentric and was conducted at the dermatology departments of Aristide Le Dantec Hospital and the Hygiena Sociale Institute for about two months (from August 16, 2021, to October 10, 2021). All PLHIV followed at these two departments during the period were included. HIV infection was confirmed by retroviral serology and COVID-19 infection by polymerase chain reaction. Data was collected using a survey form that recorded socio-professional and medical data concerning the usual follow-up of HIV and COVID-19 infection. Data was processed with Epi-Info 7 and analyzed with SPSS Statistics 26.

RESULTS

We identified 57 patients living with HIV, representing a hospital frequency of 6.4%. The mean age was 47 years, with extremes of 25 and 69 years. The 40–60

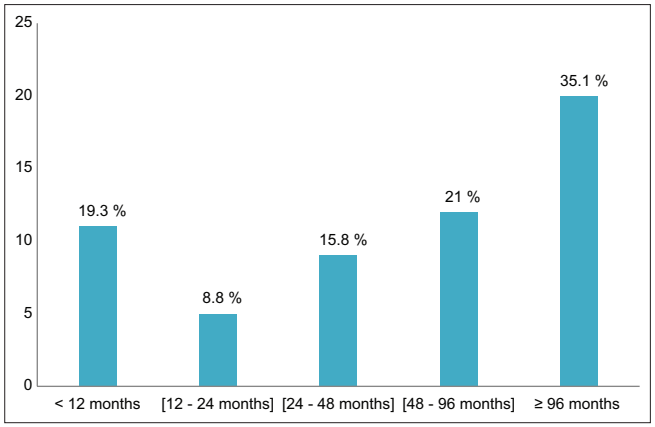

Figure 2: Follow-up duration of the PL HIV.

age group was the most represented. The sex ratio was 0.5. The majority of PLHIV were shopkeepers (24.6%) and housewives (37%). Socioeconomic status was low to medium in 87.8% of the cases. The geographical origin (Fig. 1) of the patients was 55 cases from Senegal, one case from Guinea Conakry, and one case from Guinea Bissau. The patients' serological status was 89.5% in HIV1 and 10.5% in HIV2. Fig. 2 shows the average length of follow-up. The causes of HIV infection were 49.2% from infectious diseases, 26.4% from inflammatory dermatoses, and 15.6% from screening (Table 1). Viral load was undetectable in 24.5%. Other HIV-associated sexually transmitted infections were noted in 14 cases (Table 2). Table 3 illustrates antiretroviral treatment administered to the patients according to national protocols. HIV infection was associated with COVID-19 infection in 14.1% of cases. All PLHIV had a mild form of COVID-19 symptoms with outpatient management and complete remission.

Table 1: Circumstances of HIV discovery

Circumstances of HIV discovery	N	%	N (%)
Screening			
Spouse	5	8.4	9 (15.6%)
Health check	1	1.8	
Prenatal consultation	1	1.8	
Blood exposure			
Blood sampling	1	1.8	
Tattoo	1	1.8	
Inflammatory diseases			
Prurigo	12	21	15 (26.4%)
Lichen planus	1	1.8	
Generalized pruritus	1	1.8	
Erythrodermic Psoriasis	1	1.8	
Infectious diseases			
Viral			
Herpes zoster	17	29.8	28 (49.2%)
Kaposi's disease	3	5.2	
Genital warts	2	3.5	
Chickenpox	1	1.8	
Flu syndrome	1	1.8	
Bacterial			
Scrofuloderma tuberculosis	2	3.5	
Pyoderma	1	1.8	
Fungal			
Ringworm of the scalp	1	1.8	
Other			
Alteration of general state	2	3.5	5 (8.8%)
Chronic diarrhea	2	3.5	
Leg ulcer	1	1.8	
Total	57	100	

Table 2: HIV-associated co-infections

HIV-associated co-infections	Number	Percentage (%)
Hepatitis B virus	4	28.7
Hepatitis C virus	2	14.3
Genital warts	2	14.3
Syphilis	2	14.3
Genital herpes	1	7.1
Trichomonas vaginalis	1	7.1
Urogenital mycoplasma	1	7.1
Gonorrhea	1	7.1
Total	14	100

Table 3: Antiretroviral treatment protocol

ART Protocol	Type of HIV		Total
	HIV 1 n (%)	HIV 2 n (%)	
First line treatment Tenofovir 300 mg Lamivudine 300 mg Dolutegravir 50 mg	47 (83)	6 (10)	53 (93%)
Second line treatment Tenofovir 300 mg Lamivudine 300 mg Lopinavir/ritonavir	2 (3.5)		2 (3.5)
ART stopped	2 (3.5)	0	2 (3.5)
Total	51 (100)	6 (10)	57 (100)

The rate of vaccination of PLHIV with COVID-19 was noted to be 31.6% (Table 4). Adverse events were noted in 27.3% of the cases. The reasons for refusing vaccination are shown in Table 5. In terms of regular follow-up, missed appointments were noted in 28.1% of the cases. Duration of follow-up was less than one month in 62.2% of the cases, between 2 and 6 months in 25.2%, and over 10 months in 12.6%. The reasons for missed appointments were related to COVID-19 in 37.6% of the cases (Table 6). Access to ARV treatment was assured in 96.5% of the cases. The occurrence of opportunistic infections was noted in 31.6% of the cases. Psychological impact was noted in 64.9% of the cases, with anxiety and depression associated with suicidal ideation. Table 7 shows the distribution of patients according to psychological impact. Psychological support was provided by experienced psychiatrists in 94.7% of the cases. On the social front, 45.6% of the patients had a worsening perception of loneliness. The reasons were stigmatization, social isolation, financial difficulties linked to COVID-19, and psychosocial stress. On the economic front, financial difficulties were noted in 41 cases. This included loss of employment reduced monthly income and expensive hospitalization costs. Quality of life was impaired in 34 cases (59.6%), with mood disorders and stress. Alcohol and cigarette abuse were noted in two cases.

DISCUSSION

We report the first study to assess the psychosocial and economic impact of COVID-19 on the follow-up of PLHIV at dermatological care centers Senegal. The majority of studies have been conducted in developed countries [7-14]. The limitation of our study was our small sample size, which was linked to the reduced number of consultations during the COVID-19 pandemic. Nevertheless, we noted a 14.1% prevalence of COVID-19 infection among people living with HIV. We noted a higher frequency of COVID-19 in PLHIV compared with previous studies reported in the literature (Table 8). In our series, the clinical form of COVID-19 disease was mild in all patients. No severe forms were noted. The patients were managed on an outpatient basis. Several studies have reported that COVID-19-related mortality in PLHIV does not differ from that in the general population [18-20]. The high mortality rate reported in other studies seems to be linked to the advanced age of PLHIV, the existence of several co-morbidities, a high plasma viral load, and irregular intake of antiretroviral treatment [18-20]. In our study, PLHIV infected with COVID-19 had an average age of 45 years, with no sex predominance.

Table 4: COVID-19 vaccination profile of the PLHIV

Type of vaccine	n	Number of doses		Side effects			
				No	Yes		
		1	2		Fever	Pain at the injection site	Both
AstraZeneca	8	0	8	6	1	1	0
Janssen	3	3		1	0	2	0
Sinopharm	7	3	4	6	0	0	1
Total	18	6	12	13		5	

Table 5: Reasons for not vaccinating the PLHIV

Reasons for not vaccinating PLHIV	N	%	N (%)
Hesitation			
Fear of side effects of vaccination	12	30	30 (76.9)
Waiting for my doctor's advice	7	17	
Difficulty accessing the vaccine	6	153	
Fear of the effects of the vaccine on my disease	3	7	
Queue (fear of contracting COVID-19)	1	2.6	
Husband refuses	1	2.6	
Fear of combining the vaccine with my medication	0	0	
Refusal			
Not convinced of the usefulness of the vaccine	8	20.5	9 (23.1)
Pregnancy	1	2.6	
Total	39	100	

Table 6: Reasons for missed appointments

Reasons for the missed appointment	n	%
Related to COVID-19	6	37.6
Travel difficulties related to COVID-19	4	25
Fear of going to hospitals	1	6.3
Economic hardship related to COVID-19	1	6.3
Difficulty obtaining an appointment related to COVID-19	0	0
Not related to COVID-19	10	62.4
Climate (rain)	3	18.3
Death/illness of a parent	2	12.6
Religious festival	2	12.6
Poor treatment compliance	2	12.6
Summoned to Court	1	6.3
Total	16	100

Table 7: Type of psychological impact of the pandemic on people living with HIV

Type of psychological impact	n	%	Total	
			n	(%)
Acute				
Anxiety (anxiety attack)	2	5.4	7	18
Anguish + insomnia	5	13.5		
Chronic				
Anxiety	27	73	30	81
Anxiety + depression	2	5.4		
Depression + suicidal ideation	1	2.7		
Total	37	100	37	100

Table 8: Prevalence of COVID-19 infection among people living with HIV

Authors	Year	City/ Country	Number of case	Prevalence of COVID-19
Our study	2021	Dakar	57	14.1%
Vizcarra [10]	2020	Madrid	1339	3.8%
L. Bronner [15]	2021	France	421	5.5%
Guo W. [8]	2020	China	1174	0.7%
Jose M. Miró [16]	2020	Barcelona	5649	0.7%
Narda M. [17]	2021	Guatemala	3677	1.2%
Hadi Yousaf [18]	2020	United States	404	19.3%

These results were similar to those reported in the literature [13,21,22,26]. Viral load was available and undetectable in 25% of PLHIV with COVID-19 infection. Some authors report that PLHIV who are on antiretroviral treatment and have a satisfactory immuno-virological status do not present a higher risk of severe COVID-19 infection. Their prognosis was identical to that of the general population with the same comorbidities. However, close monitoring of viral load at one month of COVID-19 infection is questionable in these patients [23].

Vaccinated PLHIV represented 31.6%, among which 83.3% had completed their vaccination dose. AstraZeneca, Sinopharm, and Janssen vaccines were used due to their availability in our country. Side effects of vaccination in PLHIV were present in 27.3% of the cases, with most minor. The choice of vaccination was influenced by misinformation spread through social networks, collective denial, and religious beliefs. The low rate of PLHIV vaccinated at the beginning of the COVID-19 vaccination campaign could be explained by the difficulty in access to vaccines [4]. In our series, the rate of PLHIV vaccinated gradually increased thanks to the availability of vaccines and awareness campaigns. Concerning the impact of the COVID-19 pandemic on the follow-up of PLHIV, we noted that 28.1% were absent from appointments. Motivations were unrelated to the COVID-19 pandemic in 62.4% of the cases, and those related to COVID-19 were attributed to health restrictions on inter-city travel, hospital phobia, and financial difficulties linked to COVID-19. Some authors report that the implementation of telemedicine ensured continuity of patient care during a pandemic and reduced the risk of exposure to COVID-19 [24]. The circumstances of transmission of HIV infection were dominated by skin manifestations in 75.6% and screening in 15.6%, which is in line with the literature. Psychologically, there was an impact on the mental

health of PLHIV in 64.9% of the cases. These results were also reported in the U.S. and Peru [25-27]. In Senegal, psychological support was provided in 94.7% of cases. Socially, the perception of loneliness increased in 45.6% during the pandemic. In Peru, the prevalence of perceived loneliness, stigmatization, and rejection increased by over 50% [28]. An economic impact was noted in 71.9%. In Indonesia, many patients lost their jobs as a result of COVID-19 [5]. In Peru, 71% of the economically active population was forced to accept informal jobs with no fixed salary [29]. The quality of life of PLHIV was impaired in 59.6%. Isolation, unemployment and financial loss had a negative impact on the quality of life of PLHIV. In our study, 3.5% of patients used tobacco and alcohol to cope with stress. Tobacco and alcohol abuse were also reported by some authors during the COVID-19 pandemic [25,30].

CONCLUSION

The COVID-19 pandemic has had considerable repercussions on the follow-up of patients living with HIV in Senegal. A psychosocial and economic impact was noted in the study. Multidisciplinary management and therapeutic patient education helped to improve the patients' quality of life and ensure continuity of care. Sentinel epidemiological surveillance in terms of virology proves useful in preventing such endemics.

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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Original Article

Chronic dermatoses and quality of life: A prospective study on 127 cases at the National Hospital of Niamey, Niger

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ABSTRACT

Background: Chronic dermatoses are frequent, particularly in sub-Sahelian countries. Most are not life-threatening, yet often have a major impact on the psychological state of the patient and their social relationships, daily activities, and quality of life. **Materials and Methods:** For this, we conducted a cross-sectional, descriptive, and analytical study on patients aged fifteen or older with chronic dermatoses, followed at the Department of Dermatology and Venereology of the National Hospital of Niamey from January 1 to June 30, 2017 (for a period of six months). **Results:** There were a total of 127 patients. We employed the Dermatology Life Quality Index (DLQI) to measure the quality of life of the patients. The aim of our study was to improve the quality of life of patients suffering from chronic dermatoses by the use of the DLQI score. **Conclusion:** Chronic dermatoses are frequent in our context. They have an impact on the quality of life of the patients, as evidenced by our study.

Key words: Chronic dermatoses, Quality of life, DLQI score, Niamey, Niger

INTRODUCTION

Chronic dermatoses are frequent, particularly in sub-Sahelian countries. Most are not life-threatening yet often have a major impact on the psychological state of the patient and their social relationships, daily activities, and quality of life. The aim of our study was to identify the impact of chronic dermatoses on the quality of life of patients aged fifteen and older at the Department of Dermatology Venerology of the National Hospital of Niamey, Niger. Thus, we employed the Dermatology Life Quality Index (DLQI) to measure the quality of life of the patients. It is based on ten questions rated from 0 to 3 relating to pruritus, general discomfort, interference with clothing, hobbies, sport, sexuality, and work. The DLQI score is obtained by summing the scores assigned to each question. It varies from 0 (best quality of life) to 30 (most impaired quality of life) [1-3].

RESULTS

During the study, 127 patients had chronic dermatoses out of a total of 504 patients consulted (25.19%). The average age was 33.38 years, and the age groups of 15–24 years and 25–34 years accounted for 59.08%. Females constituted 57%, giving a male-to-female ratio of 0.76. Living in the urban environment was noted in 88.18%, and 37.79% of the patients

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had reached high school education. Civil servants accounted for 23.62%. The socioeconomic level was average in 67.71% (Table 1). Inflammatory dermatoses predominated in 44.08%, and acne was the most frequent pathology (28.44%) (Table 2). The average duration of the disease was 3.22 years, and in 53.54% of the cases, the evolution was shorter than one year (Table 3). Systemic treatment associated with topical application was performed in 58.26% (Table 4). The average DLQI score was 7.08, reflecting a moderate deterioration in quality of life in 40.94% of the cases (Table 5). This alteration was moderate in both sexes equally. There was no statistically significant link between sex and quality of life ($p = 0.39$). Quality of life was more impaired from the age of 65 years, with an average DLQI of 12.14. There was a statistically significant link between patient age and quality of life ($p = 0.00$) (Table 6). However, while looking for the relationship between age and the DLQI score according to sex, we noted that quality of life was impaired in females after the age of 55 years ($p = 0.01$) and in males after the age of 65 years ($p = 0.00$). Quality of life was more impaired with a statistically significant link among farmers ($p = 0.006$), patients with no schooling ($p = 0.014$), those from rural areas ($p = 0.00$), those of low socio-economic level ($p = 0.003$), patients with autoimmune dermatoses (systemic scleroderma, systemic lupus, pemphigus vulgaris) ($p = 0.00$), those whose disease duration exceeding ten years ($p = 0.00$), and those performing a systemic treatment associated with topical application ($p = 0.00$).

Table 1: Distribution of the 127 patients according to sociodemographic characteristics.

Sociodemographic characteristic	Number	Percentage (%)
Age (yrs.)		
15–24	37	29.13
25–34	38	29.95
35–44	27	21.25
45–54	12	9.44
55–64	6	4.72
≥65	7	5.51
Sex		
Male	55	43
Female	72	57
Origin		
Urban	112	88.18
Rural	15	11.82
Education level		
Unschooled	17	13.38
Primary school	17	13.28
High school	48	37.79
College	36	28.37
Koranic school	9	7.08
Profession		
Official	30	23.62
Trader	11	8.66
Farmer	7	5.01
Unemployed	4	3.14
Student	20	15.70
Pupil	21	16.53
House wife	27	21.05
Retired	2	1.57
Other*	5	4.72
Marital status		
Married	63	49.60
Single	56	44.09
Divorce	5	3.95
Widower	3	2.36
Socioeconomic level		
High	5	3.95
Average	86	67.71
Low	36	28.34

Table 2: Distribution of the 127 patients according to clinical diagnosis.

Clinical diagnosis	Number	Percentage (%)
Autoimmune disease	*n*=13	10.2
Systemic scleroderma	4	3.14
Lupus erythematosus	4	3.14
Behçet's disease	1	0.78
Pemphigus vulgaris	4	3.14
Inflammatory dermatoses	N=56	44.08
Atopic dermatitis	27	21.27
Psoriasis	6	4.72
Lichen planus	13	10.23
Chronic urticaria	9	7.08
Erythroderma	1	0.78
Tumor dermatoses	N=3	2.36
Recklinghausen's neurofibromatosis	1	0.78
Keloid disease	2	1.57
Dyschromia	N=12	9.44
Ochronosis	3	2.36
Vitiligo	9	7.08
Adnexal pathology	N=38	30
Acne	36	28.44
Trichoepithelioma	1	0.78
Alopecia areata	1	0.78
Other*	N=5	3.93
Post-zoster pain	5	3.93

Table 3: Distribution of the 127 patients according to the duration of evolution.

Duration (Yrs.)	Number	Percentage (%)
≤ 1	68	53.54
2–5	40	31.49
6–10	12	9.46
>10	7	5.51
Total	127	100

Table 4: Distribution of the 127 patients according to the type of treatment.

Type of treatment	Number	Percentage (%)
Topical	21	16.53
General route	23	18.14
General route+topical	74	58.26
Surgery	1	0.78
Cryotherapy	1	0.78
No treatment	7	5.51
Total	127	100

Table 5: Distribution of the 127 patients according to DLQI score.

DLQI Score	Number	Percentage (%)
0–1: no effect	2	1.5
2–5: low effect	51	40.16
6–10: moderate effect	52	40.94
11–20: significant effect	19	14.95
21–30: extremely significant effect	3	2.45
Total	127	100

Table 6: Distribution of the 127 patients according to age group and DLQI score.

Age group (Yrs.)	DLQI score	*n*	Standard deviation	*p*
15–24	5.48	37	2.96	0.00
25–34	6.60	38	3.26	
35–44	8.40	27	4.2	
45–54	7.33	12	1.81	
55–64	8	6	3.13	
≥65	12.14	7	7.07	

DISCUSSION

Chronic dermatoses are frequent and their impact on quality of life (QOL) has not yet been studied in Niger, Beyond that, we did not find similar studies through our documentary review. In developing countries, epidemiological data collected on dermatological diseases comes mainly from the files of specialized center and do not necessarily reflect the real prevalence in the community, whereas dermatological problems are among the most frequent reasons for consultation in primary care, around 30% of patients in black Africa [4]. In Niger, the sociocultural context, the symbolic meaning of the disease and the religious belief mean that there is a certain fatality, which means that patients complain little. Over 90% of the population is Muslim [5]. Nevertheless, we found a statistically significant link between the sociodemographic, clinical characteristics, and quality of life of our patients. Advanced age, low level of education, precariousness, professions that expose to environmental factors, late consultation, non-compliance with treatment, and cultural influences, particularly in rural areas, are all often associated factors that alter the quality of life of patients suffering from chronic dermatoses. In our Sahel–Saharan context, most of the population lives in rural areas, with a low level of education and precarious financial means. The poorest are also the most likely to be affected by certain types of dermatoses due to higher levels of risky behavior (harmful cultural practices, unhealthy living conditions, psychosocial stress, recourse to traditional healers, self-medication) and highly limited access to quality care. In addition, they are more exposed to environmental factors (sun, wind, torrential rains), chemicals (fertilizers, herbicides), and allergens (pollen), likely to trigger or aggravate certain dermatoses. These patients are most often seen by the specialist at an advanced stage of their pathology causing complications and serious psychological and socioeconomic repercussions (disability, impoverishment, aggravation of already existing poverty, marital conflict and divorce). On the other hand, the clinical manifestations observed during autoimmune dermatoses may be disabling. This is the case for long-term scleroderma, systemic lupus erythematosus (SLE), and pemphigus vulgaris. A meta-analysis concluded that people with systemic sclerosis are part of a 15% segment of the population with the worst quality of life in terms of health [6]. Terrab, in Morocco, reported that pemphigus caused a significant alteration in health-related QOL [7]. Several studies reported that the QOL of patients with SLE is reduced in all areas assessed and that SLE has a great impact on QOL [8-11]. In our study, acne was the most frequent pathology, yet it slightly affected the patients' quality of life (average DLQI: 4.69). Acne affects the quality of life of patients regardless of age and sex, yet to different degrees. Ouédraogo et al. [12] found that there was an alteration in the QOL of acne-prone pupils in Ouagadougou and that this alteration was significant for 36.78%, average for 37.51%, and slight for 25.71%. The domains of QOL affected by acne vary according to the sociocultural context: the symbolic meaning of the disease and cultural beliefs [13,14]. In Africa, acne is readily considered a banal temporary disease, even normal; it does not appear likely to alter the quality of life, although its impact on the quality of life of patients has been well documented in several countries in Europe, America, and Asia, in particular on self-esteem and mood in adolescents [15]. The chronicity of these dermatoses and the complexity of the treatment pose the problem of therapeutic compliance as in other chronic diseases (fatigue of the patient, false impression by the patient of the mastery of the treatment). The longer the duration of follow-up, the greater is the risk of poor compliance [16,17]. These last factors are often the cause of complications, recurrences, and impaired quality of life, hence the importance of good therapeutic education.

CONCLUSION

Chronic dermatoses are frequent in our context. They have an impact on the quality of life of patients, as evidenced by our study. The factors influencing this alteration are multiple and often concomitant.

A periodic assessment of quality of life is desirable in order to improve their management. The latter must be global, sometimes requiring the cooperation of the dermatologist and psychiatrist.

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

Beneficial properties of olive tree leaves concerning personal care ingredients: Herbal tincture

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ABSTRACT

Background: The skin is essential for our survival and daily functioning. Everyday use and constant exposure to a wide range of personal care products and different types of chemicals coming from various sources may cause serious problems. Therefore, the use of natural and organic cosmetics becomes increasingly essential. The olive tree is one of the oldest cultivated fruit trees and has been used in cosmetics for centuries. This study aimed to present a method for the easy preparation of an olive tree leaf tincture that may be incorporated into a cosmetic product and reproduced in a domestic environment. **Materials and Methods:** All equipment employed was cleaned and disinfected beforehand. Fresh olive tree leaves were ground to a powder. A 20% olive tree leaf tincture was made. Olive tree leaves and alcohol were mixed in a sterilized jar. The mixture was shaken daily for two weeks. **Results:** The pH of the olive tree leaf tincture was determined with pH stripes and was in the range of 5.5 to 6.5. This may impact how much of the tincture will be used and how it will be used. For this reason, we suggest using it at a concentration of 1%. The chosen herb-to-solvent ratio of 1:5 (w/v) yielded a concentrated tincture with enhanced potency. A higher concentration of active constituents in the tincture is expected to offer a more potent and effective form of herbal extract. **Conclusion:** The findings in this study supported the potential of olive tree leaves as a valuable resource for developing natural and sustainable interventions targeting DNA damage and related health conditions. Continued research in this field will contribute to a better understanding of the therapeutic potential and applications of olive tree leaves in the field of natural cosmetics and medicine.

Key words: Olive Tree Leaves, Herbal Tincture, Natural Cosmetics, Natural Ingredients

INTRODUCTION

Our skin is a beautiful mystery, shrouded in feelings, opinions, and questions. It has a multitude of functions not covered by others, from survival to social communication. The skin is both a barrier against the outside world and a bridge to our own being. How others perceive our skin may affect our mental health. The skin is essential for our survival and daily functioning [1].

People are exposed to various chemicals in daily life, most of which occur naturally in the environment. Still, others originate from human activities and are present in food, water, and various products of daily use. Since our skin is the body's largest surface area that interacts with the external environment, it is exposed involuntarily to abiotic and biotic factors and voluntarily through personal care and cosmetic products [2]. Everyday use and constant exposure to a wide range of personal care products and different types of chemicals coming from different sources may cause the so-called "cocktail effect" due to the synergistic interaction of other substances, as well as the "additive effect" due to the presence of the same ingredient in numerous products [3]. Therefore, the use of natural and organic cosmetics becomes increasingly essential.

Olives

Olives (*Olea europaea*) are the fruits of the olive tree, a species of the *Oleaceae* family. The olive tree is one of the oldest cultivated fruit trees, and the use of olives

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has been documented as early as the late Stone Age at the site of Kfar Samirin in Israel. In the Greco-Roman civilization, olive oil and wine were closely linked due to the similarities in their processing and economic importance. They were used not only in daily life yet also in trade, religious rites, and art. Since prehistoric times, the olive tree has been of great cultural importance in this region and still has symbolic and religious significance today. Olive trees are generally found in the coastal areas of the eastern Mediterranean, the adjacent coastal areas of southeastern Europe, northern Iran at the southern end of the Caspian Sea, western Asia, and northern Africa. The best olive oil should be acidic, from the first cold pressing, preferably from organic farming [4,5].

Olive oil is rich in molecules with antioxidant and anti-inflammatory effects, such as polyunsaturated ω-3 fatty acids, monounsaturated ω-9 fatty acids, and phenolic compounds [6]. Olive oil is recommended in the diet of pregnant women as it promotes the healthy development of the baby's brain and nervous system before and after birth. It also allows for better mineralization of the bones. Olive oil prevents the accumulation of fats in the liver, lowers blood pressure, prevents arteriosclerosis, and prevents thrombosis. Olive oil may benefit another group of dementias: the tauopathies. It could also prevent diseases related to oxidative damage, such as coronary heart disease, stroke, and various types of cancer. Olive oil may also have an anti-aging effect. Olive oil is often used in soaps and massage oils [7]. It is excellent for macerating aromatic plants and flowers for therapeutic and culinary purposes.

Virgin olive oil provides a safe and stable emulsion system [8]. The antioxidant activity of olives makes them a candidate for moderating the effects of the aging process on the skin by limiting biochemical consequences of oxidation [9] due to their high content of squalene and β-sitosterol and its richness in oleic acid (a skin emollient). As such, virgin olive oil is ideal for the direct protection of the skin [10]. Oleuropein is used in cosmetics for its antioxidant, antiviral, antimicrobial, anti-inflammatory, skin-protecting, and anti-aging properties. Fatty acids increase hydration, softness, and elasticity and act as a protective barrier [11].

Olive tree leaves contain a rich array of bioactive compounds, including phenolic compounds (such as oleuropein, hydroxytyrosol, and tyrosol), flavonoids, triterpenoids, and secoiridoids. These phytochemicals contribute to the antioxidant, anti-inflammatory, antimicrobial, and anticancer properties of the leaves [12].

Herbal Tinctures

Herbal tinctures are alcoholic or aqueous-alcoholic solutions prepared from fresh or dried plant substances. Two basic processes are used in tincturing: maceration and percolation. One may use the *folk method* in the maceration method, which does not require measurement. However, since the substances are not measured, the result is inaccurate in terms of the strength of the tincture. The strength of the tincture refers to the amount of herbs that have been concentrated in a certain amount of solution. The other method is the *weight-to-volume (w/v)* method. The weight of the herb and the volume of the medium is measured and noted to obtain a specific tincture strength [13]. The most commonly found tincture strengths are 1:5 and 1:10 for dry plant preparations and 1:2 for fresh plant preparations. However, any relation may be used.

Regarding percolation, it is a method of extracting a herb's soluble components by allowing a solvent to slowly pass through a column of dried, powdered plant that has been contained in a unique type of equipment known as a percolator [13].

Study Objective

Considering the properties of alcohol as an extraction solvent suitable to extract cosmetically active principals from olive tree leaves, this study aimed to present a method for the easy preparation of an olive tree leaves tincture that may be incorporated into a cosmetic product and reproduced in a domestic environment.

MATERIALS AND METHODS

Chemicals

Alcohol 70% (CAS Number 64-17-5) was purchased at Sigma-Aldrich (St. Louis, Missouri, EUA).

Olive Tree Leaf Harvest and Preparation

Olive tree leaves (*Cobrançosa* variety) were selected in Portugal's Trás-os-Montes region and obtained from an organic farmer in December 2022. This region is bordered by the province of Minho to the west, the

Douro region to the south, the Douro River to the east, and Spain to the north. Trás-os-Montes is the second most important Portuguese olive-growing area, accounting for 12–15% of national olive oil production. The most important varieties are *Cobrançosa*, *Madural*, and *Verdeal* [14,15]. In the Trás-os-Montes region, forty native varieties are grown [16]. Therefore, natural ingredients are easy to obtain in this area. It is also the region with the largest number of organic farmers, and the climatic, topographical, and pedological differences predestine this region for agricultural diversity [17].

Before the experiment, fresh olive tree leaves were ground with a coffee mill, with particles smaller than 2 mm (Figs. 1a and 1b).

Equipment Cleaning and Disinfection

It is necessary to clean and disinfect the equipment to minimize the risk of contamination. To do this, a cleaning solution, denatured alcohol (at least 60% alcohol by volume) in a spray bottle, boiled water, and clean rags are needed.

Protective clothing was worn, and the hair was tied back. The work surfaces were cleaned with a cleaning solution and sprayed with alcohol. Surfaces were dried with a disposable paper towel. Metal, silicone, and glass containers were disinfected and sterilized. For this purpose, the equipment was boiled in water for twenty minutes and dried with a disposable paper towel. Then, each item was sprayed with alcohol, ensuring it also found itself inside the containers and lids. The items were dried with a disposable paper towel. Tools and non-heat-resistant plastic containers were sprayed with alcohol, taking care that it also reached the inside of the containers. The containers and tools were air-dried.

Olive Tincture

The weight-to-volume method was employed. A 20% olive tree leaf tincture was made (or 1:5 w/v). The exact formulation was as follows (Table 1):

1. 15 g of fresh olive tree leaves were weighed into a sterilized vessel.
2. The alcohol was measured out and added to the olive tree leaves (Fig. 2a).
3. The mixture was stirred to ensure the moistness of the olive tree leaves (Fig. 2b).
4. A square piece of natural wax paper was placed on top of the vessel, and the vessel was sealed with the lid (this prevented any contamination from the chemical coating that might have been on the lid).
5. The mixture was shaken daily for two weeks and then left to sit for another day.
6. The preparation was filtered through a coffee filter, then labeled and sealed.

Figure 1: Olive tree leaves: a) fresh olive tree leaves, b) powdered olive tree leaves.

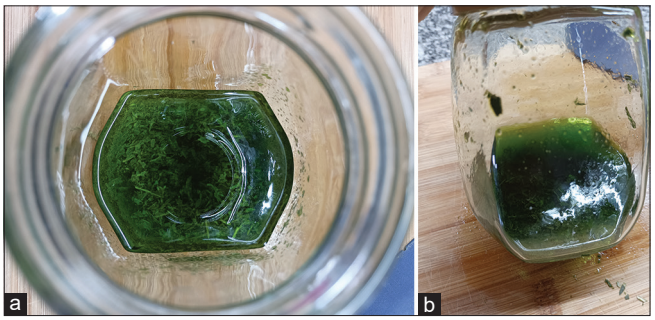

Figure 2: Steps of the preparation: a) mixture of alcohol and fresh olive tree leaves, b) mixture after stirring.

Table 1: Olive tree leaf tincture formulation.

Ingredient	Weight (g)
70% alcohol	75
Olive tree leaves	15

The mixture was stored in an airtight, light-resistant container. Direct sunlight and excessive heat were avoided.

RESULTS

The pH of the olive tree leaf tincture was determined with pH stripes and was in the range of 5.5 to 6.5. This may have an impact on how much of the tincture will be used and how it will be used. For this reason, we suggest using it at a concentration of 1%. The chosen herb-to-solvent ratio of 1:5 (w/v) yielded a concentrated tincture with enhanced potency.

The higher concentration of active constituents in the tincture is expected to offer a more potent and effective form of herbal extract.

The tincture may be incorporated into formulations such as emulsions, hydrogels, and water solutions. For homemade cosmetics, stability testing should also be conducted in a domestic setting to ensure the final product will continue performing as intended, remain unmodified, and be safe. Homemade stability tests often cannot be conducted in laboratory settings or with specialized equipment, yet they yield valuable information. Additionally needed is a paper outlining the manufacturing processes for each batch. In the batch manufacturing report, the following information should be included: batch number, composition, size and weight, storage requirements, master formula of the batch, start and end process dates, product expiration dates, and, if the batch is intended for sale, the manufacturer's license number.

DISCUSSION

The preparation of the olive tree leaf tincture using the weight-to-volume method proved to be effective in extracting the beneficial compounds from the leaves. The use of a 20% tincture concentration allowed for a sufficient extraction of the active components present in the olive tree leaves. The weight-to-volume method involves the accurate measurement of the leaves and the alcohol to ensure a proper ratio. This method has been widely used in herbal tincture preparations due to its simplicity and reproducibility.

The shaking process during the two-week period allowed for the optimal extraction of bioactive compounds from the olive tree leaves. The agitation facilitated the release of the compounds into the alcohol, resulting in a concentrated tincture.

The use of alcohol as a solvent during the tincture preparation process is anticipated to enhance the stability and shelf life of the extract. This ensures the preservation of the bioactive compounds over an extended period, allowing for the long-term storage and use of the tincture.

Filtering the tincture through a coffee filter ensured the removal of any solid particles or plant debris, enhancing the purity and clarity of the final product. Proper labeling and storage in an airtight, light-resistant container preserved the integrity of the tincture, preventing degradation or loss of its therapeutic properties.

The olive tree leaf tincture holds significant importance in the realm of cosmetics. The tincture is derived from fresh olive tree leaves, known for their beneficial properties and traditionally used in skincare and beauty preparations. The tincture becomes a valuable ingredient in cosmetic formulations by harnessing the active compounds in the leaves. Olive tree leaves and herbal tinctures derived from them possess a remarkable range of bioactive compounds and exhibit significant pharmacological activities. Their antioxidant, anti-inflammatory, antimicrobial, and potential anticancer properties make them valuable candidates for further exploration in the field of natural medicine. Continued research and clinical studies are warranted to fully elucidate their mechanisms of action and therapeutic potential.

One of the notable advantages of the olive tree leaf tincture is its versatility. It may be easily incorporated into various cosmetic products, such as emulsions, hydrogels, and water solutions. This adaptability allows formulators to explore a wide range of possibilities in creating skincare, haircare, and body care products with added benefits.

The olive tree leaf tincture provides several advantageous properties. It is known for its antioxidant activity, which helps protect the skin against free radicals and oxidative stress, contributing to the overall health and youthful appearance of the skin. Additionally, the tincture possesses anti-inflammatory properties, making it beneficial for soothing sensitive or irritated skin. In addition to the successful preparation of the olive tree leaf tincture, it is important to note that olive tree leaves have been reported to possess antigenotoxicological properties. Several studies have indicated that extracts derived from olive tree leaves exhibit potential protective effects against DNA damage and oxidative stress [18]. The inclusion of olive tree leaves in the tincture formulation suggests the possibility of harnessing these antigenotoxicological properties for potential therapeutic applications. Further research and investigations are necessary to elucidate the underlying mechanisms and identify the specific compounds responsible for the observed effects.

Furthermore, the tincture contains compounds promoting moisturization and hydration, improving

skin elasticity and suppleness. It may also assist in the revitalization of dull and tired-looking skin, lending it a radiant and refreshed appearance.

The obtained tincture may now be subjected to further analysis and evaluation to determine its phytochemical composition, including the presence of bioactive compounds such as phenolic compounds, flavonoids, and other constituents. Subsequent studies should explore the potential antioxidant, anti-inflammatory, antimicrobial, and other pharmacological activities of the tincture.

CONCLUSION

Consumers are becoming increasingly interested in products less harmful to the environment. These days, cosmetics are becoming progressively more "green." A cosmetic may be considered "green" if its formulation contains active ingredients derived from plants, such as minerals and plants, rather than analogous active ingredients chemically reproduced in the laboratory. It is preferable if it is produced in an environmentally sustainable manner, using processing methods that respect nature and plants in accordance with organic crops.

The use of natural ingredients, such as olive tree leaf tincture, is becoming increasingly popular in the cosmetic industry as consumers seek gentle, sustainable, and effective products. The tincture aligns with these preferences, as it is derived from organic sources and offers a more environmentally friendly alternative to synthetic ingredients.

While further research and stability testing are necessary to explore the full potential of the olive tree leaf tincture in cosmetics, its incorporation into formulations holds promise for enhancing the efficacy and appeal of beauty products. With its diverse range of beneficial properties and compatibility with various formulations, the olive tree leaves tincture emerges as a valuable and sought-after ingredient in the cosmetics industry, catering to the growing demand for natural and effective skincare solutions.

Overall, the findings of this study support the potential of olive tree leaves as a valuable resource for developing natural and sustainable interventions targeting DNA damage and related health conditions. Continued research in this field will contribute to a better understanding of the therapeutic potential and applications of olive tree leaves in the field of natural cosmetics and medicine.

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Statement of Human and Animal Rights

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

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Our Dermatology Online

Original Article

Pemphigus and cancer: A single-center experience over 30 years in Morocco

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ABSTRACT

Background: The aim of this study was to investigate the association between pemphigus and cancer and to analyze the characteristics of pemphigus in which a neoplasm occurs. **Materials and Methods:** This was a retrospective, descriptive study conducted at the Dermatology Department of Ibn Sina Hospital in Rabat from January 1993 to December 2022, including all pemphigus cases in which cancer was diagnosed before, during, or after the onset of pemphigus. **Results:** Among 302 pemphigus cases, 13 patients presented an associated cancer (4,3%). Only one patient had a paraneoplastic pemphigus. There was an increased incidence of various solid cancers (11/13) in deep pemphigus types yet without temporal relationship. When hematological malignancy occurred (3/13), it was mainly non-lymphoproliferative and preceded deep pemphigus types with good prognosis. Patient comorbidities and immunosuppressive treatments did not influence the onset of cancer. **Conclusion:** Our manuscript suggests an increased incidence of solid cancers in deep pemphigus subtypes, independently of the timeline of the latter onset. These pemphigus cases carry a good prognosis.

Key words: Pemphigus, Cancer, Paraneoplastic pemphigus, Paraneoplastic autoimmune multiorgan syndrome

INTRODUCTION

Paraneoplastic pemphigus (PNP) was first described in 1990 by Anhalt et al. as the co-existence of a neoplasm and polymorphic mucocutaneous clinical manifestations and the histopathological aspect of pemphigus, bullous pemphigoid, and erythema multiform. It was initially considered a unique autoimmune blistering disease secondary to autoantibodies directed against desmoplakin I and bullous pemphigoid major antigen (BP230) in immunology, in addition to IgG and C3 deposits along the dermo-epidermal junction and between keratinocytes [1].

However, since the initial publication, numerous atypical cases have been reported that do not meet the proper criteria of PNP [2]. This concept has, therefore, evolved into paraneoplastic autoimmune multi-organ syndrome (PAMS) [3,4], which is still distinct from traditional pemphigus associated with cancers.

Herein, we report a case series of pemphigus with underlying neoplasms at the Dermatology Department of Ibn Sina Hospital in Rabat during the last 30 years. The aim of the study was to investigate the association between pemphigus and cancer and to analyze the characteristics of pemphigus in which a neoplasm occurs.

MATERIALS AND METHODS

We performed a retrospective, descriptive study including all pemphigus cases associated with a neoplasm at the Dermatology Department of Ibn Sina Hospital in Rabat over 30 years (between January 1993 and December 2022). We included all pemphigus cases in which cancer was diagnosed before, during, or after the onset of pemphigus.

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RESULTS

Epidemiologic Findings

We collected thirteen cases of pemphigus associated with cancer among 302 pemphigus cases hospitalized during the last 30 years [5], which corresponded to 4.3% (Table 1).

There were six males and seven females, yielding a sex ratio of 0.9. The mean age on diagnosis was 61.7 years (with extremes ranging from 45 to 81 years).

Regarding cardiovascular comorbidities, 3/13 cases presented hypertension, 5/13 were diabetic, 2/13 were overweight, 1/13 was moderately obese, and 1/13 was a chronic smoker.

Auto-immunity was associated in 1/13 patient (Hashimoto thyroiditis), and 1/13 patient suffered from chronic urticaria.

Concerning infectious diseases, 1/13 presented COVID-19, 1/13 suffered from acute viral pericarditis, 1/13 developed angiocholitis, and 1/13 had been cured of a pulmonary hydatid cyst.

Neurological comorbidities were present in 2/13 patients (epilepsy and mental retardation).

Clinical Findings

The predominant clinical form was deep pemphigus, present in 6 patients, mainly represented by pemphigus vulgaris (4/13). There was only 1/13 case of paraneoplastic pemphigus.

The PDAI was mainly moderate (10/13), with extremes ranging from 14 to 188. The highest PDAI was noticed in paraneoplastic pemphigus.

Pruritus was present in six cases.

Among the thirteen patients, five patients did not have mucosal involvement. When the mucosa was affected, it was mainly the buccal mucosa (6/8).

Regarding additional neoplasms, either solid cancers or hematological ones, there was a predominance of non-hematological cancers in 10/13 patients. Indeed, 2/13 had papillary thyroid carcinoma, 2/13 suffered from colon adenocarcinoma, 2/13 were cured of squamous cell carcinoma (skin, nail, and palatin), 1/13 was treated for dermatofibrosarcoma protuberans, 1/13 had papillary cystadenocarcinoma of the ovary, 1/13 suffered from breast adenocarcinoma, 1/13 had prostate carcinoma, and 1/13 was treated for neuroendocrine small bowel tumor.

Among hematological ones, the only lymphoproliferative disease of the series was associated with paraneoplastic pemphigus (B-cell chronic lymphocytic leukemia).

Pemphigus lesions appeared before the onset of cancer in 4 patients (patients 2, 7, 8, and 12) after a mean time of 6 years (1 to 10 years). All were under oral corticosteroids (2 mg/kg/day), and patient 8 was under additional azathioprine (2 mg/kg/day). Nine patients developed cancer before the diagnosis of pemphigus, including the case with paraneoplastic pemphigus (patients 1, 3, 4, 5, 6, 9, 10, 11, and 13), with a mean time of 2.4 years. One patient (patient 4) had four concomitant neoplasms (three squamous cell carcinomas of the skin and nails and one myelodysplasia).

Histopathologic and Immunologic Findings

In 11 cases out of the 13, there was intraepidermal acantholysis, either suprabasal acantholysis with a tombstone aspect of the remaining basal cells and intact blister (in deep pemphigus cases, 6/13), or subcorneal acantholysis (in superficial ones, 5/13). One biopsy specimen revealed additional spongiosis with eosinophils (pemphigus herpetiformis), and one tissue specimen presented an ulcerated epidermis with numerous necrotized keratinocytes and dermal polymorphous inflammatory infiltrate (PAMS).

Direct immunofluorescence (DIF) was performed in nine cases, revealing intercellular deposition of IgG and C3 resembling a chicken wire in five cases and only IgG in three cases. In the case with PAMS, the DIF was negative.

Indirect immunofluorescence (IIF) revealed intercellular fluorescence in nine cases, and additional fluorescence along the dermo-epidermal junction was seen in one case (PAMS). IIF was negative in three cases.

Neither immunoblot nor enzyme-linked immunosorbent assay (ELISA) was performed because of their inaccessibility in Morocco.

Treatment

Eleven patients out of the thirteen received a high dose of oral prednisone as first-line therapy (2 mg/kg/day),

Table 1: Characteristics of the patients with pemphigus and associated malignancy at the Dermatology Department of Ibn Sina Hospital in Rabat.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (yrs.)/sex	68/F	49/F	67/M	59/F	80/M	56/M	55/M	81/F	45/M	53/F	64/F	56/F	70/M
Comorbidities	Hypertension Diabetes COVID-19	Angiocholitis	-	Diabetes Overweigh	Overweigh	-	Smoking Pulmonary hydatid cyst	Diabetes Pericarditis	-	Hypertension Epilepsy	Diabetes Hashimoto's thyroiditis	Hypertension Diabetes Moderate obesity Chronic urticaria	-
Clinical aspect	P vulgaris	P vegetans	P vulgaris + EM + PB	P vegetans	P vulgaris	P foliaceus	P vulgaris	P seborrheic	P herpetiformis	P vulgaris	P foliaceus	P seborrheic	P seborrheic
- Cutaneous lesions	+	+	+	+	+	+	+	+	+	+	+	+	+
- Mucosal lesions	B+G+A	B+N+A	O+B+N+G	G	B	-	B	-	B+G	G	-	-	-
- Pruritus	+	-	-	+	-	-	+	-		+	+	-	+
- PDAI	27	14	188	16	16	79	39	19	- 34	20	33	18	34
Histologic aspect	Intraepidermal suprabasal acantholysis and intact blister	Intraepidermal suprabasal acantholysis and papillomatous overlying epidermis	Ulcerated epidermis with numerous necrotized keratinocytes and dermal polymorphous inflammatory infiltrate	Intraepidermal suprabasal acantholysis and papillomatous overlying epidermis	Intraepidermal suprabasal acantholysis and intact blister	Intraepidermal subcorneal acantholysis	Intraepidermal suprabasal acantholysis and intact blister	Intraepidermal subcorneal acantholysis	Intraepidermal acantholysis + spongiosis with eosinophils	Intraepidermal suprabasal acantholysis and intact blister	Intraepidermal subcorneal acantholysis	Intraepidermal subcorneal acantholysis	Intraepidermal subcorneal acantholysis
DIF													
- IgG	Intercellular	Intercellular	-	Intercellular	Intercellular	NP	NP	Intercellular	NP	NP	Intercellular	Intercellular	Intercellular
- C3	Intercellular	-	-	Intercellular	Intercellular	NP	NP	Intercellular	NP	NP	-	Intercellular	-
IIF													
- Anti-intercellular substance antibodies	+ (1/1280)	+ (1/640)	+ (1/1280)	-	+ (1/320)	+ (1/1280)	+ (1/1280)	+ (1/80)	+ (1/20)	-	+ (1/120)	-	+ (1/320)
- Anti-basement membrane antibodies	-	-	+ (1/1280)	-	-	-	-	-	-	-	-	-	-
Associated cancer	Papillary thyroid carcinoma	Colon adenocarcinoma	B-cell chronic lymphocytic leukemia	3 squamous cell carcinoma (nail and skin) - Myelodysplasia - Concomitant with P	Prostate adenocarcinoma	Colon adenocarcinoma	Dermatofibrosarcoma protuberans	Papillary cystadenocarcinoma of the ovary	Squamous cell carcinoma of the palatin	Myelodysplasia	Breast adenocarcinoma	Papillary thyroid carcinoma	Neuroendocrine small bowel tumor
Time period to pemphigus onset	Concomitant with P	6 years after P	2 years before P	- 1 year before P	Concomitant with P	12 years before P	7 years after P	1 year after P	Concomitant with P	1 year before P	5 years before P	10 years after P	1 year before P

(Contd...)

Table 1: *(Continued).*

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Treatment													
- Pemphigus	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	-	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day) + Oral Azathioprine (2mg/kg per day) Total hysterectomy and adnexectomy	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)	Oral prednisone (2mg/kg per day)
- Cancer	Total thyroidectomy	Hemicolectomy	-	-Surgery with margins -Transfusion	Hormonal therapy	Hemicolectomy	Surgery with margins		Surgery with margins	Follow up	Tumorectomy + radiotherapy + hormonal therapy	Total thyroidectomy + iratherapy	Somatulin injection + small bowel resection
Evolution													
- Pemphigus	- Total healing after 90 days	- Total healing after 90 days, flare after 9 years	- Death after 3 weeks	Lost from follow-up	- Total healing after 180 days	- Total healing after 60 days, flare+ death after 12 years (sepsis)	- Total healing after 30 days, flare after 6 years	Total healing after 180 days, flare after 1 year	Lost from follow up	- Total healing after 45 days	- Total healing after 37 days	- Total healing after 37 days	- Total healing after 40 days
- Cancer	- Cured	- Cured			- Cured	- Cured	- Cured	- Cured		- Stabilized	- Cutaneous metastasis	- Cured	- Progression

F female, M male, P pemphigus, EM erythema multiform
O ocular B buccal N nasal G genital
NP not performed
PDAI pemphigus disease area index

one patient needed the adjunction of oral azathioprine (patient 8 at a dose of 2 mg/kg/day), and the case with PAMS died before treatment could be instituted.

Follow-up

Most patients (7/13) revealed complete healing of pemphigus lesions, after a mean time of 69.8 days. Four patients presented a pemphigus flare, after a mean period of six years with no cancer recurrence. Two patients were lost to follow-up. Two died (the patient with PAMS died three weeks after the onset of pemphigus from respiratory failure probably related to bronchiolitis obliterans).

Only two patients presented a progression of their cancer yet without a pemphigus flare.

DISCUSSION

The first cases of PPN published in the literature were highly severe and corresponded to diagnostic criteria defined by Anhalt et al. in 1990 [1]. These criteria have evolved to include atypical forms, such as cases without mucosal [2] or cutaneous involvement or detectable anti-plakin antibodies. They have been revised several times, in particular, by Camisa et al., Czernikc et al., Joly et al., and Grando et al. [6], without always specifying the number of criteria needed to establish the diagnosis. Therefore, the term *paraneoplastic autoimmune multiorgan syndrome* (PAMS) was proposed by Grando et al. in 2001 [3,4] to designate paraneoplastic disease with epithelial involvement, including PNP. The most consistently found criteria are severe mucosal involvement, polymorphic rash, acantholysis and lichenoid dermatitis in histopathology, and underlying neoplasia.

Our retrospective, descriptive study collected thirteen cases of pemphigus associated with cancer, in which only one case was classified to have PAMS (patient 3). He had a lymphoproliferative neoplasm occurring before the onset of pemphigus and developed polymorphous cutaneous manifestations with severe mucosal involvement. The autoantibodies directed against intercellular substance and basement membrane were present in IIF, and death occurred quickly after the onset of pemphigus from bronchiolitis obliterans.

Therefore, there appear to be cases of neoplasia fortuitously associated with classical pemphigus, and they have a better prognosis [6-12]. Joly et al. compared

34 cases of pemphigus associated with neoplasia, and only 22 were classified as cases of PNP (according to the PAMS criteria of classification) [6]. In our case series, 11 out of the 13 patients had a traditional form of pemphigus, 10 were moderately severe, and 7 presented complete healing of pemphigus lesions after a mean of 69.8 days without a flare. These findings highlight the better prognosis of these forms, in which there is an excellent therapeutic response and longer survival.

Only several studies have reported the relationship of pemphigus with neoplasia [13-16], and to the best of our knowledge, there is no data concerning this association in the Maghreb region. It is established in the literature that there is a statistically increased risk of solid malignancies in pemphigus. Ogawa et al. revealed in their study on 496 pemphigus cases that 5% developed an internal neoplasm, which was higher than in a group control of the same age (0.61%) [14]. Our findings were coherent with this data, as in our series on 302 cases of pemphigus, 4.3% had an associated neoplasm.

When a hematological malignancy was associated with pemphigus (patients 3, 4, and 10 in our case series), cancer developed before the onset of pemphigus. In all cases, there was a deep form of pemphigus, which is in accordance with the literature [14,15]. This result suggests that neoplasms triggered pemphigus, as in real paraneoplastic pemphigus. Schulze et al. reported the percentage of hematological malignancies in pemphigus vulgaris to be 3.9% vs. 0.23% in our series [15]. Lymphoproliferative malignancies were predominant, in contrast with our study. In our experience, there were mainly non-lymphoproliferative neoplasms among hematological malignancies, and they triggered the classical pemphigus type with moderate severity and good prognosis.

Regarding solid neoplasms, there is a statistically increased risk of oropharyngeal cancers (0.4% to 0.9%) [15,16], laryngeal cancer (0.6%) [15], and colon carcinomas (3.7% vs 0.15% in our case series) [15,16] in pemphigus vulgaris that have been established in the literature. However, there is no temporal relationship between pemphigus and internal malignancy, as in our series (patients 2 and 6 both with colon carcinoma). When mucosal cancer develops in pre-existing pemphigus, the chronic inflammation is responsible for genetic mutations and carcinogenesis, as in patient 2 with deep pemphigus and anal involvement, who developed colon carcinoma six years after pemphigus lesions. On the other hand, when mucosal cancer appears before pemphigus, it is stipulated that the neoplasm exposes specific antigens to the immune system, which triggers auto-immunity in pemphigus. However, patient 6, who had pre-existing colon carcinoma had a superficial pemphigus form with no mucosal involvement. This suggests that there might be other factors triggering both pemphigus and malignancy [17].

Concerning non-melanoma skin and mucosal cancers, we collected two cases of squamous cell carcinoma (patients 4 and 9) and one of sarcoma (patient 7), which corresponded to 0.23%. They all occurred in deep pemphigus types, again with no temporal relationship. This finding contrasts with the literature, in which non-melanoma skin cancers developed before the onset of pemphigus and were linked with pemphigus foliaceous in 16.5% of cases [15].

Our case series revealed that pemphigus immunosuppressive treatments did not trigger neoplasm as there is no temporal relationship between pemphigus and cancer occurrence, as in the literature [15,16]. And when cancer progresses, it is not followed by pemphigus recurrence (patients 2, 6, 7, and 8). This supports the hypothesis that there might be other factors involved in both pemphigus and cancer occurrence and is against a direct relationship between the two conditions [17].

At last, Kridin et al. demonstrated that comorbidity control did not significantly affect cancer incidence in pemphigus through statistical estimates [16]. In our series, comorbidities did not modify pemphigus response to therapeutics, and there were no malignancy-specific risk factors among comorbidities.

CONCLUSION

Our study had numerous limitations regarding the retrospective and monocentric analysis and the limited number of patients. However, our findings were coherent with the literature concerning an increased incidence of solid cancers in deep pemphigus subtypes without a temporal relationship. Patient comorbidities and pemphigus immunosuppressive treatments seemed not to be involved in the occurrence of malignancies. Regardless of the reason for this association, we should keep in mind a possible associated neoplasm in patients with deep pemphigus and perform a detailed examination for early diagnosis, although these cases seem to have a good prognosis. Further studies are still needed to characterize this association more fully.

Statement of Human and Animal Rights

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

Statement of Informed Consent

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

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Our Dermatology Online

Original Article

Atopic dermatitis associated with tropical endemic limbo-conjunctivitis: Epidemiology, clinical phenotypes, and allergological investigations

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ABSTRACT

Background: Atopic dermatitis (AD) is on the increase worldwide. In Africa, 40% of cases are associated with tropical endemic limbo-conjunctivitis (TELC). Its predominance in early childhood has a major impact on the quality of life of children and their parents, leading to absenteeism from school and work. The aim of this study was to assess the particularities of AD associated with TELC in Dakar. **Materials and Methods:** This was a cross-sectional, multicenter study with prospective data collection over a six-month period, conducted at dermatology and ophthalmology departments in Dakar. All patients treated for atopic dermatitis with or without TELC were included in the study. Data entry and analysis were performed with SPSS 18. **Results:** From the study, 97 cases of atopic dermatitis were identified. Among these, 49 had AD associated with TELC. The sex ratio was 1.18 (36 boys and 13 girls). The mean age of patients was ten years. The age range between 5 and 10 years was more represented. There was atopy equivalent to allergic rhinitis in 44 cases, asthma in 16 cases, allergic conjunctivitis in 14 cases, and food allergy in 20 cases. 31 cases of AD were mild, 16 moderate, and 2 severe according to SCORAD. Patients were in stage I in 26 cases and in stage II in 13 cases according to Diallo's TECL classification. All patients were managed by dermatologists and ophthalmologists. Aeroallergen prick tests were performed in thirty cases. Tests were positive for house dust mites in 23 cases (92%), animal dander in 11 cases (44%), molds in 7 cases (28%), and pollens in 2 cases (8%). *Dermatophagoides pteronyssinus* and *farinae* were the most common aeroallergens. Patch tests were positive for potassium dichromate in 4 cases, cobalt in 4 cases, nickel in 3 cases, and lanolin in 4 cases. **Conclusion:** AD associated with TECL remains common in tropical environments. They share common aggravating environmental factors, notably hypersensitivity to aeroallergens and a predominance in early childhood. The major impact on functional prognosis makes therapeutic education and multidisciplinary management of patients essential.

Key words: Atopic dermatitis, Tropical limbo-conjunctivitis, Dakar

INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic inflammatory dermatosis that progresses through flare-ups and remissions. It is a multifactorial disease combining genetic and environmental factors [1]. It is often associated with other atopic equivalents such as allergic rhinitis, allergic conjunctivitis, or asthma [2,3]. It affects at least 230 million people worldwide, and its prevalence rose in 30 years from 5% to 25% [4,5]. Several studies have shown an association between AD and tropical endemic limbo-conjunctivitis, with an estimated prevalence of 40% [6]. TECL is an endemic limbo-conjunctivitis that occurs mainly in

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children in tropical environments. The frequency of TECL reported in Africa varies between 2.8% and 90% [7,8]. Its association with AD may be linked to common environmental factors: tropical, sunny climate, photosensitivity, and exposure to aeroallergens. Allergological investigation helps to identify trigger factors and establish avoidance measures for therapeutic education. Little work has been done in Africa on the epidemiology of patients with AD associated with TECL. The aim of this study was to determine the epidemiological, clinical, and etiological features of patients with atopic dermatitis associated with tropical endemic limbo-conjunctivitis.

MATERIALS AND METHODS

This was a descriptive, multicenter, cross-sectional study conducted over a six-month period (April 1 to September 30, 2022) at the dermatology departments of Aristide Le Dantec Hospital, Hygiena Social Institute, Albert Royer Children Hospital, and the Ophthalmology Department of Aristide Le Dantec Hospital. Our study population consisted of patients seen in consultation at these different departments. All patients presenting with atopic dermatitis associated with TECL were included in the study. The diagnosis of AD was based on the existence of pruritus and eczematous lesions on the folds, extension surfaces of the limbs, and convex areas in children, or of cutaneous xerosis and minor signs of atopy (periorbital hyperpigmentation, Dennie–Morgan double fold, keratosis pilaris, palmoplantar hyperlinearity, follicular eczematitis, achromic eczematitis). The United Kingdom Working Party diagnostic criteria were employed [9]. The diagnosis of TECL and classification into four clinical stages according to Diallo's classification [7] were performed by experienced ophthalmologists. The patients were asked to complete a questionnaire and undergo a full clinical examination. Allergological tests included patch tests using the European standard battery or personal products, respiratory or food prick tests and specific IgE assays for aeroallergens or food allergens. All patients received therapeutic education. Data entry and analysis were performed with Excel and SPSS 18. Chi-square and Fisher tests were used according to their conditions of applicability, with a significance level of $p < 0.05$.

RESULTS

We identified 49 cases of atopic dermatitis associated with TCEL out of 97 patients presenting with atopic dermatitis during our study period, giving a hospital prevalence of 50.5%. Thirty-six cases (73.4%) were followed up at the dermatology department and 13 cases (26.5%) at the ophthalmology department. The sex ratio was 1.18 (36 boys and 13 girls). The mean age of the patients was 10 years, with extremes ranging from 3 to 20 years. The age range between 5 and 10 years was more represented. Fig. 1 illustrates the distribution of patients according to age of onset of AD and TECL. There was an atopy equivalent in the form of allergic rhinitis in 44 cases, asthma in 16 cases, allergic conjunctivitis in 14 cases, and food allergy in 20 cases. Tropical endemic limbo-conjunctivitis was present in at least one family member in 32 cases (32%).

The average consultation time was 7.2 months, with extremes ranging from one week to fourteen years. According to SCORAD, atopic dermatitis was mild in 31 cases, moderate in 16 cases, and severe (Fig. 2) in 2 cases. According to Diallo's TECL classification,

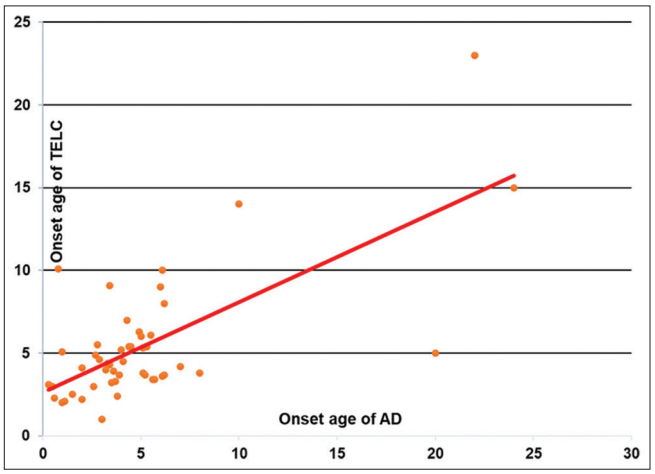

Figure 1: Distribution according to the onset age of AD and tropical endemic limbo-conjunctivitis (TECL).

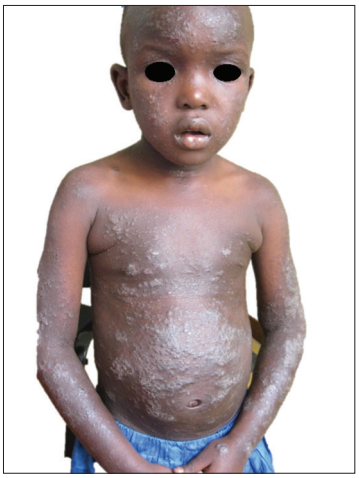

Figure 2: Five-year-old boy with severe AD associated with TECL.

Figure 3: Patient distribution according to the classification of Diallo (a: stage I, b: stage II, c: stage III, d: stage IV).

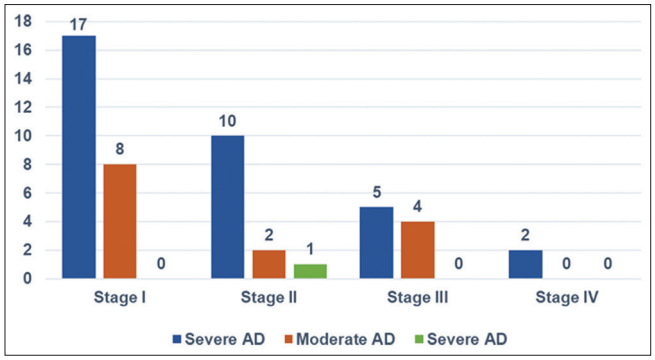

Figure 4: Patient ranged by the severity of AD and the TECL stages.

patients were stage I in 26 cases, stage II in 13 cases, stage III in 9 cases, and stage IV in 2 cases (Fig. 3). Fig. 4 illustrates the distribution of cases according to the severity of AD and TECL. All patients were mutually managed at the dermatology and ophthalmology departments. Respiratory prick tests were positive for house dust mites in 23 cases (92%), animal dander in 11 cases (44%), molds in 7 cases (28%), and pollens in 2 cases (8%). Table 1 illustrates sensitization to respiratory allergens. Patch tests showed sensitization to metals: potassium dichromate, cobalt, and nickel (Fig. 5). Table 2 shows patch test sensitizations. Food-specific IgE tests were conducted in 4 cases (4%) and were positive for shrimps and eggs.

A concordance between the European standard battery and the products reported by the patient reinforced the relevance in one case for nickel. The relevance of the tests was current in 18 cases and long-standing in 4 cases.

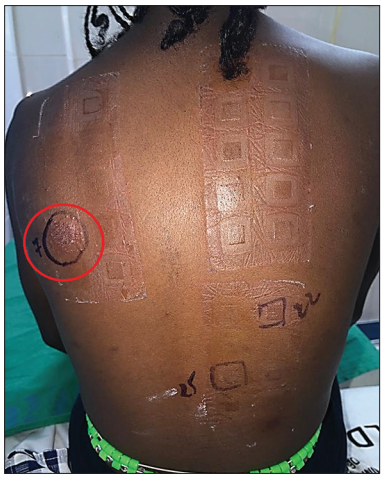

Figure 5: Nickel sensitization in a girl followed for atopic dermatitis and TECL.

Table 1: Positivity of skin tests to aeroallergens

Aeroallergen	Number (%)	
Mite		
Dermatophagoides pteronyssinus	5	13
Dermatophagoides farinae	3	12
Blomia tropicalis	3	10
Insect		
Blatte	0	0
Mold		
Alternaria alternata	2	5
Animal dander		
Dog dander	2	5
Cat dander	2	5
Pollen Gramineae pollen	1	1

Table 2: Tests positive for European standard battery allergens

Contact allergen	Number
Metal	
Potassium dichromate	2
Cobalt	4
Nickel	3
Colorant	
Paraphenylene diamine	3
Drug	
Toxicortol	3
Synthetic resin	
Epoxy resin bisphenol	1
Fragrance marker	
Fragrance Mix 1	1
Excipient	
Lanoline	3

DISCUSSION

We report 49 cases of atopic dermatitis associated with TECL. Half of the patients who consulted us for atopic dermatitis presented with TECL during our study period. The prevalence varies in Africa, with some authors estimating it at between 3.4% and

83%. [8,10]. We noted a predominance of males among patients with AD and TECL. This data is consistent with previous studies [7,11] Atopic dermatitis has always been considered a disease of early childhood, classically beginning before the age of two years and generally subsiding in adolescence [12]. We noted a predominance of DA and TECL symptoms in children under seven years of age. Tropical limbo-conjunctivitis is a pathology that classically affects children before adolescence [1,13]. The average age of the patients in our series was less than ten years [14]. It was described by Diallo in 1971, mainly affecting children between 3 and 16 years of age and is often equated with vernal keratoconjunctivitis. However, it differs from vernal keratoconjunctivitis in that its limbic involvement is more marked, and its corneal complications are the main cause of its severity [15,16]. These same factors may also be responsible for atopic dermatitis flare-ups. In fact, AD and TECL share the same environmental factors that cause flare-ups. In our series, tests were positive for house dust mites (92%), animal dander (44%), molds (28%), and pollens (8%). Our results were identical to those found in the literature. House dust mites are the aeroallergens most frequently associated with AD [17].

A clear predominance of aeroallergens (house dust mites, cockroach, dog and cat, and grass pollen) was also more prevalent in children followed for TECL in Togo [18]. Metal sensitization noted in our study is also observed in previous studies in the literature [17]. Nickel is a frequent contact allergen in the face. Sensitization may be direct, via cosmetic products or ophthalmic topicals, or indirect, via the handling of contact allergens [19].

CONCLUSION

Atopic dermatitis is frequently associated with TECL in tropical environments. They share common aggravating environmental factors, notably hypersensitivity to aeroallergens and a predominance in early childhood. The major impact on patients' functional prognosis and quality of life makes therapeutic education and multidisciplinary management essential.

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

Descriptive assay of the clinico-morphological characteristics of dermatoses presenting with reticulate pigmentation

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ABSTRACT

Background: Reticulate pigmentation is characterized by freckle-like lesions configured to form a net-like or chicken-wire configuration with varying degrees of pigmentation. It intermingles with similar terms such as *mottled pigmentation* and *dyschromia* and poses difficulty in classification. Both genetic and acquired dermatoses may present with reticulate patterns yet may vary in morphology as well as the age of onset and presentation. **Materials and methods:** This was a hospital-based, descriptive, observational study conducted on thirty-two patients over a period of fifteen months at the dermatology OPD. Patients presented with reticulate pigmentary dermatoses were enrolled in the study after giving written informed consent. A detailed history and clinical examination were performed, and findings were recorded on a standard predesigned proforma. The data was analyzed with appropriate statistical tests. **Results:** In our study, a total of thirty-two patients with reticulate pigmentary dermatoses were enrolled, fourteen males and eighteen females, yielding a male-to-female ratio of 1:1.28. The most common age group affected was 41–50 years (28.12%). The onset of lesions was in young to middle adulthood (56.25%), followed by childhood and teenage years (34.37%). The most common disorder found was erythema ab igne (15.62%), while livedoid vasculopathy, Dowling–Degos disease, and confluent reticulate papillomatosis each constituted 9.37% of cases. **Conclusion:** This study assisted to incorporate the spectrum of RPD and to assess its frequency, morphological patterns, and prognosis. Owing to the paucity of research studies on RPD, the present study will be helpful in exploring future treatment modalities, thereby decreasing the enigma and concerns associated with RPD.

Key words: Reticulate pigmentary dermatoses, Net-like lesions, Dyschromia

INTRODUCTION

Reticulate dermatoses are clinically described as a wide range of dermatological conditions with a net-like arrangement of skin lesions. One of its subset, reticulate pigmentation, denotes a group of diseases characterized by the presence of hyper- and/or hypopigmented macules with varying sizes and degrees of pigmentation [1]. However, a group of disorders with reticulate pigmentation still poses a problem regarding its categorization due to numerous conditions under the umbrella term exhibiting patterns other than reticulate yet demonstrating close similarity with terms such as *dyschromia* and *poikilodermatous disorders*. To overcome this, some authors use the broader term *mottled pigmentation*, that is, mixed, hyper- and/or hypopigmented macules in a blotchy pattern, to encompass all aforementioned conditions [2,3].

Moreover, the term *reticulate pigmentary dermatoses* (RPD) may also be preferred to incorporate a heterogenous group of disorders characterized by hyperpigmented, freckle-like macules with varying sizes and amounts of pigmentation coalescing at the margin to form a net-like/reticular pattern, sometimes associated with scattered, hypopigmented macules between hyperpigmented lesions [4,5].

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Among various reticulate pigmentary dermatoses, prototype or true reticulate pigmentary disorders have the morphology of classic freckle-like hyperpigmentation and consist of reticulate acropigmentation of Kitamura (RAPK), reticulate acropigmentation of Dohi (RAPD), and Dowling–Degos disease (DDD). Some acquired dermatoses such as lichen planus pigmentosus, livedo reticularis, and prurigo pigmentosa may also present with mixed hyper- or hypopigmented macules with a reticular pattern. This typical reticulate pattern may also be associated with autoimmune disorders such as scleroderma, lupus erythematosus, and certain metabolic, infectious, and vascular conditions [6].

Most of the true reticulate pigmentary disorders are genetically inherited and occur in infancy and early childhood, with a possible exception of DDD and RAPK, in which lesions may begin during adolescence or adult/middle age. Although genetic mutations have been identified in various true reticulate pigmentary disorders, genetic predispositions, alterations, and susceptibilities have not been elucidated comprehensively [7].

Different reticulate pigmentary dermatoses may be classified on the basis of their origin, onset, distribution, and mode of inheritance, as these features may provide a distinguishing clue between true and other acquired conditions presenting with a reticulate pattern. Yet, often, an overlap in multiple features exists due to the absence of a remarkable morphological pattern of isolated dermatoses.

In purview of the absolute scarcity of larger studies of the spectrum of dermatoses displaying the reticulate pattern and limited epidemiological data in central India, the present study may be helpful in determining the spectrum of various pigmentary patterns and in ascertaining a better clarification of closely related true and acquired dermatoses exhibiting reticulate pigmentation.

Objective

The present study aimed to assess the frequency, distribution, and clinico-morphological patterns of dermatoses presenting with reticulate pigmentation.

METHODOLOGY

A hospital-based, descriptive, observational study was conducted on thirty-two patients over a period of twelve months at the dermatology outpatient department. Patients presenting with clinical features suggestive of reticulate pigmentary lesions were enrolled in the study after giving written informed consent.

Inclusion Criteria

Patients with genetic reticulate pigmentary disorders as well as acquired dermatoses leading to mixed hyper- to hypopigmentary macules primarily or secondarily were included in the study. We enrolled disorders displaying hyper- and/or hypopigmented macules with a reticulate pattern and encompassed them under reticulate pigmentary dermatoses (RPD).

Exclusion Criteria

Patients with a reticulate pattern secondary to infections, drugs, malignancy, and syndromes were excluded due to their reticulate pattern being auxiliary and having a non-dominant mode of presentation.

A detailed history, including the age at onset, the duration and progression of lesions, and site-wise distribution along with the history of concomitant cutaneous or systemic illnesses was taken. A history of sun exposure, friction, atopy, and hereditary associations in siblings or first-degree family members were also recorded. A history of exposure to chemicals or drugs was obtained as well.

A complete clinical examination was performed, and the morphology of the lesions—color, shape, distribution, size, pigmentary density, and associated secondary changes—was evaluated. Associated changes in the teeth, nails, hairs, and orogenital mucosa, as well as Fitzpatrick skin types, were also examined and recorded on a standard predesigned proforma.

All routine investigations, including HbA1c, thyroid function test, lipid and metabolic profiles, liver and renal function tests, and peripheral smear for atypical cell, were performed. Dermoscopy and skin biopsy were done in doubtful cases. The data was compiled in an Excel sheet and analyzed with SPSS Statistics.

RESULTS

In our study, thirty-two patients out of all patients visiting the dermatology OPD over a period of fifteen months had reticulate pigmentary lesions, with a frequency of study-specific dermatoses of 0.09%.

Among the enrolled patients, female cases (18) outweighed male (14), with a male-to-female ratio of 1:1.28. The mean age of the patients was 31.63 ± 15.24 years, with an almost equal proportion of young adults belonging to the 21–40 year age group and middle-aged adults belonging to the 41–60 year age group. Cases of the extreme age group constituted 18.75% (Fig. 1).

The onset of the lesions was in young to middle adulthood (56.25%), followed by childhood and teenage years (34.37%). Similarly to the age of presentation, the onset of the lesions was the least (9.37%) in polar ages. The onset of the lesions was insidious in 66.6% and abrupt in the remaining 33.62% of cases of RPD. The average duration of the lesions was 1–5 years in almost half of all cases of RPD, with an equal proportion of cases (16.12%) falling into less than six months, as well as 6–12 months, with a mean duration of 5.97 ± 6.17 years.

The progression of RPDs did not follow the typical spread in the majority of cases and was proximal to distal acral or vice versa in 43.75% of the cases from the commencement of the lesions till complete evolution. Due to the changing pattern of RPDs, our study provided a definite difference between the age of onset and the age of presentation with a special reference to site-specific changes.

An advancing rate of progression of pigmented lesions had a marginal edge on steady lesions so was true in the pattern of density of RPDs, in which discrete lesions had a precedence over confluent ones. The average size of the lesions ranged from 3–5 mm in 65.62% of all RPD cases, with pin-point lesions constituting only around one-fifth of all cases. The intensity of pigmentation was higher in the flexures when compared to the trunk or face (Table 1).

We adopted the classification proposed by Sinha [2] and Sardana [3] to further classify various RPDs, and found true RPD in seven cases, genetic disorders with secondary reticulate pigmentation in two cases, dermatoses with reticulate pigmentation in fifteen cases, and autoimmune and miscellaneous conditions in two and six cases, respectively (Table 2).

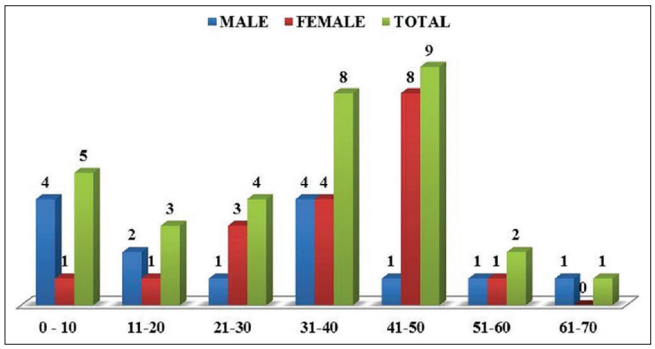

Figure 1: Age and sex distribution of RPDs.

As per the overall site-specific involvement of RPD, the upper limbs constituted 46.87%, closely followed by the lower limbs in 40.62%, the trunk in 31.25%, and the back in 21.87%. The face and neck were involved in 15.62%. The site-specific onset of the lesions differed from that of site-wise distribution at the time of presentation and was attributed to the progressive nature of disorders in around half of them (Table 2).

The most common disorder found in this study was erythema ab igne (15.62%). Livedoid vasculopathy, Dowling–Degos disease, and confluent and reticulated papillomatosis each constituted 9.37%. Among the most common dermatoses in the studied population, truncal involvement was observed by large in 60% of all cases of erythema ab igne, while upper and lower limb involvement was observed in 40% of the cases each. The legs were exclusively affected in three out of four cases (75%) of livedoid vasculopathy, while the

Table 1: Morphological patterns of the reticulate pigmentary dermatoses

Feature	*n* (%)
Age of onset	
Since birth	2 (6.25%)
Childhood (till 12 yrs. of age)	5 (15.62%)
Teenage	6 (18.75%)
Adulthood	18 (56.25%)
Old age	1 (3.12%)
Duration of lesions	
< 6 months	5 (15.62%)
6–12 months	5 (15.62%)
1–5 yrs.	16 (50%)
> 5 yrs.	6 (18.75%)
Manner of progression	
Acral	14 (43.75%)
Centripetal	7 (21.87%)
Centrifugal	11 (34.37%)
Course of lesions	
Static	14 (43.7%)
Progressive	18 (56.25%)
Size of lesions	
< 1 mm	7 (21.87%)
1–3 mm	2 (6.25%)
3–5 mm	21 (65.62%)
> 5 mm	2 (6.25%)
Density of pigment	
Confluent	15 (46.87%)
Discrete	17 (53.12%)

Table 2: Site-wise distribution of the reticulate dermatoses

	Disorder	Area of distribution
True (genetic) RPD	Dowling–Degos disease = 3 (9.37%)	Neck, axilla, hands = 1 Forearms and hands = 2
	Reticulate acropigmentation of Dohi = 2 (6.25%)	Dorsum of hands = 1 Dorsum of feet and legs = 1
	Reticulate acropigmentation of Kitamura = 2 (6.25%)	Dorsum of Hands = 1 Dorsa of hands and feet = 1
Genetic disorders with secondary reticulate pigmentation	Epidermolysis bullosa with mottled pigmentation = 1(3.12%)	Arms, forearms, abdomen = 1
	Cutis marmorata telangiectatica congenita =1 (3.12%)	Face, legs, abdomen = 1
Dermatoses presenting with de novo or secondary reticulate pigmentation	Confluent and reticulate papillomatosis = 3 (9.37%)	Neck, axilla, inframammary area, trunk = 2 Back = 1
	Prurigo pigmentosa = 1 (3.12%)	Trunk and thighs = 1
	Dyschromic amyloidosis = 2 (6.25%)	Shoulders and upper back=1 Arms and back = 1
	Cutis marmorata = 2 (6.25%)	Face and upper limbs = 1 Trunk and legs = 1
	Livedo reticularis = 2 (6.25%)	Lower legs = 2
	Livedoid vasculopathy = 3 (9.37%)	Face and feet = 1 Legs = 2
	Lichen planus pigmentosus = 2 (6.25%)	Trunk = 1 Trunk and upper limbs = 1
Autoimmune disorders with mottled pigmentation	Systemic sclerosis = 2 (6.25%)	Back, forearms, legs = 2
Miscellaneous conditions	Erythema ab igne = 5 (15.62%)	Trunk and forearms = 1 Forearms and thighs = 1 Trunk and back = 2 Thighs = 1
	Atrophoderma vermiculatum = 1 (3.12%)	Cheeks = 1

upper limbs were predominant sites in all three cases of Dowling–Degos disease. Confluent and reticulated papillomatosis involved the trunk in 66.6% and the back in 33.3% of cases.

Among the various RPDs, systemic involvement was seen in the total seven patients (21.87%). Individually, one case of dyschromic amyloidosis was associated with hypertension and diabetes, two cases of livedoid vasculopathy, and one of livedo reticularis were associated with varicose veins. Asymmetry of the limbs and hip dysplasia were the anomalies found in cutis marmorata telangiectatica congenita. Among the autoimmune dermatoses, interstitial lung disease was present in both cases of systemic sclerosis.

DISCUSSION

The net-like configuration of reticulate pigmentary dermatoses, although peculiar, is not essentially found in all true and acquired subtypes, therefore leads to problems in primarily recognizing them according to the dominant morphology. Also, the variable pigmentation pattern among each subtype and related conditions such as mottled pigmentation and dyschromia adds further hurdles due to the different phenotypical expressions of a similar gene defect, hence the terms are often used interchangeably, leading to difficulty in defining each disorder and finding appropriate demographic data.

Based on our experience from the present study and literature research, the term *reticulate pigmentary dermatoses* (RPD) was found to be expedient to explicate dermatoses enrolled in our study, which presented with hyperpigmented macules with varying sizes and amounts of pigmentation, arranged in a net-like pattern with or without hypopigmented macules.

Considering the female predominance and erythema ab igne being the most common individual RPD in our study, similar sex preponderance was seen in the study done on patients with erythema ab igne by Murat Ozturk et al. [8], who observed a male-to-female ratio of 1:2. In terms of true RPD, the present study mirrored the case series conducted by Chandramohan et al. [9], in which the male-to-female ratio was 1:2.

The most common age group affected (41–50 years) and the mean age of cases (31.63 years) in the present study differed from the study by Namitha et al. [10] on a case series of five cases of dyschromia, in which the most common age group affected was 21–30 years

(60%), with a mean age of 19.2 years. This negates the preconcert belief of the early age onset of RPDs, although the assertive number of acquired RPDs with a relatively later presentation cannot be overlooked.

The most common age of onset (adulthood: 56.25%) and the mean duration (5.97 years) belonging to our study slightly differed from the study conducted by Katoulis et al. [11] on fifty patients with poikiloderma of Civatte, among which the mean age at diagnosis was 47.8 years for females and 61.7 years for males, with a mean duration from onset to diagnosis of 6.2 years. Our assumption concerning the onset of lesions would have been earlier if the study involved only true RPDs with a possible exception of some secondary disorders complying an early advent.

In our study, acral progression of the lesions was found in approx. 2/5 of the cases, and the association with systemic illnesses was found in approx. 1/5 of all RPD cases. A comparison could not be done due to a lack of specific data in the literature and in view of the limited sample size. Similarly, other variables such as the rate, size, and density of RPDs were the first to be described comprehensively in the present study.

Individual Dermatosis and Distribution

Erythema ab igne

It is an acquired dermatosis characterized by erythematous to violaceous patches with a reticular configuration usually on the sites of exposure to heat or thermal radiation. It accounted for 5 (15.62 %) cases in our study, with 4 out of 5 patients in the age group of 41–50 years. The trunk (60%) and thighs (40%) were the most common sites affected (Fig. 2a). This observation was synonymous with the study by Raza et al. [12], in which 0.3% of 4563 registered patients were diagnosed with erythema ab igne and 42.8% of the cases fell into the 41–50 year age group.

Livedo vasculopathy and livedo reticularis

Livedo vasculopathy is a disorder characterized by painful, purpuric lesions predominantly on the gaiter area of the lower limbs, while livedo reticularis predominantly presents with blotchy, reddish-blue to purple, net-like discolorations on the legs. In our study, livedo vasculopathy was present in 3 (9.37%) patients, with 2 cases (66.6%) in 2–3 decades of life, while livedo reticularis was noted on the legs in 2 (6.25%) cases (Fig. 2b). In a study conducted by Emily et al. [13] on seventy patients with livedoid vasculopathy, 47% of the cases presented between 21–40 years of age.

Confluent and reticulate papillomatosis (CRP)

CRP is a benign acquired keratinization disorder characterized by scaly, brownish, centrally confluent, reticulate macules that coalesce to form patches. In the present study, CRP was found in 9.37% of the cases, with 66.6% belonging to the 21–30 year age group and a male-to-female ratio of 2:1. In an analogous study conducted by Shashikumar et al. [14] on thirty patients with CRP, the mean age at the onset of eruptions was 17–48 years and the male-to-female ratio was 1:1.5.

Dowling–Degos disease

Among all reticulate disorders, DDD was found in 9.37% of our cases, among which 2 patients (66.6%) were females and 1 (33.33%) was male (Figs. 3a and 3b). None showed systemic abnormalities. These findings differed from the study by Agut Busquet et al. [15] on fifteen patients with DDD, revealing males in 53% of the cases and females in 47%, with 20% of the cases being hypertensive.

Reticulate acropigmentation of Kitamura (RAPK)

RAPK is an autosomal dominant disorder characterized by reticulate, atrophic, freckle-like hyperpigmentation most commonly on acral areas. In the present study, RAPK was found in 2 patients, a mother and daughter from the same family (Fig. 2c). The lesions involved the

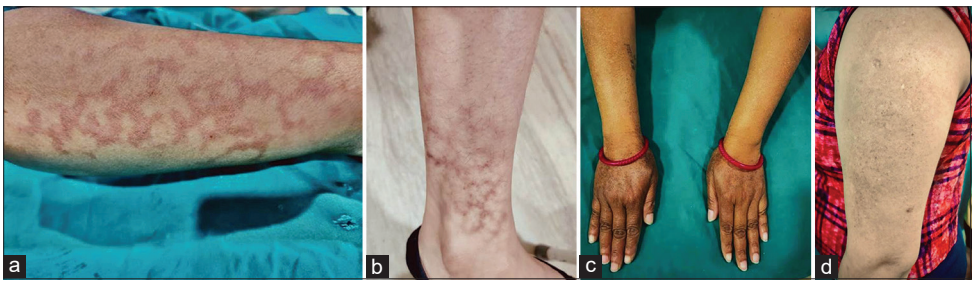

Figure 2: (a) Erythema ab igne: erythematous, reticulate pattern on the extensor aspect of the forearm. (b) Primary livedo reticularis: erythematous-to-pigmented, blotchy lesions on the leg. (c) Reticulate acropigmentation of Kitamura: hyperpigmented macules on the bilateral hands. (d) Dyschromic amyloidosis: mixed, hypo- to hyperpigmented lesions on the arms.

face, hands, and feet. A study conducted by Kocaturk et al. [16] reported a familial case of acropigmentation of Kitamura in a 53-year-old female and her daughter with a similar presentation. We also witnessed the circumstantial shift of disorders within the same spectrum with changes in the site-specific distribution of disease in 3 out of 5 patients with DDD and RAPK collectively.

Reticulate acropigmentation of Dohi (RAPD)

RAPD was found in 6.25% of the cases who presented with hypopigmented macules on the dorsal extremities (Figs. 4a and 4b). A similar observation was seen by Peng et al. [17] in a study on 25 patients with dyschromatosis symmetrica hereditarian, with the typical sites being the extremities in 48% of the cases.

Dyschromic amyloidosis

In the present study, dyschromic amyloidosis, a rare form of typical reticulate hyperpigmentation interspersed with hypopigmented-to-depigmented macules was present in 2 (6.25 %) cases, with a female preponderance and the involvement of the arms and back in both cases (Fig. 2d). This was analogous to a case study on amyloidosis cutis dyschromica by Yang et al. [18] on two female siblings, who both presented with diffuse, mottled hyperpigmentation and hypopigmentation involving the trunk, upper limbs, and thighs.

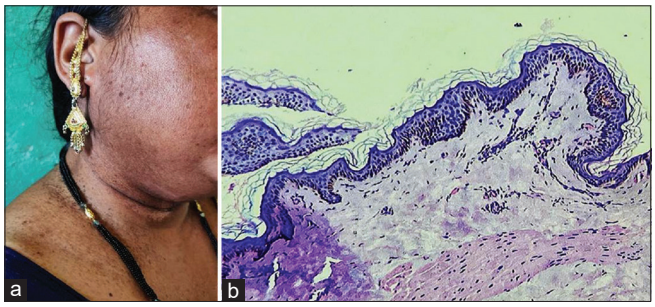

Figure 3: Dowling–Degos disease: (a) hyperpigmented macular lesions on the face, neck, and shoulders; (b) photomicrograph of DDD showing atrophic epidermis and flattened rete ridges with an antler-like appearance without pigment incontinence (H&E, 40×).

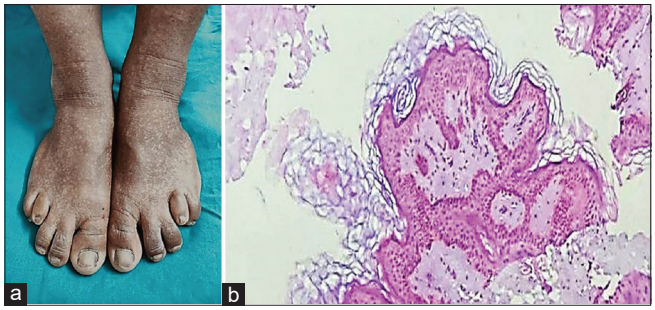

Figure 4: (a and b) Reticulate acropigmentation of Dohi: a) admixture of mottled pigmentation on the bilateral feet; b) photomicrograph of RAPD showing focal thinning of the epidermis, dilated follicular infundibula with a keratin cyst, and basal layer hyperpigmentation (H&E, 40×).

Lichen planus pigmentosus

The trunk (100%) and upper limbs (50%) were the predominant sites in 2 enrolled cases of lichen planus pigmentosus with an equal sex dominance and a reticular variant in both. A case report of lichen planus presenting as reticulate pigmentation by Sinha et al. [19] involving a 61-year-old male patient had a network-like pattern of pigmentation on the trunk and limbs.

Prurigo pigmentosa

In our study, we found a single case of prurigo pigmentosa, which is a rare entity, also known as Nagashima disease [20]. The distribution of hyperpigmented, reticular lesions was generalized, involving predominantly the trunk and limbs for four months in our only patient with prurigo pigmentosa. Similar features were recorded in a case series by Schevchenko et al. [21] on two patients, who presented with erythematous and hyperpigmented, reticulate eruption on the back, trunk, and shoulders apparent for two weeks and three months, respectively.

Cutis marmorata telangiectatica congenita (CMTC)

We found a single case of CMTC, in a male child (Fig. 5) who presented with erythematous, net-like lesions on the face, abdomen, and thighs, while Kienast et al. [22], in a prospective study of 27 cases, reported leg involvement in 74% of the cases and the face in 15%.

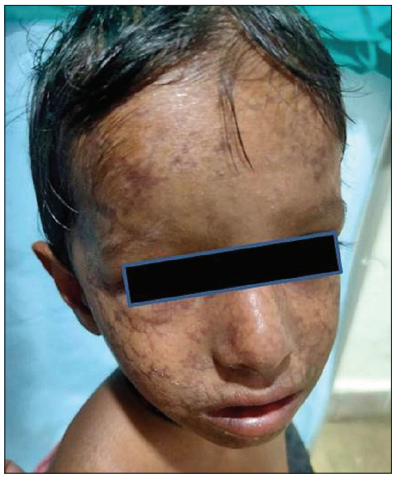

Figure 5: Cutis marmorata telangiectatica congenital: net-like, erythematous, telangiectatic lesions on the face in a child.

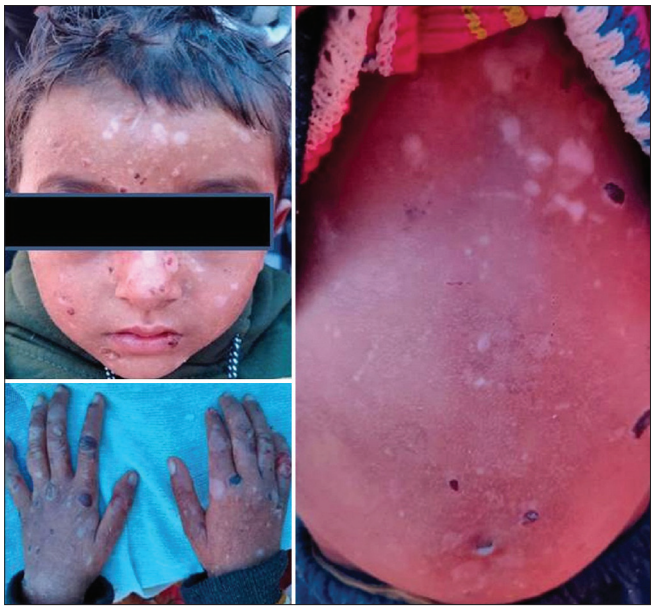

Figure 6: Epidermolysis bullosa simplex: bullae with crusts on the face and hands with mottled pigmentation on the abdomen.

Epidermolysis bullosa simplex with mottled pigmentation (EBS)

We found one case of EBS (3.12%) in a male child, who presented with bullae and crusted lesions on the face, limbs, and abdomen along with mottling on the abdomen (Fig. 6). A case of EBS with mottled pigmentation reported by Browning et al. [23] presented with hyperpigmentation involving the axilla, forearms, anterior shin, and dorsa of the feet in a seven-year-old boy.

Reticulate pigmentary dermatoses found in our study, although progressive, were expected to have a favorable outcome in the majority. A detailed evaluation of the patients assisted in more precise understanding of morphology, patterns, onset, and possible progression potential, whose analysis had been substantially missing in individual case reports or case series so far.

A positive family history in some RPDs served as an aid in genetic counseling. Studying some of the acquired reticulate dermatoses, such as dyschromic amyloidosis, erythema ab igne, lichen planus pigmentosus, revealed possible etiological and predisposing factors imperative to the pathogenesis of the diseases.

CONCLUSION

In this study, we attempted to rationally classify all reticulate pigmentary dermatoses and analyze each condition clinically and demographically, which helped us to predict their prevalence, various demographic and morphological features, and management strategy. Through these cases and this literature review, it was our initial effort to incorporate the spectrum of RPDs and, from the epitome of morphological uncertainty, we hoped to delineate the unique clinical, histological, and genetic features of such a diverse group of dermatoses.

This study also helped to predict the impending recurrences and other systemic features accompanying reticulate dermatoses that could prepare the patient and the treating physician to expect a realistic diagnostic and therapeutic outcome. These observations may also be noticeable for equivalent succeeding cases to further explore any remote association. This short literature was an attempt to fill the existing lacunae in the research of RPD and to discover future modalities to provide aesthetic confidence to patients with treatable RPD and to decrease the associated enigma and concerns associated with these dermatoses.

Study Limitations

The major limitations of this study were a relative unavailability of comparative research data on reticulate pigmentary disorders, a lack of clearance regarding inconclusive histopathological findings in differentiating overlapping disorders of the same group, and restricted resources in conducting higher and specific diagnostic interventions, such as immunofluorescence.

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

Evaluation of the therapeutic efficacy of topical 50% hydrogen peroxide vs. 100% trichloroacetic acid vs. 5% 5-fluorouracil in the treatment of warts

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ABSTRACT

Background: Warts (verruca) are caused by human papilloma virus (HPV), which is known to affect the skin and mucosae. Over two hundred strains of HPV have been identified to date, among which few strains cause cutaneous lesions. Various treatment modalities have been elucidated in treating verruca lesions, yet the best therapeutic option is yet to be determined. **Objectives:** To evaluate the efficacy and safety of topical 50% hydrogen peroxide (H_2O_2), 100% trichloroacetic acid (TCA), and 5% 5-fluorouracil (5-FU) as a topical application in the treatment of warts. **Methods:** This was a prospective, interventional, clinical trial that included sixty patients with warts randomly allotted into three groups. Group A and group B were treated every week with topical 50% H_2O_2 and 100% TCA, respectively, and group C with 5% 5-FU under tape occlusion twice a day. The treatment was executed for a maximum period of eight weeks. The patients were evaluated with the Physician Wart Assessment (PWA) every two weeks of treatment and at three months after treatment completion. **Results:** At the end of the eight weeks of treatment, 13 patients (65%) in the H_2O_2 group, 11 patients (55%) in the TCA group, and 8 patients (40%) in the 5% 5-FU group displayed complete clearance of warts (PWA grade 0). In our study, side effects were significantly higher in the TCA group (70%) and in the 5% 5-FU group (60%), notably lower in the H_2O_2 group (30%) ($p = 0.011$). The most frequent side effect was irritation (25%), which was reported in all groups. No relapse was encountered at three months of treatment completion. **Conclusion:** According to our study, H_2O_2 and TCA have the advantage of earlier action over 5% 5-FU. However, H_2O_2 remarkably stands as a safer therapeutic option concerning the clearance of lesions, patient tolerability, and side effects.

Key words: Warts, H_2O_2, TCA, 5% 5-FU

INTRODUCTION

Warts (verruca) are caused by human papilloma virus (HPV) [1], which is ubiquitous in nature and is known to affect the skin and mucosae. Over two hundred strains of HPV have been characterized to date [2]. They manifest in the form of common warts, mucosal warts, palmoplantar warts, epidermodysplasia verruciformis, and focal epithelial hyperplasia [3].

Although resistant, verruca has been dealt with a plethora of conventional treatment modalities, such as occlusion, cautery, curettage, cryotherapy, radiofrequency ablation, laser ablation, podophyllin, keratolytics, antiproliferative agents, immunotherapy, and photodynamic therapy [4].

Hydrogen peroxide (H_2O_2) is a weakly acidic and strong oxidizing agent. It exerts its antiviral effect releasing reactive oxygen species and membrane lipid

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peroxidation causing apoptosis. It has been used as a peeling agent and as a chemical cautery agent [5]. Trichloroacetic acid (TCA) causes cellular protein hydrolysis causing tissue damage owing to its caustic property [6]. Being an antimetabolite, 5fluorouracil (5-FU) inhibits nucleic acid synthesis, thereby arresting cell proliferation [6]. This mechanism enhances the killing of human papilloma virus (HPV).

Despite the availability of various treatments to deal with warts, the amenable therapeutic option is yet to be determined. This study was undertaken to determine the efficacy of different topical agents in the clearance of warts.

Objectives

The objective was to evaluate the efficacy and safety of topical 50% hydrogen peroxide (H_2O_2), 100% trichloroacetic acid (TCA), and 5% 5-fluorouracil as a topical application in the treatment of warts.

MATERIALS AND METHODS

This was a prospective, interventional, clinical trial conducted at a tertiary-care hospital for a period of six months after obtaining informed consent from patients and institutional ethical clearance.

All naive patients with warts aged above twelve years and willing to comply with the protocol were included in the study. The exclusion criteria were pregnancy and lactation, immunosuppression, patients with a treatment history of warts prior to enrollment in the study, and patients with unrealistic expectations. On detailed history taking and clinical examination, a total of sixty patients with a clinical diagnosis of warts, randomly divided into three groups, twenty patients in each, were allotted to the study.

At the baseline visit, the lesions were evaluated for type, site, number, and size of warts and photographed in each patient. Group A was treated with topical 50% H_2O_2 solution, group B with topical 100% TCA, and group C with topical 5% 5-FU. TCA and H_2O_2 solutions were applied to warts in weekly intervals. The solutions were applied with a wooden toothpick after protecting the surrounding tissue by applying petroleum jelly. The solution was applied, and the formation of white frost was noted on the lesions. Group C patients were advised to apply 5% 5-FU on the lesions with a cotton tip applicator, followed by two-hour occlusion with duct tape twice a day.

The treatment lasted until the total clearance of lesions or a maximum period of eight weeks. Clinical assessments were done at baseline, every two weeks of treatment and after the completion of treatment. Side effects were noted. The patients were also enquired about systemic complaints at each visit. After treatment, follow-up was done three months after treatment completion to check for recurrence.

The following Physician Wart Assessment (PWA) scores were used to assess treatment response:
Grade 0: clear.
Grade 1: < 3mm (near clear).
Grade 2: 3–6 mm.
Grade 3: > 6 mm.

Treatment response was noted at each visit and analyzed by a statistician. Data was expressed as mean ± SD quantitative variables and as numbers and percentages as applicable. Chi-squared test and Fisher's exact tests were used to compare categorical data. An independent sample t-test was used for comparing quantitative data. A p value below 0.05 was considered statistically significant.

RESULTS

There were 32 (53.3%) males and 28 (46.6%) females out of the total of sixty patients. Age distribution was between 20 and 40 years, with a mean of 31.36 ± 10.28 years. Regarding clinical types, 18 patients had common warts distributed on the trunk and extremities, 13 had palmar warts, 10 had plantar warts, 2 had both palmoplantar warts, 9 had filiform warts distributed on the face and neck, 5 had genital warts, and 3 had plane warts distributed on the face (Table 1). All three groups had comparable demographic data with no significant p value.

Evaluation was conducted every two weeks (Table 2). By the end of eight weeks, i.e., the completion of all sessions, 13 patients (65%) in the H_2O_2 group (Figs. 1a and 1b), 11 patients (55%) in the TCA group (Figs. 2a – 2c), and 8 patients (40%) in the 5-FU group (Figs. 3a and 3b) displayed complete clearance of the lesions (PWA grade 0) (Table 3). Treatment responses were compared among the three groups, and no statistically significant difference was noted between the groups.

A near-clear response (PWA grade 1) was seen in 5 patients (25%) in the H_2O_2 group, 5 patients (25%) in the TCA group, and 3 patients (15%) in the 5-FU group. In addition, no response was noted in 3 patients (15%) in the 5-FU group and 1 patient each in the H_2O_2 and TCA groups.

All three groups exhibited good improvement in terms of reduction in size and number compared to the baseline (Table 4). The H_2O_2 group had a better reduction with a significant *p* value of 0.0001, followed by the TCA group with a significant *p* value of 0.0002 and the 5-FU group with a *p* value of 0.018.

Burning and irritation were the most reported side effects in the H_2O_2 group and TCA group. Erythema was most reported in the 5-FU group, followed by pain and scaling. Ulceration was noted in one patient in the TCA Group. Overall, side effects were less often reported in the H_2O_2 group (Table 5). Although irritation and pain were reported more often in groups H_2O_2 and TCA, symptoms tended to subside post-procedure in the H_2O_2 group yet lasted longer in the TCA group.

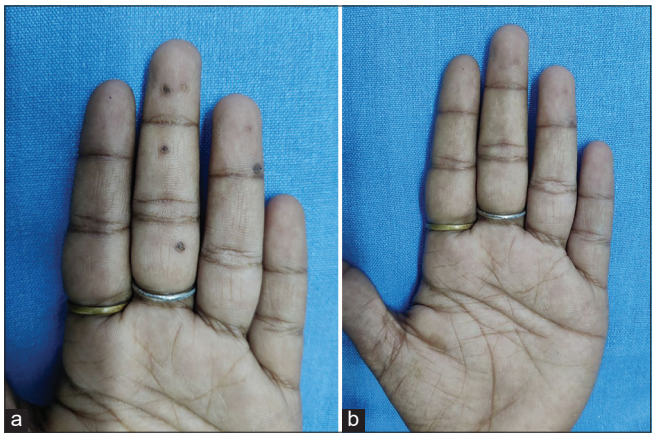

Figure 1: (a and b) Clinical response in palmar warts with H_2O_2.

Table 1: Types of warts.

Type of wart	H_2O_2 Group	TCA Group	5-FU Group	Total	%
Common warts	6	4	8	18	30%
Palmar warts	3	8	2	13	21.6%
Plantar warts	3	2	5	10	16.6%
Palmoplantar warts	2	0	0	2	3.3%
Plane warts	0	1	2	3	5%
Genital warts	2	3	0	5	8.3%
Filiform warts	4	2	3	9	15%
Total	20	20	20	60	100%

DISCUSSION

Warts are known to be notorious for their unpredictable treatment responses. They occur worldwide and are estimated to involve 30% of children and young adults and 3–5% of adults [7]. They have always been a puzzling entity for clinicians to choose a prudent therapeutic option. The incubation period varies from several weeks to around a year and the number of lesions varies from individual to individual and in the same individual from site to site. Lesions may recur even after obtaining clinical resolution or may regress on their own to recur later. The infection of the host is acquired through direct contact with viral particles or indirect contact via fomites, such as flooring, shoes, clothes, and other equipment [8]. Although not an alarming disease, warts are responsible for psychosocial discomfort [9].

It remains a pressing concern to pick up an efficacious and safe modality of treatment that will cause no recurrences and side effects among currently available treatment options. Sixty patients completed our study, among which 32 (53.3%) were males and 28 (46.6%) were females. Most were in age group 20–40 years. In 2018, Khopkar et al. reported a higher prevalence among males than females, with the highest prevalence in age group 25–29 years [10].

Hydrogen peroxide causes protein denaturation and cell death, which ensures the killing of HPV virus. In our study, after eight weeks of treatment with 50% H_2O_2, complete wart clearance (PWA grade 0) was noted in 65% of the patients. Similarly, in a trial conducted by Smith et al., patients had a twice-weekly application of 45% H_2O_2, and statistically significant target wart clearance was achieved in 37.3% out of 76 patients in eight weeks [11]. A study by Kaur et al., in which 40% H_2O_2 was applied in three sessions at two weeks intervals, revealed a more than 75% reduction in wart size in 30% of twenty patients with genital warts, similarly to our study [5].

Table 2: PWA score at 2, 4, and 6 weeks of treatment.

PWA score	H_2O_2 Group			TCA Group			5-FU Group		
	2 weeks	4 weeks	6 weeks	2 weeks	4 weeks	6 weeks	2 weeks	4 weeks	6 weeks
3 (> 6 mm)	16	2	2	16	5	3	17	17	7
2 (3–6 mm)	4	11	3	4	10	5	3	2	5
1 (near clear)	0	6	10	0	5	8	0	1	6
0 (clear)	0	1	5	0	0	4	0	0	2

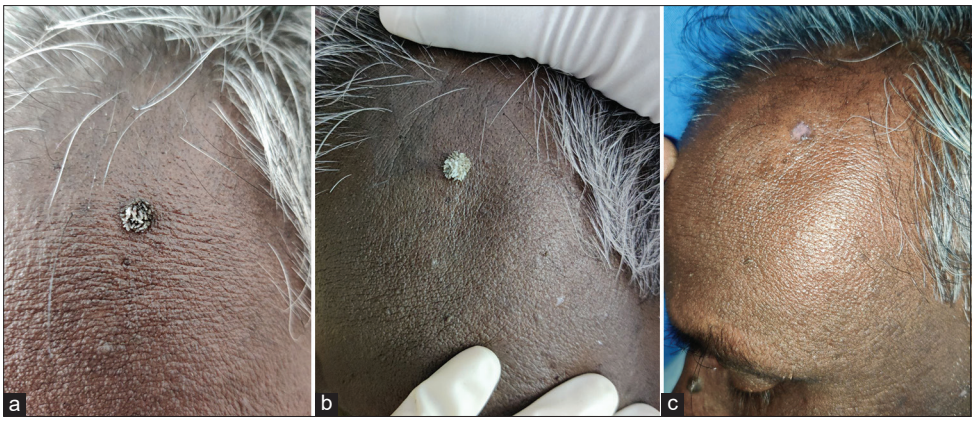

Figure 2: (a-c) Clinical response in filiform warts with TCA application. Note the side effect hypopigmentation after treatment.

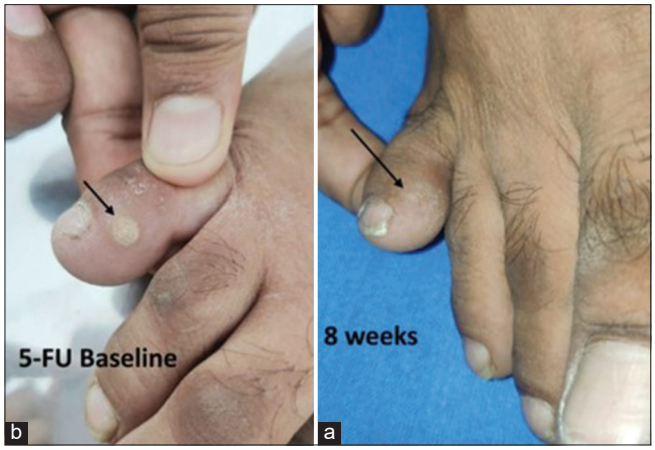

Figure 3: (a and b) Clinical response in plantar warts with 5% 5-FU.

Table 3: PWA score at the end of eight weeks of treatment.

PWA Score	3 (> 6 mm)	2 (3–6 mm)	1 (near clear)	0 (clear)
H_2O_2 Group	1	1	5	13
TCA Group	1	3	5	11
5-FU Group	5	4	3	8

Table 4: Mean number of lesions before and after treatment.

	No. of Lesions Before		No. of Lesions After 8 Weeks		*t* Value	*p* Value
	Mean	SD	Mean	SD		
H_2O_2 Group	4.75	2.78	1.3	1.17	5.113	0.0001
TCA Group	3.35	2.11	1.2	1.01	4.11	0.0002
5-FU Group	3.55	2.6	1.85	1.67	2.465	0.018

TCA has been a time-tested modality for the treatment of warts. In our study, after eight weeks of treatment with 100% TCA, complete wart clearance (PWA grade 0) was noted in 55% of the patients. Similarly, a study by Qayum et al. objectified the efficacy of 100% TCA in anogenital warts. Six sessions of treatment gave an 82% clearance rate in ninety patients [12]. Pouran et al. reported 80% TCA solution being more efficacious than 35% TCA (weekly application in six sessions) yet advised the clinician to be careful in its application [13]. A study conducted by Taner et al. reported the successful treatment of genital warts with 85% TCA (2–4 sittings) in fifty-one female patients, which was in accordance with our study [14].

5-FU blocks DNA synthesis and damages basal layer cells of the epidermis, hindering the proliferation of viral warts. In our study, after eight weeks of treatment with 5% 5-FU, complete wart clearance (PWA grade 0) was obtained in 40% of the patients. Salk et al. studied the efficacy of topical 5% 5-FU in plantar warts under occlusion and observed that 19 out of 20 patients (95%) had complete eradication of all plantar warts within twelve weeks of treatment [15], which would necessitate a longer duration of treatment with 5-FU for better results.

In our study, all three modalities had significant improvement in warts. 50% H_2O_2 stands ahead of 100% TCA and 5-FU, with a 65% significant improvement vs. 55% (100% TCA) and 40% (5-FU). Meanwhile, the 80% TCA group had a 70% improvement when compared to 40% H_2O_2 (63% improvement) according to Kaur et al. [5].

50% H_2O_2 treated patients (group A) had less discomfort and minimal side effects. Few reported irritation and pain, which subsided post-application. 100% of the TCA (group B) patients had more irritation and pain, which lasted longer. Hypopigmentation was noted in two patients (10%). Ulceration was noted in one (5%) patient, also reported in a study by Pouran et al. [13] 5% 5-fluorouracil treated patients (group C) reported irritation, pain, and erythema. Owing to the safety profile, the H_2O_2 group had minimal side effects and subsided in a short span of time, which was in accordance with a report by Kaur et al. [5].

Table 5: Side effects among the groups.

Side effect	Group 1 (50% H_2O_2)	%	Group 2 (100% TCA)	%	Group 3 (5% 5-FU)	%	Chi-Squared Value	*p* Value
None	14	70%	6	30%	8	40%	8.943	0.011
Irritation	3	15%	7	35%	5	25%	3.733	0.155
Pain	2	10%	3	15%	4	20%	0.342	0.741
Erythema	1	5%	1	5%	3	15%	0.341	0.739
Scaling	0	0%	2	10%	0	0%	2.105	0.147
Ulceration	1	5%	1	5%	0	0%	2.034	0.362

5-FU treated patients had low response rates in the initial weeks yet had a good response at the end of the eight weeks. At the end of three months of post-treatment follow-up, all three groups had similar results, and no recurrence was encountered.

CONCLUSION

According to our study, H_2O_2 and TCA have the advantage of earlier action over 5% 5-FU. However, H_2O_2 stands remarkably as a safer therapeutic option with respect to the clearance of lesions, patient tolerability, and side effects.

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

Skin cancers of cephalic extremity epidemiology and their anatomical, clinical, therapeutic, and evolutive aspects: A series of 260 cases

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ABSTRACT

Background: The most malignant skin tumors of the head are dominated by epithelial cancers, particularly basal cell carcinomas, followed by squamous cell carcinomas and melanomas. Herein, we present a case series of malignant skin cancers in the cephalic region. We address their epidemiological, clinical, histological, and therapeutic profiles in our context. **Materials and Methods:** This was a prospective study conducted for descriptive purposes on cases of skin cancer, including melanoma, squamous cell carcinoma, and basal cell carcinoma, followed at the dermatology department of CHU Hassan II Fez between June 2017 and December 2021. **Results:** We collected a total of 260 patients with different types of skin cancer. 147 cases (57%) were in the cephalic location: 56% presented squamous cell carcinoma, followed by melanoma (22%) and basal cell carcinoma (21%). **Conclusion:** The early detection of skin cancer is essential to reduce the functional morbidity and mortality associated with these tumors, especially in these cephalic locations.

Key words: Cutaneous tumors, Cephalic region, Early diagnosis

INTRODUCTION

The head may be affected by all types of skin cancer, the most common being basal cell carcinoma, followed by squamous cell carcinoma and melanoma [1]. Surgery remains the reference treatment yet is still subject to the constraints of mutilation in advanced cases despite the comfort reported by reconstructive surgery. Nevertheless, in the face of clinical scalability, decisions may only be collegial, and respect to the patient and their choices remains essential. The adequate management of these tumors is based on a good knowledge of their epidemiological profiles and diagnostic methods and the different therapeutic methods. Our objective was to determine the epidemiological, anatomical, clinical, therapeutic, and evolutionary profiles of malignant tumors in the cephalic region.

MATERIALS AND METHODS

We conducted a descriptive, retro-prospective study including melanomas, squamous cell carcinomas, and basal cell carcinomas of the cephalic region followed at the dermatology department of CHU Hassan II Fez between June 2017 and December 2021. Epidemiological, clinical, histological, therapeutic, and evolutive data was collected in a pre-established exploitation sheet.

RESULTS

We collected a total of 260 patients with different types of skin cancer (BCC, melanoma, SCC) in different locations (Figs. 1a, 1b, and 2). Among these patients, 147 cases (57%) had a cephalic localization, with an average age of 61.9 years and extremes ranging from

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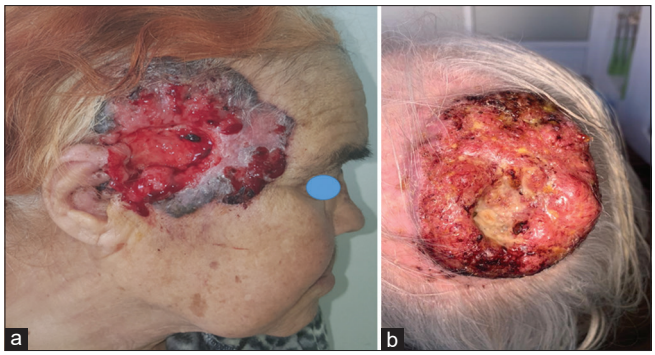

Figure 1: (a) Histologically confirmed temporal basal cell carcinoma. (b) Histologically confirmed squamous cell carcinoma of the scalp.

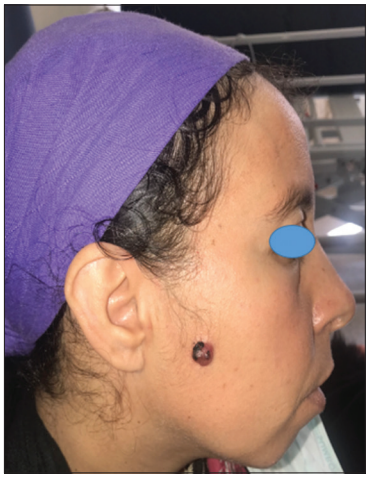

Figure 2: Histologically confirmed facial melanoma.

twenty years to one hundred years, and a sex ratio of 1.24 (144 males and 116 females). The average diagnosis time, hospitalization waiting time, hospital time were 40.20 and 33 days, respectively.

The average time between the symptomatology and initial consultation, the average time of diagnosis in our patients, was 43 months, 40 days. Eighty-seven percent of the patients came from rural areas. Phototypes III and IV were predominant. All patients were exposed to the sun during their childhood and adolescence, without noticeable protection. The patients were mainly farmers, masons, itinerant day laborers, or without professions. Self-medication was noted in 20% of the cases. Sixty percent of the patients consulted with the general practitioner and 20% with the dermatologist, among whom 80% received symptomatic treatment and only 20% had a skin biopsy taken. All patients had benefited from anatomopathological confirmation prior to oncological excision. The diagnostic biopsy revealed 56% squamous cell carcinomas, 22% melanomas, and 21% basal cell carcinomas.

Table 1 shows the distribution of BCC, SCC, and melanoma (Table 1).

Table 2 shows the received therapeutic management (Table 2).

The cephalic tip may be affected by all types of skin cancers, among which the most common are BCC, followed by SCC and melanoma [1]. In our study, it was noted that SCC was the most frequent followed by melanoma and BCC, which may be explained by the selection of generally aggressive cancers requiring hospitalization at our department. Although the risk of developing carcinoma depends on genetic, phenotypic, and environmental factors, it is well established that UV radiation is the main risk factor for developing skin cancer [2,3]. In our series, most patients were male, of phototypes III and IV, and of rural origin. This may be explained by the fact that males are more exposed to the sun given the nature of their work, and that the majority of them do not use means of protection unlike females. In our series, as in most Maghreb and African publications, the diagnostic time was long [4]. The reasons for late diagnosis were dominated by financial problems and diagnostic errors. The cephalic region may be affected by any type of skin cancer, among which the most common are BCC followed by SCC and melanoma [1]. Basal cell carcinoma is characterized by a local invasive potential, yet it may cause significant tissue destruction to the cephalic region [5,6]. Current guidelines subdivide BCC into low-risk (nodular and superficial) and high-risk (micronodular, infiltrating and morphoeic, squamous differentiation subtypes) [3,4]. Nodular and sclerodermiform BCC is most often located on the head and neck and near the orifices of the face, while the superficial form is mainly located on the trunk and limbs [7]. Our study corroborated the data from the literature in that we observed that the nodular form presented 63% of the cases, followed by sclerodermiform carcinoma (21%). For squamous cell carcinoma, Girish et al. noted that nasal involvement was the most common (25.5%), followed by cheek (16%), periorbital (14%), forehead (7.5%), lip (6%), and chin (2%) involvement [8]. In our work, 54% of SCC were located in the nose, orbit, ear, and mouth, 34% in the cheeks and forehead, and 12% in the scalp. The cervicofacial locations of melanomas accounted for 10% to 30% of cutaneous melanomas. It has been described that the mortality rate is more than two times higher than that of melanomas localized elsewhere [9]. Regarding the risk of invasion, these melanomas are often associated with a high Breslow

Table 1: Characteristics of malignant skin cancers.

	BCC	SCC	Melanoma
Histological type	-Nodular BCC: 19/30 cases (63%) - Scleroderma cell carcinoma: 6/30 cases (20%) - Superficial CBC: 5/30 cases (9%)	- Poorly differentiated SCC: 49/83 cases (59%) - SCC moderately differentiated: 7/83 cases (9%) - Well-differentiated SCC: 56/83 cases (32%)	- Nodular melanoma: 24/34 cases (70%) - Achromic melanoma: 2/34 cases, achromic (5%) - Dubreuil melanoma 8/34 cases: 25%
Tumor size	- Less than 1 cm: 6/30 cases (20%) - More than 1 cm: 24/30 cases (80%)	- Less than 1 cm: 73/83 cases (87%) - More than 1 cm: 10/83 cases (12%)	Breslow less than 4 m: 12% Breslow more than 4 mm: 88%
Metastases	-Without metastases: 18/30 cases (60%) -With metastases: 12/30 cases (40%)	-Without metastases: 35/83 cases (42%) - With metastases: 48/83 cases (58%)	- Without metastases: 16% - With metastases: 84%
Topography	- Scalp: 6/30 cases (20%) - Face (forehead, chin, cheeks): 14/30 cases (47%) - Periorificial: 10/30 cases (33%)	- Scalp: 10/83 cases (12%) - Face (forehead, chin, cheeks): 28/83 cases (34%) - Periorificial: 36/83 cases (54%)	34 cases in the cephalic region

Table 2: Distribution of the different patient management strategies.

	Melanoma	SCC	BCC
Surgery alone	29/34 cases (85%)	65/83 cases (78%)	25/30 cases (83%)
Adjuvant radiation therapy or combined chemotherapy	3/34 cases (15%)	13/83 cases (22%)	5/30 cases (27%)

index and have more high-risk histological features, including neurotropism, lymphovascular invasion, and satellite metastases [9,10]. Our study revealed the predominance of nodular forms (76%), and less common Dubreuil's melanoma (23%). Almost all of these melanomas were diagnosed late, with a Breslow index greater than 4 mm. This may be explained by the capillary cover [11] in this region and a higher blood and lymphatic flow responsible for a high proportion of rapidly growing, vertically growing melanomas, such as nodular and desmoplastic melanomas [12].

Surgery remains the treatment of choice for skin tumors of the cephalic region. The use of non-surgical treatments that are exclusive or complementary to surgery may be indicated [13]. External beam radiation therapy is most often complementary after surgery for some aggressive tumors [14,15]. In our study, most patients (89%) had received surgical treatment and around 11% had received treatment with either chemotherapy or adjuvant radiotherapy. The evolution was favorable in 66–80% of the patients. However, there was an increase in 14% and death in 6%.

CONCLUSION

Skin cancers of the cephalic region are the most frequent integumentary pathology in the daily practice of the dermatologist and maxilloplastic surgeon in our country. The advanced form of these cancers is a provider of functional morbidity and aesthetic sequelae, and in some situations, is life-threatening, which defines their severity and the difficulties of management both for carcinological excision and reconstruction. The early detection of skin cancer is, therefore, crucial to reduce the functional morbidity and mortality associated with these tumors. As a result, the establishment of continuing medical education programs on the subject as well as the organization of public awareness campaigns are necessary.

Statement of Human and Animal Rights

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

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Our Dermatology Online

Brief Report

Trichoscopy of connectivitises: Discoid lupus erythematosus or dermatomyositis?

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ABSTRACT

Background: Discoid lupus erythematosus (DLE) and Sdermatomyositis (DM) are two connectivitises with frequent scalp involvement and similar clinical features. **Objective:** The objective of this study was to evaluate and compare the trichoscopic findings in patients with DM and DLE and to determine the distinctive feature of each pathology that may help in the differential diagnosis. **Materials and Methods:** We performed an analytical, comparative primary study of trichoscopic images belonging to 32 patients (18 cases of lupus and 14 of dermatomyositis) with a total of seventy lesions over a period of two years. **Results:** Eighteen cases of discoid lupus and fourteen cases of dermatomyositis were included. Trichoscopic founding revealed that abnormalities of follicular openings, pigment disorders, white structures, and downy hair were more frequent in lupus, and vascular patterns and dystrophic and circular hair were more prominent in dermatomyositis. The analytical study revealed that the absence or reduced number of follicular openings ($p = 0.024$), the presence of sliding sheaths ($p = 0.048$) were significant signs in favor of lupus; and the presence of perifollicular erythema ($p = 0.0001$), linear fine vessels and telangiectasia ($p = 0.031$), and pseudo-lake structures ($p = 0.002$) were associated with dermatomyositis. **Conclusion**: Trichoscopic examination is a valuable tool for the diagnosis of connectivitis.

Key words: Trichoscopy, Scalp, Dermatomyositis, Lupus

INTRODUCTION

Discoid lupus erythematosus (DLE) and dermatomyositis (DM) are two connectivitises with frequent involvement of the scalp. Distinguishing the two conditions in a given location may be difficult as they share similar clinical features. Trichoscopic features may provide diagnostic support and differentiate between the two conditions. However, no direct comparison of these features has been made in patients with connective tissue disease. The purpose of this study was to evaluate and compare trichoscopic findings in patients with DM and DLE and to identify the characteristics of each pathology that could be helpful in differential diagnosis.

MATERIALS AND METHODS

We performed an analytical, comparative study of trichoscopic images belonging to 32 patients (18 cases of lupus and 14 of dermatomyositis) with a total of seventy lesions at the dermatology department of University Hospital Center HASSAN II in Fez, Morocco, over a period of two years from 2020 to 2022.

The inclusion criteria were the presence of clinical scalp involvement in patients with a diagnosis of DM and DLE.

The exclusion criteria were: overlapping connectivitises, the presence of other pathologies affecting the scalp,

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and the use of drugs affecting the hair growth/color cycle.

All patients were examined with the DermLite DL4 digital dermoscope with minimal pressure, and photographs were taken in several scalp locations.

The trichoscopic evaluation focused on several aspects: follicular openings, follicular stalk, perifollicular surface, interfollicular space, white structures, vascularization.

The data was entered in an Excel sheet, analyzed with SPSS, version 26, and compared with the chi-squared test.

RESULTS

There were eighteen cases of discoid lupus (1 male, 17 females), with a male-to-female ratio of 0.05 and a mean age of forty years. The clinical patterns were as follows: single alopecic patch (22%) and multiple alopecic patches (78%). The average duration of evolution was seven years.

There were fourteen cases of dermatomyositis (3 males, 11 females), with a male-to-female ratio of 0.27 and an average age of fifty years. The clinical patterns were as follows: diffuse alopecia (50%), alopecic patches (14%), and no alopecia (36%). The average duration of evolution was six years.

Table 1 summarizes the different trichoscopic characteristics of the two pathologies.

Abnormalities of the follicular openings, pigment disorders, white structures, and downy hair were more frequent in lupus (Fig. 1), while vascular patterns, dystrophic, and circular hair were more prominent in dermatomyositis (Fig. 2).

The analytical study revealed that the absence or reduced number of follicular openings ($p = 0.024$) and the presence of sliding sheaths ($p = 0.048$) were significant signs in favor of lupus; and the presence of perifollicular erythema ($p = 0.0001$), linear fine vessels and telangiectasia ($p = 0.031$), and pseudo-lake structures ($p = 0.002$) were associated with dermatomyositis.

Table 1: Comparison of trichoscopic features in the patients with discoid lupus and dermatomyositis

Trichoscopic Feature	LED	DM	*p* value
Follicular opening			
Follicular keratotic plugs	26.7%	20.0%	0.757
Absence or reduced number of follicular openings	75.6%	45.0%	0.024
Mega red spot	9.1%	0.0%	0.300
Hair shaft			
Vellus hair	71.1%	45.0%	0.55
Broken hair	22.2%	40.0%	0.229
Dystrophic hair	46.7%	75.0%	0.057
Circular hair	24.4%	50.0%	1.000
Peri-follicular surface			
Peri-follicular erythema	0.0%	45.0%	0.0001
Peri-follicular white halo	8.9%	0.0%	0.303
Peri-follicular pigmentation	35.6%	45.0%	0.196
Peri-follicular scales	68.9%	65.0%	0.780
Tubular hair casts	20.0%	0.0%	0.048
Pigmentation			
Scattered brown spotted pigmentation	64.4%	45.0%	0.177
Honeycomb pigmentation	11.1%	5.0%	0.657
Brown pigmentation without structure	11.1%	10.0%	1.000
White structures			
Rosettes	15.6%	10.0%	0.710
Chrysalids	20.0%	15.0%	1.741
White circles	2.2%	0.0%	1.000
Rounded white structures	6.7%	0.0%	0.547
Vascular structures	8.9%	5.0%	0.674
Arborescent vessels	44.4%	75.0%	0.031
Fine linear vessels, telangiectasias	31.8%	55.0%	0.101
Irregular and tortuous enlarged vessels	6.7%	0.0%	0.547
Vessels in points	6.7%	40.0%	0.002
Vascular lake-like structures			

DISCUSSION

Scalp involvement is common in connectivitis and negatively impacts the patient's quality of life [1,2], In this location, clinical signs may overlap and present a diagnostic challenge. Trichoscopy may be of great help and provide distinctive diagnostic clues. However, only several studies have presented this information [3-6]. A direct comparison of the trichoscopic findings in DM and SLE is lacking.

In DM, scalp lesions may present as erythema owing to photosensitivity or atrophic and erythematous-scaly lesions frequently accompanied by pruritus. Scalp poikiloderma and non-scarring alopecia may also occur [7-9]. Trichoscopy seems to be a useful non-invasive tool in diagnosing this condition. The first study on trichoscopy features of scalp dermatomyositis was published by Julio et al. in 2017 [5], who described scalp involvement in thirty-one patients with DM. Twenty-eight patients were evaluated by trichoscopy. The most consistent findings were the presence of enlarged capillaries, found in 20 (71.4%) cases, followed by peripilar casts (57.1%) and tufting and interfollicular scales in 14 (50%) cases.

Żychowska et al. recently reported trichoscopic findings in 15 DM patients. The most common findings were as follows: linear branched vessels (80.0%), linear vessels

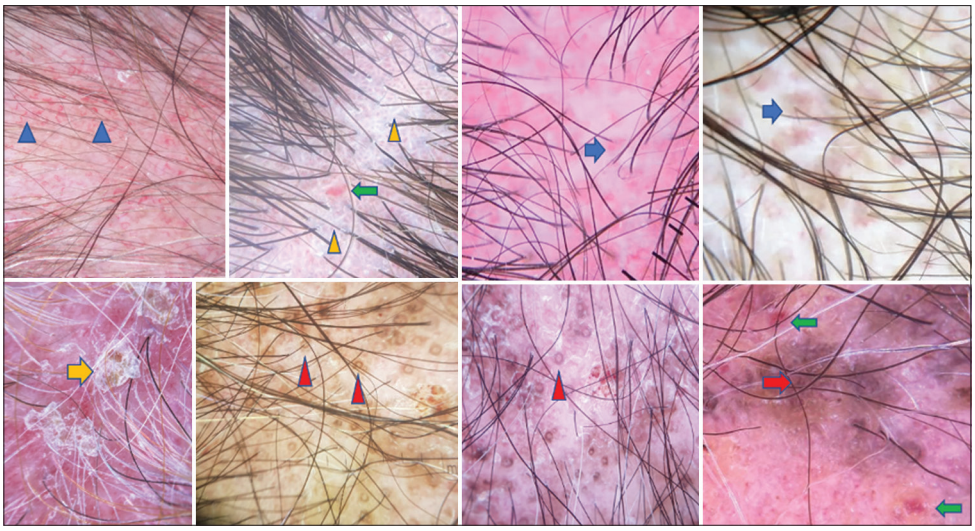

Figure 1: Scalp discoid lupus erythematosus. Trichoscopic features: scattered brown spotted pigmentation (black arrow); microhemorrhage (yellow arrow); scales (blue circle); arborescent vessels (triangle jaune); chrysalids (green triangle); pinkish-white background (red asterisk); follicular keratotic plugs (black triangle); tubular hair casts (black triangle).

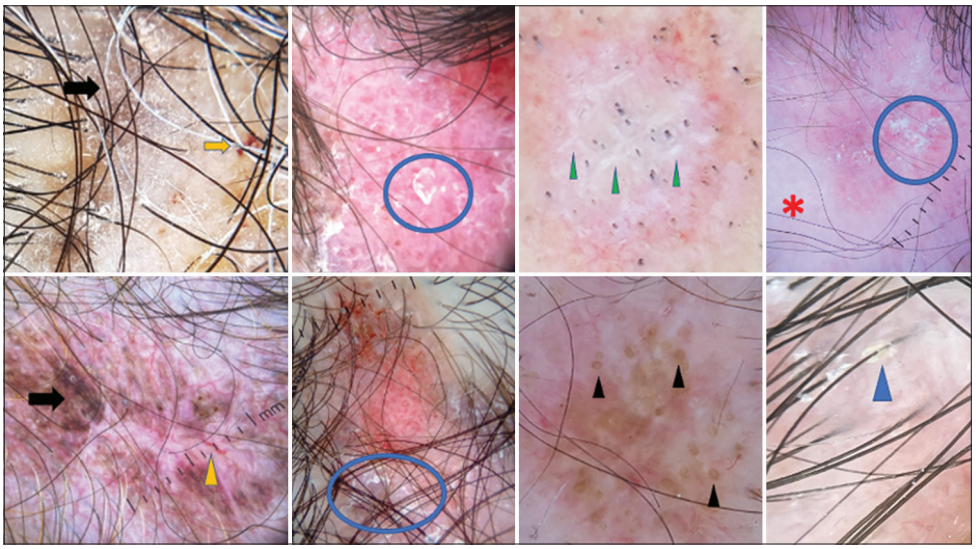

Figure 2: Scalp dermatomyositis. Trichoscopic features: enlarged, irregular, and tortuous capillaries (blue triangle); vascular, lake-like structures (green arrows); chrysalids (yellow triangle); perifollicular erythema (blue arrows); scales (yellow arrows); peri-follicular pigmentation (red triangle); interfollicular pigmentation (red arrows).

(60.0%), linear curved vessels (53.3%), perifollicular pigmentation (40.0%), perifollicular erythema (33.3%), scaling (20.0%), white (20.0%) or yellow (20%) interfollicular scales, and white (20.0%) or pinkish (13.3%) structureless areas [7].

In DLE, scalp involvement is frequent and inaugural in more than half of cases and may remain isolated in 10% of cases [10]. Females are primarily affected and these tend to be young (mean age: 30 years). The scalp is affected in the form of single or multiple alopecic plaques, well limited, inflammatory, and scaly with follicular hyperkeratosis at the beginning, then secondarily atrophic and dyschromic, leaving definitive scarring alopecia after healing [11].

The dermatoscopic appearance reported in DLE varies according to the stage of evolution. A recent systematic review of the literature summarized and analyzed the dermoscopic features of DLE lesions in various anatomical locations. In scalp DLE, the most common findings were as follows: white structureless areas (62%), arborizing vessels (57.8%), white scales (54.2%), follicular keratotic plugs (47%), absent follicular openings (45.8%), perifollicular scaling (43.9%), pinkish-white background (40.4%), speckled

brown pigmentation (38%), and fibrotic white dots (33.7%) [12].

The present study provided new insights into the trichoscopic values of patients with DM and DLE. To our knowledge, we are the first to compare trichoscopic features among these two conditions. We identified distinctive findings that may help in differentiating the two entities.

The pseudo-lake vascular structures (defined as ectatic vascular structures filled with red-blood cells) reported in a study by Julio [5] were associated with dermatomyositis in our study [2]. The absence or reduced number of follicular openings were specific signs in discoid lupus.

CONCLUSION

Scalp involvement is prevalent in discoid lupus erythematosus (DLE) and dermatomyositis (DM). Our study allowed us to determine the specific trichoscopic features of each pathology that could help in the differential diagnosis.

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

Fulminant monkeypox: A part of the clinical spectrum of immune reconstitution inflammatory syndrome?

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ABSTRACT

Monkeypox (*mpox*) is caused by a zoonotic DNA virus of the *Orthopoxvirus* genus. Fulminant mpox is characterized by necrotizing, disseminated lesions with extracutaneous complications that may require admission to the intensive care unit. Herein, we present the case of a patient with severe mucocutaneous involvement in the setting of recently diagnosed and treated HIV. Severe manifestations of mpox may be related to immunosuppression. Currently, there is no treatment approved specifically for mpox virus infection. Medical options used for smallpox are believed to be helpful for this disease, that is, tecovirimat, cidofovir, brincidofovir, and vaccinia immune globulin. Case rate fatality ranges from 1% to 10%, yet in the current outbreak of patients that have required admission to the ICU, mortality reaches up to 20%.

Key words: Monkeypox, HIV, Immune reconstitution inflammatory syndrome

INTRODUCTION

Monkeypox (*mpox*) is caused by a zoonotic DNA virus of the *Orthopoxvirus* genus. Since May 2022, more than 87,000 cases have been documented worldwide. Fulminant mpox is characterized by necrotizing, disseminated lesions with extracutaneous complications that may require admission to the intensive care unit. Herein, we present the case of a patient with severe mucocutaneous involvement in the setting of recently diagnosed and treated HIV [1,2].

CASE REPORT

A thirty-year-old male presented to the emergency room with a three-week dermatosis characterized by disseminated, oval, erythematous plaques. They were of multiple sizes, with some being confluent and umbilicated. His right hand had significant edema associated with excruciating pain. The patient was diagnosed with HIV in August 2022, two months before presenting to the emergency room. At the time of his first examination, he had a reported viral load of 31,285 copies/mm^3 and a CD4 cell count of 27/cells/mm^3. He just began antiretroviral therapy with bictegravir, tenofovir alafenamide, and emtricitabine in September 2022. The patient was hospitalized on October 13, 2022, due to intense pain and suspicion of a soft tissue infection of the hand. The patient reported dysphagia, hence upper endoscopy was also performed, in which these lesions were found (Fig. 1). Throughout his hospital stay, the number and size of the lesions increased, with many of them turning necrotic. He developed compartmental syndrome in the right hand, requiring fasciotomy on two occasions. The lesions found in the mouth and tongue led to significant oral edema and conditioned tongue protrusion, which evolved into airway obstruction that required tracheostomy (Fig. 2) and admission to the ICU one week after initial hospitalization. No

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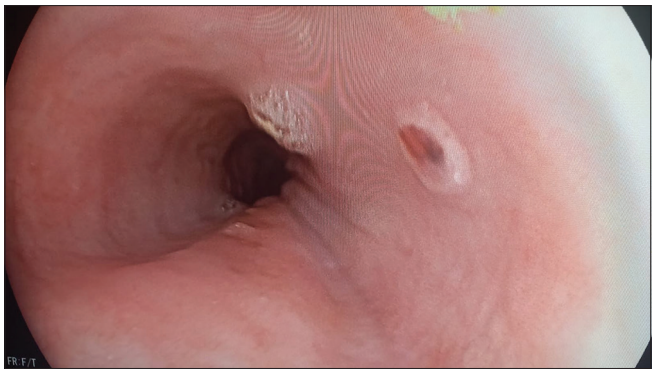

Figure 1: Mpox esophageal infiltration.

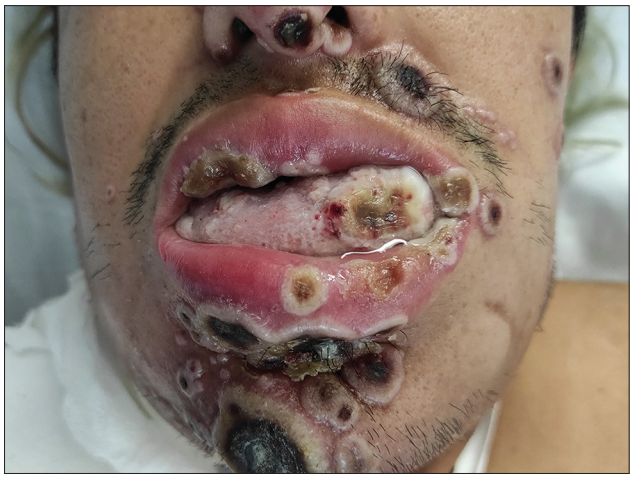

Figure 2: Umbilicated, necrotic lesions in the mouth.

specific treatment was available at the time, and only supportive measures were provided, which included intravenous fluids, parenteral nutrition, analgesia, broad-spectrum antibiotics, and supplemental oxygen. The patient was not treated with topical or systemic steroids. His evolution was torpid, with progressive deterioration of renal, pulmonary, and neurological function. He eventually developed refractory septic shock, requiring high-dose vasopressors and invasive mechanical ventilation. The patient died four days after the admission to the ICU.

DISCUSSION

The classical clinical presentation of mpox has an incubation period of 4–21 days. The illness begins with a non-specific prodromal syndrome that lasts 1–5 days consisting of fever, chills, headache, fatigue, sore throat, myalgias, and lymphadenopathy. Within 1–5 days from the onset of fever, a rash evolves and resolves over 2 to 4 weeks. The rash usually debuts with macules. Over the course of 8–13 days, it evolves into papules, then turning into vesicles that may be umbilicated. Finally, a central scab develops in the pustule, which detaches in 1–2 weeks. Once all scabs have detached, the patient is considered no longer infectious [3].

Our case was compatible with severe mucocutaneous manifestations of mpox. Recently, the term *fulminant mpox* was coined, which is characterized by disseminated, necrotizing lesions with extracutaneous complications that may require admission to the intensive care unit. Fulminant mpox has been described mainly in individuals with advanced HIV [2]. RT-PCR is the diagnostic method of choice. However, the Centers for Disease Control and Prevention (CDC) suggest a biopsy in severely immunocompromised patients, in whom it may be challenging to discern which signs and symptoms are caused by mpox and which may be associated with other opportunistic infections [4].

In the current outbreak, genital and perianal lesions have been reported in contrast with endemic mpox [1].

Severe manifestations of mpox may be related to immunosuppression [5]. Fulminant mpox is more common in people with less than 100 cells CD4/mm^3. A clinical picture compatible with immune-inflammatory reconstitution syndrome has been described in individuals with advanced HIV that were not on ART and began treatment during mpox infection [2,6].

Previous cases have documented tissue necrosis due to disseminated mpox on autopsy, as well as bacterial superinfections [5]. Only one case of esophageal infiltration due to mpox has been reported, which described a patient with HIV infection, yet with virological and immunological control and without severity data on the mpox. Esophageal involvement symptoms are unclear, yet dysphagia and odynophagia may be present [7].

As for treatment, antivirals should be considered in severe forms of the disease, as in with the involvement of anatomic areas, which may result in serious sequelae that include scarring or strictures, in people who are at risk of presenting severe disease (severe immunodeficiency, pediatric populations < 1 year, pregnant or breastfeeding, and people with a condition affecting skin integrity). Currently, there is no treatment approved specifically for mpox virus infection. Medical options employed for smallpox are believed to be helpful for this disease, that is, tecovirimat, cidofovir, brincidofovir, and vaccinia immune globulin (VIGIV) [8].

In a described series on patients with mpox, 93% received oral tecovirimat, 65% intravenous tecovirimat, 51% VIGIV, and 23% intravenous cidofovir. It is important to note that all patients who received cidofovir or VIGIV also received tecovirimat. Tecovirimat is the first line of treatment for mpox virus infections. Currently, the Tecovirimat for Human Monkeypox Virus (STOMP) trial is trying to evaluate its effectiveness [4]. Case rate fatality ranges from 1% to 10%, yet in the current outbreak of patients that have required admission to the ICU, mortality reaches up to 20% [5].

CONCLUSION

This case illustrated fulminant mpox with a severe airway compromise. Such cases as this have a great rate of mortality even with treatment, and it is important to be aware that, in some cases, this outcome is not associated with mpox per se because beginning ART may contribute to fatality and torpid evolution. Therefore, it is controversial yet in people with a new diagnosis of HIV and concurrent fulminant mpox, delaying ART may be a safer action in these 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

Zoster eruption in COVID-19 multiple-shot vaccinated patients: A report of two cases

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ABSTRACT

Herein, we present two cases of COVID-19 multi-shot vaccinated patients (four and five doses) who developed a zoster eruption after receiving the last injection. Fortunately, the outcome of these patients was favorable. However, the increasing incidence of these adverse reactions suggests a relationship with COVID-19 vaccines and raises serious concerns about the safety of repeated COVID-19 vaccine injections. If possible, heterologous vaccination should also be avoided and careful observation by health agencies should be undertaken. Several patients have also reported unusual skin reactions, such as rash or itching, that they had not observed before COVID-19 vaccinations.

Key words: COVID-19 vaccination, Zoster eruption, Multiple doses

INTRODUCTION

After the introduction of the first COVID-19 vaccines, only limited information on adverse reactions was available from laboratories. However, with the introduction of open sources for the declarations of these adverse effects, we have now a more accurate scope of these complications. Among these complications dermatologic reactions are frequent, and most are mild or moderate [1]. Although it was not the most frequent dermatologic complication, we had already reported one case of zoster eruption after the AstraZeneca vaccine at the beginning of the pandemic after the first injection [2], yet we now observed two other cases in a different context as they had received multiple COVID-19 vaccine shots; these are presented in this paper.

CASE REPORTS

Case 1

A sixty-year-old French female living in Switzerland visited our office for a painful left thoracic eruption that appeared several days before following approximately the D7-D8 dermatome. The multiple crusty vesicles were typical of a zoster infection (Fig. 1). She had received a four-dose heterologous COVID-19 vaccine scheme with three Moderna doses in Switzerland and one Comirnaty dose in France. The time between the last injection and the eruption was six weeks. In her medical history, she had breast cancer treated in 2018 by hormonotherapy. She tested positive for COVID-19 after the second vaccine dose, and she mentioned no history of an allergy or previous zoster infection. A biological investigation revealed no perturbation in the hemogram (leucocytes at 6.14 G/L with 36.2% of lymphocytes). The D-dimer level was at 486 μg/L. Treatment with aciclovir at 200 mg (five tablets per day) for seven days was prescribed, and she healed normally without residual neuralgia. The French health authority was informed about the incident.

Case 2

An 81-year-old male patient visited our office for a painful left ear for the previous ten days. During the clinical examination, a parietal eruption above the ear following the direction of the Arnold's occipital nerve was noticed (Fig. 2). The left ear was swollen and extremely sensitive. The patient mentioned only

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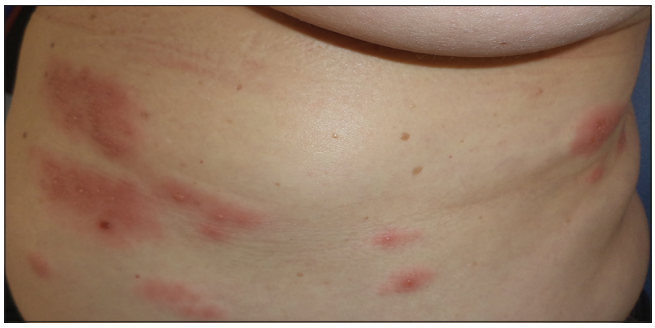

Figure 1: Lateral left thoracic eruption with multiple vesicles and marked erythema.

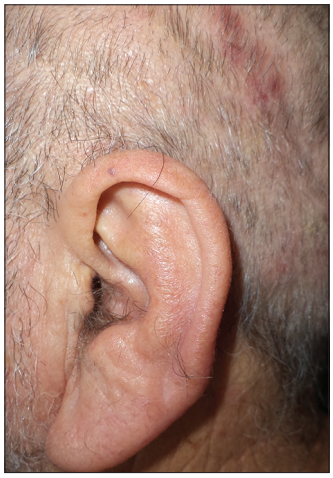

Figure 2: Swollen left ear with a parietal skin eruption.

cardiac arrhythmia in his medical history yet no allergy or previous zoster infection. A biological investigation revealed no inflammatory reaction with the D-dimer level at 316 µg/L. Treatment with aciclovir 200 mg (five tablets per day) was undertaken for seven days. The lesions healed rapidly after the treatment, yet he developed basal cell carcinoma on the left temporal skin several weeks later, which is currently under treatment. The French health authority was informed about the incident.

DISCUSSION

Adverse cutaneous reactions after COVID-19 vaccines are now well documented [3]. Most of the cutaneous reactions are immediate and limited to the point of injection, usual after any type of vaccine, yet delayed reactions such as multiple COVID-18 arms or V-REPP (vaccine-related eruption of papules and plaques) may be impressive, as described by a French survey on 192 patients [4].

In the OpenVAERS database, shingles is the most frequently declared dermatologic complication (15,721 cases as of May 19, 2023). Relative to the number of COVID-19 vaccines administered around the world, this is a low incidence, yet it is likely that the number of cases is underestimated. Furthermore, there are increasing reports of herpes zoster reactivation with COVID-19 vaccines in the medical literature [5]. Other epidemiologic data extracted from OpenVAERS reveal a double incidence in Comirnaty vaccinated patients. However, this is to be expected as the vaccine has been the most frequently injected in the world. Another relevant epidemiological data is that there is now a worldwide report of post-vaccinal zoster eruptions on all populations with all types of vaccines. Furthermore, an additional problem raised by the first case is the difficulty to attribute the origin of the complication with patients receiving a heterologous vaccination, and this problem is recurrent in other complications with COVID-19 vaccines. Thus, we recommend using the same type of vaccine for a booster injection. Our two cases raise two other questions.

The first is whether there is a relationship between COVID-19 vaccines and zoster eruption. To address this question, the onset time of the eruption must be carefully studied. As most appear between five and ten days of the last injection [5], the likelihood of a relationship was debatable in our first case as it appeared six weeks after the injection yet cannot be rejected. She had received an atypic vaccination scheme and there was no reference for this case in the medical literature.

The second question is whether there is an increasing incidence of zoster in the case of COVID-19 vaccines. It is extremely difficult to demonstrate this even with meta-analysis as there is no register of zoster cases in the general population and, thus, no control group [6-8]. However, a recent well-designed study with two matched cohorts has demonstrated a statistical increase in zoster eruptions in COVID-19 vaccinated patients [9]. Our real-life practice also questioned us as we had already observed four cases in an area of 100,000 residents since the beginning of the pandemic, yet none three years before.

In conclusion, we have observed in our daily practice an unusual occurrence of zoster eruption. These clinical observations suggested a possible link between COVID-19 vaccines and zoster eruption or its reactivation. Fortunately, these zoster eruptions had a favorable outcome with a standard treatment, yet general practitioners and dermatologists should

be aware of this adverse effect to avoid a misleading diagnosis and introduce the appropriate treatment rapidly.

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

Co-existent Dowling–Degos disease, reticulate acropigmentation of Kitamura, and acropigmentation of Dohi in two generations: An overlap or concept of a single disease?

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ABSTRACT

Reticulate pigmentary disorders (RPDs) are a group of rare autosomal dominant dermatoses with a distinctive clinical net-like pattern with specific arrangements and distributions in each entity. A forty-year-old female presented with asymptomatic, light and dark, macular lesions existing for over fifteen years with perioral scars and palmer pits and her twenty-year-old daughter beginning to develop similar lesions four years earlier. Cutaneous and histopathological examinations suggested a diagnosis of Dowling–Degos disease co-existent with reticulate acropigmentation of Kitamura in the mother and Dowling–Degos disease co-existent with acropigmentation of Dohi in the daughter. The co-existence of three infrequently encountered dermatoses with an irregular disease presentation within the family suggested the possibility of differing entities in the reticulate pigmentary group of disorders belonging to the diverse spectrums of the same disease.

Key words: Reticulate pigmentary disorders, Dowling–Degos disease, Reticulate acropigmentation of Kitamura, Reticulate acropigmentation of Dohi

INTRODUCTION

Reticulate pigmentary disorders are a group of rare pigmentary genodermatoses with autosomal dominant inheritance, comprising Dowling–Degos disease (DDD), reticulate acropigmentation of Kitamura (RAPK), and reticulate acropigmentation of Dohi (RAPD), with specific arrangements and distributions in each entity. This group of dermatoses presents clinically with freckle-like hyperpigmentation seen in inherited reticulate pigmentary disorders, while acquired disorders have the morphology of a reticulate/net-like pattern [1]. They are characterized by hyperpigmented, macular lesions with or without alternating, hypopigmented macules, pits present on the palms, soles, and perioral area, and comedo-like lesions in their various morphological subtypes. Herein, the authors describe an interesting co-existence of such lesions in a family running in two generations.

CASE REPORT

A forty-year-old, otherwise healthy, female presented with asymptomatic, light and dark, macular lesions on the dorsum of the hands, extensors of the forearms and arms, shoulders, upper trunk, neck, and face, sparing the flexors. The initial lesion appeared at the age of eighteen and progressed over fifteen years. Initially, the morphological pattern of the lesions was predominantly hyperpigmented admixed with some hypopigmented, pinhead-sized macules on the dorsum of both hands, which progressed proximally to involve the extensors of the forearms over the next five years. Further progression resulted in the involvement of

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the extensor aspects of the arms, nape, lateral, and frontal aspect of the neck, front, and back of the upper trunk in a sequential manner over the next ten years. The earlier lesions were light brown, with an eventual increase in pigmentation and size, as well as eruptions of new lesions noticed over the next fifteen years. The patient noticed some depressed lesions on the face and both palms with multiple, perioral, minute scars ten years into the disease onset. The lesion spread out was relatively slow in the initial five years, followed by accelerated spread out over the next decade and a halt thereafter.

Her twenty-year-old daughter began developing similar lesions four years earlier, which progressed in a similar distal-to-proximal manner with the exception of being predominantly hypopigmented and with multiple freckle-like lesions on the axilla and the absence of perioral scars and palmar pits. Both mother and daughter revealed an unequal distribution of pigmentation with intensely pigmented lesions on the face and dorsal aspects of the hands in the mother and a confluence of hyperpigmented lesions on the face in the daughter.

The patient (mother) revealed a family history of hyperpigmented, macular lesions in similar anatomical locations in her father, predicting an autosomal dominant pattern of lesions in three generations of the family. Both the patient's and the daughter's medical history were insignificant, and there was no history of consanguinity in the family, adverse cutaneous drug reactions, a history of chemical contact, or photosensitivity.

After obtaining written informed consent, a dermatological examination of the mother revealed numerous, widely distributed, pinpoint to pinhead-sized, predominantly hyperpigmented macules involving the dorsum of both hands and forearms, the neck, including the anterior, lateral, and nape of the neck, and upper back with pitted scars at the dorsa of the hands, as well as atrophic, hyperpigmented macules on the face, especially on the centrofacial and perioral areas (Figs. 1a – 1c). Multiple non-macular scars were also observed on both cheeks, chin, and upper lips. Multiple minute, atrophic pits were also present on both her palms (Fig. 1d).

A dermatological examination of the daughter revealed predominantly hypopigmented macules presented on the dorsa of the hands, forearms, and feet with hyperpigmented macular lesions on the axillae, inner aspects of both arms, anterior, lateral and posterior part of the neck, forehead, perioral, and malar area (Fig. 2a). Interestingly, hypopigmented macules on the dorsa of the hands and feet were observed on a hyperpigmented background. No palmar pits or perioral scars were observed in the daughter. The presence of axillary, freckle-like lesions and hypopigmented macules on the dorsa of the hands and feet were the distinctive findings in the daughter from the mother (Figs. 2b – 2d). The patient's (mother) father was unavailable for clinical examination.

Both patients' routine lab investigations, including a complete blood count, liver and kidney profile, blood glucose, ECG, chest X-ray, and peripheral smear for atypical cells, were all within normal range.

A skin biopsy from the mother, taken from a hyperpigmented macule on the upper back revealed focal thinning of the epidermis, dilated follicular infundibula with a keratin cyst, and a pigmented basal layer having one focus showing elongation of rete ridges. Except for minimal perivascular lymphocytic infiltrates, there was no evidence of pigment incontinence in the dermis (Fig. 3a).

A skin biopsy taken from a single hyperpigmented lesion on the inner aspect of the arm of the daughter and a further histopathological examination revealed flattening of rete ridges, an atrophic epidermis, marked basal hyperpigmentation with focal areas showing a reticulate, interdigitating, antler-like pattern of rete ridges without evidence of pigment incontinence. The dermis appeared normal except for collagenization (Fig. 3b). The histomorphological impression suggested Dowling–Degos disease. Histomorphology suggested a similar impression to that of the mother.

On the bases of the history, cutaneous examination, and its histopathological correlation, the diagnosis of reticulate pigmentary dermatosis was reached with predominant features of Dowling–Degos disease co-existent with reticulate acropigmentation of Kitamura in the mother and features suggestive of Dowling–Degos disease co-existent with acropigmentation of Dohi in the daughter.

DISCUSSION

Reticulate pigmentary disorders (RPDs) are a group of rare autosomal dominant dermatoses with

Figure 1: (a) Clinical photographs of the mother showing numerous hyperpigmented macules on the centrofacial and perioral area with minute pits. (b) Clinical photographs of the mother showing hyperpigmented macules on the upper back and lateral aspect of the neck. (c) Clinical photographs of the mother showing hyperpigmented macules on the dorsum of the hand with atrophy. (d) Clinical photographs of the mother showing multiple pitted scars on both palms.

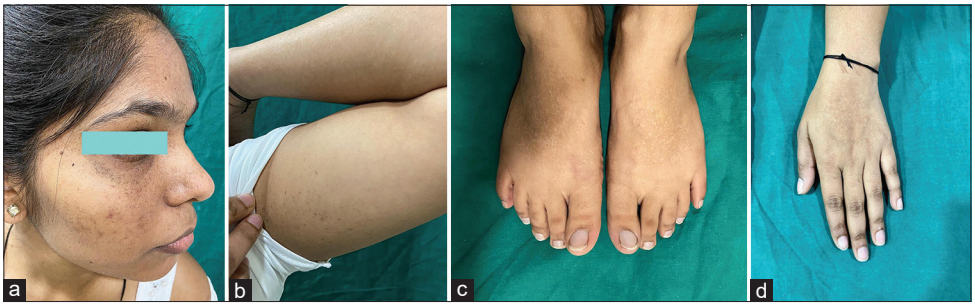

Figure 2: (a) Clinical photographs of the daughter showing multiple hyperpigmented macules on the face. (b) Clinical photographs of the daughter showing hyperpigmented macules on the axilla. (c) Clinical photographs of the daughter showing a hypopigmented lesion on the dorsum of feet. (d) Clinical photographs of the daughter showing a hypopigmented lesion on the dorsum of the hands.

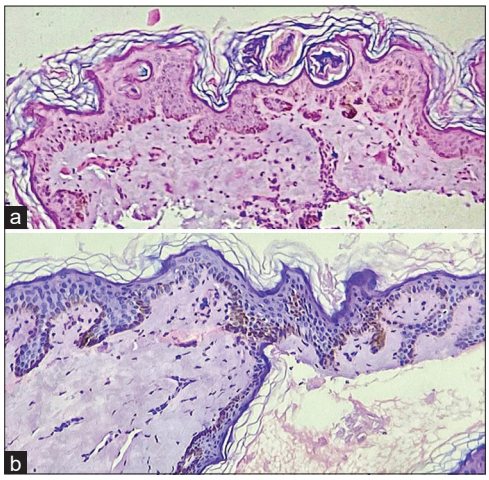

Figure 3: (a) Histopathological examination of the hyperpigmented lesion in the mother showing focal thinning of the epidermis, dilated follicular infundibula with a keratin cyst, and a pigmented basal layer (H&E, 40×). (b) Histopathological examination of the hyperpigmented lesion in the daughter showing flattening of rete ridges, an atrophic epidermis, and marked basal hyperpigmentation with an antler-like pattern of rete ridges without pigment incontinence (H&E, 40×).

variable penetrance, having a specific pattern of distribution and consisting of variously named disorders, primarily Dowling–Degos disease (DDD), characterized by asymptomatic, pigmented, reticulate macules. Reticular hyperpigmentation of Kitamura (RAPK) is characterized by asymptomatic, pigmented macules on the dorsa of the hands, forearms, and feet with palmoplantar pits. Likewise, reticulate acropigmentation of Dohi (RAPD) is characterized by a combination of hypo- and hyperpigmented macules on the hands and feet.

DDD, first described by Dowling in 1938 and by Degos in 1954, often has a late-onset presentation of reticulate, pigmented lesions on flexures, that is, the axillae, groin, and neck, with comedo-like lesions and pitted perioral scars [2]. In addition, DDD has reportedly been associated with other diseases, such as hidradenitis suppurativa, multiple keratoacanthomas, and squamous cell carcinoma [3-5].

Likewise, reticulate pigmentation of Kitamura (RAPK), described by Kitamura and Akamatsu in 1943, has increasingly been reported across the world, with a presentation beginning usually in childhood or early teenage years. Lesions of RAPK are described as symmetrical, hyperpigmented macules in a reticulate pattern on the dorsa of the hands and feet, with atrophy being the characteristic feature of early lesions [6]. Progressive extension of lesions occurs

proximally with age, along with pitted lesions on the palmoplantar surfaces with altered dermatoglyphics and the disruption of epidermal ridges.

Reticulate acropigmentation of Dohi (RAPD) presents as areas of hyper- and hypopigmentation on the dorsal and ventral aspects of the hands and feet, which may extend proximally to involve the knees and elbows [7]. Lesions of RAPD appear during the first decade of life and their progression decelerates by adolescence. This condition spares the mucosae and does not usually exhibit specific palmoplantar pits or perioral pitted scars. The predominance of hypopigmented macules in this subset makes it distinctive in terms of presentation, unlike other common variants of RPDS.

Our two patients (mother and daughter) exhibited interesting features of a complex hereditary disorder, with DDD and RAPK being consistent in both, yet in overlapping/co-existent patterns, as well as the evolution of early features of RAPD as hypopigmented macules in the daughter, gradually shifting to evolved features of DDD and RAPK in the form of hyperpigmented macules in mother, suggesting the distinct nature of the disease in terms of the transformation of phenotypic expression in the subsequent generation. The feature has not been reported elsewhere so far, although photo-aggravated changes and the darkening of macules of prototype APD cannot be excluded in the mother in this case.

We also observed a relatively faster rate of transition of RAPD features (hypopigmented macules to hyperpigmented macules) in the daughter, possibly explained by variable point mutations being expressed sporadically [8].

The daughter revealed hypopigmented macules on a hyperpigmented background on the dorsa of the hands, forearms, and feet (suggestive of RAPD). Some hyperpigmented macules were present on the axillae, inner aspect of the arms, and cento-facial area (suggestive of DDD), without hyperpigmented macules on the dorsa of the forearms or palmar pits, features typical of RAPK.

Similarly, pitted hyperpigmented macules chiefly on the perioral and periorbital areas, on the neck, upper back, and axillae in the mother were suggestive of DDD. Multiple pits on both palms along with hyperpigmented, atrophic macules on both forearms supported RAPK clinically, lacking morphological features of RAPD, although, earlier, the patient had hypopigmented macules on both forearms, which gradually darkened over years, chronologically suggesting the gradual transformation of one subset of RPD to another, considering the pattern and evolution of similar lesions on the forearms in the daughter at the time.

The clinical presentations of various RPDS depend upon the age at which they present, the selective predominance of specific subtypes of RPDS, and the impact of morphological variations on a selective group of populations with genotypic heterogeneity to manifest the predominant or co-existent RPDS [9].

There have been numerous case reports of the co-existence of different cases of RPDS in the literature, suggesting an overlap or a single entity with variants [10-12].

The pathogenesis of RPDS has not been understood clearly, with some studies indicating mutations in RNA-specific adenosine deaminase genes in RAPD, a mutation in the ADAM10 and PAX2 genes in RAPK and a loss of mutation in KRT5 in DDD. Wei Tai Yu et al. found an increased percentage of stage 4 melanosomes in basal and suprabasal keratinocytes in lesional skin, suggesting the involvement of defective melanosome transfer and maturation in the pathogenesis of DDD [9].

Our study found a similar overlap as described by Thami et al. in 1998, yet we found an apparent overlap in two subsequent generations with the polarization of genodermatoses in the mother and impending phenotypic expression in the daughter, making the current report interesting and unique. [10].

CONCLUSION

The possibility of variable phenotypic expressions of a single disease entity depending upon the age of presentation, site, duration, and various environmental and internal factors should be considered. The co-existence of three infrequently encountered dermatoses with an irregular disease presentation within the members of the same lineage with a lack of distinguishing histomorphological features should raise the question of diverse features of a single disease entity.

There have been numerous reports on the co-existence of RAPK and DDD in the literature, and numerous

authors have suggested the possibility of differing entities in the reticulate pigmentary group of disorders belonging to the diverse spectrums of the same disease. Our report showed a non-idiosyncratic co-existence of the reticulate pigmentary group as a single entity in two generations of a family with different phenotypic outcomes, making it a thought-provoking observation.

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

Vulvar dermatofibrosarcoma of Darier and Ferrand in a young woman: About a new observation

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ABSTRACT

Darier and Ferrand Dermatofibrosarcoma is a rare mesenchymal tumor in young adults, often located in the trunk. We report an observation of a vulvar localization of dermatofibrosarcoma Darier and Ferrand. It was a young patient, aged 25, who presented a tumor of the vulvar region. This tumor has been evolving for about 10 years in two phases, the first of which is longer, with very slow development, and a second phase characterized by rapid growth of the tumor coinciding with the start of pregnancy. The examination noted a tumor developed at the expense of the vulvar region. The diagnosis of dermatofibrosarcoma was retained in view of a characteristic histopathological appearance. The treatment consisted of resection surgery with margins of about 5 cm followed by reconstruction by direct suture. The evolution, in the immediate aftermath, was good. Vulvar localization of dermatofibrosarcoma is possible.

Key words: Darier and Ferrand dermatofibrosarcoma, Vulva, Young woman

INTRODUCTION

Dermatofibrosarcoma of Darier and Ferrand is a rare fibroblastic mesenchymal tumor characterized by slow progression, high potential for local recurrence, and rare metastasis [1]. It usually appears in young adults and is located with predilection in the trunk and proximal extremities. Vulvar localization is a rare entity, described in only about fifty cases in the literature [2]. We report a new observation of a vulvar localization of a Dermatofibrosarcoma of Darier and Ferrand in a young woman.

CASE REPORT

This was a 25-year-old woman, married and mother of 3 children, the last of whom was 2 months old, with a history of spontaneous abortion during her first pregnancy, who was seen in consultation for a vulvar tumor.

The history of the disease would go back to about 10 years with the occurrence of a small lesion that appeared after a fall from a height of about 1 m with impact of the genitals on an object. The lesion would evolve very slowly during the first years until the beginning of the pregnancies. Then it starts to increase in volume as the pregnancies follow one another. There were no symptoms, in particular, there was neither pain nor pruritus, but there was a hindrance to sexual activity with a fairly significant psychological impact. The evolution would have accelerated during the last pregnancy with an increase in the volume of the tumor which had

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become very important at the end of the pregnancy. The patient, after vaginal delivery in an obstetrical environment, was referred to our department for better care.

On admission, the patient was conscious and in good general condition with a Glasgow score of 15/15. The dermatological examination revealed a genital tumor measuring approximately 10 cm, painless to palpation, of firm consistency, located at the level of the left lip, with superior development towards the pubis, erasing the vulvar relief and hindering the opening of the vaginal orifice. There was no discharge or genital ulceration (Fig. 1). Examination of the spleno-ganglionic system did not show any adenopathy at the inguinal level or at other sites. The rest of the clinical examination was normal.

A biopsy was performed and showed a sarcomatous proliferation with spindle-shaped cells containing elongated and moderately dyskaryotic nuclei with elongated cytoplasm. Examination noted a storiform arrangement of tumor cells with a fishbone appearance. Mitoses were few, less than 10 mitoses per 10 fields at high magnification. The stroma was fibrillar and the surface epithelium was regular (Figgs. 2a and 2b). The diagnosis of dermatofibrosarcoma of Darier and Ferrand was thus retained. An extension workup was performed and included a thoraco-abdomino-pelvic CT scan which showed a suspicious vulvar mass, lateralized to the left, measuring 45×39 mm, strongly enhanced by contrast medium, without infiltration of the perineal region, nor extension to the vaginal level. In addition, there was no suspicious lesion of secondary appearance in the thoraco-abdomino-pelvic region. In a multidisciplinary consultation meeting (RCP), the decision was made to perform excision surgery followed by neoadjuvant radiotherapy. The patient underwent a monobloc excision with wide margins of 5 cm except for the clitoris and the urethra where the margins were reduced to 2 cm. Then, a reconstruction by simple suture was performed (Fig. 3). Anatomopathological examination of the excision specimen confirmed the diagnosis of Darier and Ferrand dermatofibrosarcoma and showed healthy resection margins. The postoperative course was good with complete healing and a reduction of the vaginal perimeter but without functional damage to the organs of the region such as the clitoris and the urethra. Neoadjuvant radiotherapy was not performed. Surveillance was instituted including, at least, a clinical examination every 3 to 6 months for at least 3 years.

DISCUSSION

Dermatofibrosarcoma was first described by Taylor in 1890 and individualized as a true anatomoclinical entity in 1924 by Jean Darier and Marcel Ferrand [3].

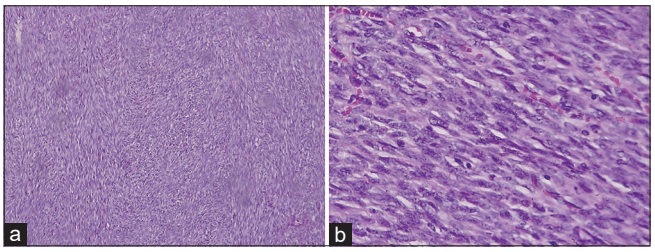

Figure 2: Dermatofibrosarcoma of Darier and Ferrand. (a) Storiform arrangement of spindle cells (Haematoxylin-Eosin, magnification ×10), Anatomo-cytopathology laboratory, Cheikh Anta Diop University (UCAD), Dakar (x10). (b) Mitoses less than 10 (Hematoxylin-eosin, magnification ×100), Anatomo-cytopathology laboratory, Cheikh Anta Diop University, Dakar (x100).

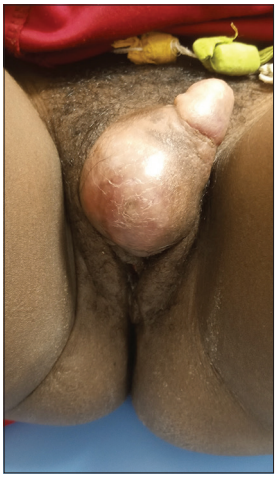

Figure 1: Dermatofibrosarcoma of Darrier-Ferrand with vulvar location.

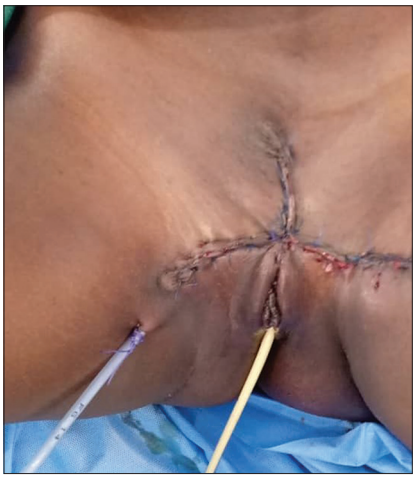

Figure 3: Post-surgical aspect of vulvar Dermatofibrosarcoma of Darrier et Ferrand, seen in the immediate postoperative period.

It is a tumor with a dermal origin, of intermediate malignancy between fibroma and true sarcoma. It represents less than 2% of all soft tissue sarcomas [4]. The young age of our patient, who was 25 years old at the time of diagnosis, corroborates the data in the literature, which report the occurrence of this tumor in young adults aged, on average, between 28 and 47 years [5,6]. However, the tumor has been reported to evolve since adolescence, i.e., around the age of 15 years, which corresponds to a younger age of onset. Cases of dermatofibrosarcoma with pediatric onset have been reported [7]. This late diagnosis would be due to the very slow rate of development of dermatofibrosarcoma, which remained asymptomatic for a long time. The evolution would have been accelerated by the pregnancies with a growth which would be more rapid during the last pregnancy. A probable accelerating role of pregnancy on Darier and Ferrand dermatofibrosarcoma is suggested by some authors [8]. Moreover, the notion of previous trauma, as noted in our observation, is reported in the literature, without a precise explanation being given as to the role of trauma in the occurrence of Darier and Ferrand dermatofibrosarcoma [5,9]. However, an accelerating role of trauma on the growth of dermatofibrosarcoma is well established [10]. This seems to be confirmed in our case, where a more rapid growth was noted during the pregnancies and which, on the one hand, could be linked to the trauma generated by the various successive vaginal deliveries.

This condition may be located on any organ, but it affects the trunk with predilection [11], then the limbs, head and neck [5]. Vulvar localization is rare, described mostly in isolated cases in the literature [2].

Clinically, there is great variability in its presentation. Initially, the appearance is that of a small nodule or a single firm plaque. This initial lesion slowly grows over several months or years to a painless tumor formation. At a more advanced stage, the plaque spreads, the surface becomes irregular, bumpy, realizing after some time a multinodular, polychromatic mass of variable size or sometimes uninodular. We presented a case of uninodular, protuberant dermatofibrosarcoma of Darier and Ferrand with taut, shiny and erythematous skin giving the impression of imminent fistulization. However, despite this rather characteristic clinical presentation, the diagnosis of certainty is based on anatomopathological examination, which classically shows a proliferation of dense, spindle-shaped cells of regular size, most often organized in tangled bundles in all directions, adopting a swirling or storiform structure. These cells have an oval nucleus, with dense granular chromatin, without major atypia and with rare mitoses. The proliferation is monomorphic and intradermal invading all the dermis, then it infiltrates deeply and invades the hypodermis. The tumor is poorly limited and lacks its own capsule and the central area is more cellular than the periphery. The epidermis is usually thinned [12]. However, despite this very suggestive description, histopathologic distinction between Darier and Ferrand dermatofibrosarcoma and other spindle cell tumors such as histiocytofibroma, fibrosarcoma, and nodular fasciitis is sometimes difficult. In these cases, the use of immunohistochemistry techniques is necessary to make the diagnosis. Indeed, dermatofibrosarcoma tumor cells consistently express CD34, but not PS100 or factor XIIIa [13]. However, this marker is not specific to dermatofibrosarcoma and can be expressed by other tumors such as fibromas, fibromyxomas and Kaposi's disease [14].

The reference treatment today remains excisional surgery, which should be performed in monobloc with resection margins of at least 4 cm, down to the fascial plane in depth [15]. An alternative to this wide surgery is the Mohs micrographic technique, which involves an extemporaneous examination and 3 cm margins [16]. It offers the main advantage of removing the entire tumor with the smallest possible margin of safety, but its disadvantage is its high cost and the longer duration of the procedure. Our patient was operated on using an excisional technique with wide margins, 5 cm except for the clitoris and the urethra to preserve the function of these two organs. The anatomopathological examination of the surgical specimen showed healthy resection margins.

The other challenge in the therapeutic management of these tumors remains reconstruction after removal. This is an essential aspect given the importance of the loss of substance caused by the surgery of these tumors, in a sensitive anatomical region because it includes essential organs whose destruction leaves important unaesthetic and functional sequelae. Several reconstruction techniques are available, including direct suture, thin skin grafting, and flap grafting [17]. The latter is more suitable for covering large losses of substance [18]. In our case, the reconstruction was done by direct suture leaving part of the vaginal orifice free.

Recurrence is one of the essential characteristics of Darier and Ferrand's dermatofibrosarcoma and it is essential to take it into account in the therapeutic decision. It may occur several years after excision and is more frequent when the margins are reduced [17]. This is why, to reduce this risk, complementary treatments are sometimes proposed. For example, some authors have used radiotherapy for recurrent tumors [19]. Oral imatinib mesylate is a tumor cell-targeted therapy that has also been used in recurrent, metastatic or unresectable tumors with encouraging results [20]. In our case, neoadjuvant radiotherapy was proposed in a multidisciplinary consultation meeting but not performed because of technical failure.

The absence of lesions suspected of metastasis in our observation is in agreement with the data of the literature which report the rarity of metastasis in Darier and Ferrand dermatofibrosarcoma. However, the follow-up was not sufficient to appreciate their existence because metastases are described as occurring on average 6 years after the first tumor removal [17]. The evolution of the postoperative course was good in our case, at the cost of an amputation of part of the affected vulva. On the other hand, considering the high potential of recurrence of Dermatofibrosarcoma, a surveillance was instituted including a clinical examination every 3 months, then every 6 months during the first 3 years [1].

CONCLUSION

Dermatofibrosarcoma of Darier-Ferrand is a rare tumor of intermediate and local malignancy, exposing to the risk of recurrence. Our observation confirms the possibility of a vulvar localization of this pathology that should be evoked in front of any vulvar tumor in a young woman. Surgery is the cornerstone of treatment but it must face the challenge of safeguarding the function of the organs in the region.

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

Pagetoid reticulosis Woringer–Kolopp type: A report of two cases at a third-level center

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ABSTRACT

Pagetoid reticulosis is a clinical and histological variant of mycosis fungoides that shows epidermotropism in histology and a classic clinic with acral disease. Herein, we present two clinical cases, an 84-year-old male and a nineteen-year-old male with clinical, immunophenotype, topography, and genotype compatible with mycosis fungoides-variety pagetoid reticulosis, both showing excellent responses to radiation therapy and in clinical remission. Despite the low frequency of this type of mycosis fungoides, we should keep it in mind in our differential diagnoses since, despite its benign course, it requires different treatment options and long-term follow-up.

Key words: Pagetoid reticulosis, Woringer–Kolopp disease, Cutaneous T-cell lymphoma, Radiotherapy

INTRODUCTION

Primary cutaneous lymphomas are a heterogeneous group of diseases of the B and T lymphoid lineage, defined as non-Hodgkin lymphomas of primary involvement to the skin without presenting manifestations in another organ at the time of diagnosis. It is reported that 75% to 80% correspond to cutaneous lymphomas of T cells. Mycosis fungoides (MF) represent 50% of all primary cutaneous lymphomas [1]. Three variants of MF have been recognized according to the 2018 classification of the World Health Organization-European Organization for Cancer Research and Treatment (WHO-EORTC): folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin. Each has its clinical behavior, histological characteristics, and prognostics [2].

Pagetoid reticulosis, first described in 1939 by Woringer and Kolopp, was recognized as an entity that presents histological similarities to epidermotropic lymphoid cells with intraepidermic adenocarcinomatous cells of Paget's disease of the nipple. [3] Pagetoid reticulosis Woringer–Kolop type (localized variant), other than the disseminated type or Ketron–Goodman type, is characterized by intraepidermal proliferation of neoplastic CD3+, CD4+, CD8- or CD3+, CD4+, and CD8+, with a frequent expression of CD30+, and clinically expressed as keratotic or psoriasiform-looking solitary patches or plaques that usually affect the limbs, of slow progression, without an aggressive course. There are no reports at the time of extracutaneous involvement or deaths related to the disease [1,4].

Herein, we present two cases diagnosed at a third-level care center in Mexico City.

CASE REPORTS

Case 1

An 84-year-old male presented to the dermatology service with erythematous plaques in the interdigital

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folds of the left foot with severe, thick, adhered scaling of eight months of evolution and onychomycosis. He was first diagnosed with tinea pedis and onychomycosis and was treated with oral terbinafine and clioquinol for three months. There was an improvement in most lesions and onychomycosis. Still, a plaque persisted between the fourth and fifth fingers. The plaque had indurated edges and an infiltrated appearance with thick scales adhered in the periphery (Figs. 1a and 1b). On dermatoscopy, there were red and white areas without a structure (Fig. 1c). Dermatosis was painful, with limited walking. A biopsy of the persistent plaque was taken, with the clinical diagnosis of suspected epidermoid carcinoma.

In histology, a lichenoid infiltrate with lymphocyte epidermotropism was found, with immunohistochemical CD3 (+), CD4 (+), CD5 (-), CD7 (-), and CD8 (-), and monoclonality was demonstrated for the T lymphocyte receptor (TCR) (Figs. 2a – 2e). Extension studies were performed, in which extracutaneous activity was not evident (Figs. 3a and 3b). The patient received 8GY single-dose radiation therapy for the treatment of the interdigital lesion. There was, at two weeks, interdigital erythema and scaling with painless and gradual improvement. The patient did not have evidence of recurrence after eighteen months of follow-up.

Case 2

A nineteen-year-old male presented with hypopigmented lesions in the thenar eminence and dorsal area of the hand after ten years of evolution, with a gradual progression to form psoriasiform plaques and achromic spots in the interdigital region. An external approach was taken, and a biopsy was performed, which was

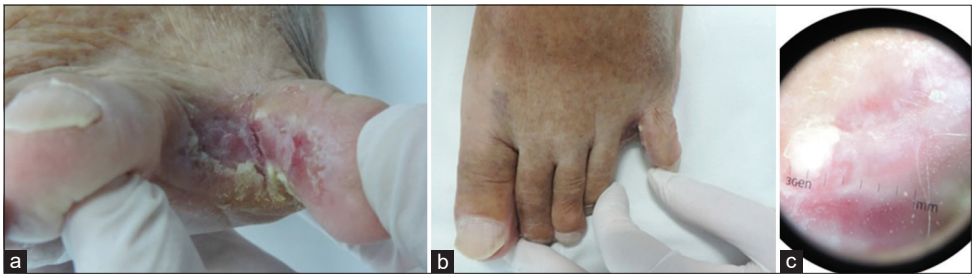


Figure 1: (a-b) Plaque with indurated edges and an infiltrated appearance with thick scales adhered to the periphery. (c) Dermatoscopy revealing red and white areas without a structure.

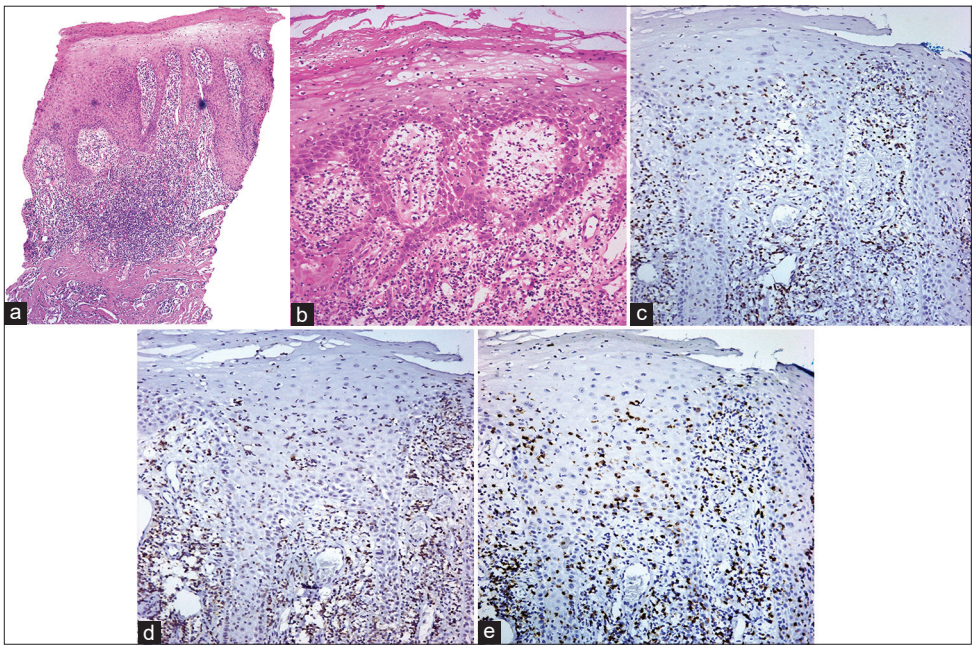
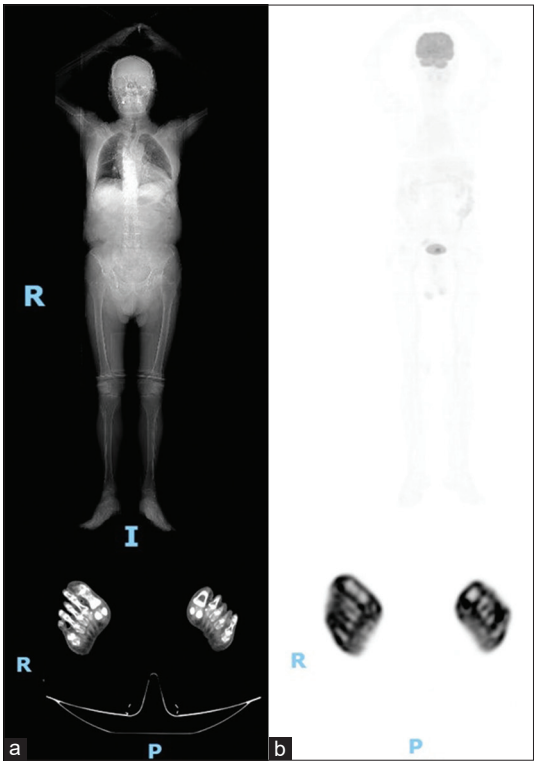


Figure 2: (a-b) Histological sections (H&E; 2x) showing a pattern of pseudoepitheliomatous hyperplasia associated with parakeratosis and vacuolar degeneration of the basal layer with necrotic keratinocytes. Lymphocytic infiltrate with a band arrangement accompanied by epidermotropism. Infiltrate consisting of irregular lymphocytes of small to medium nuclei, hyperchromatic and cerebriform. (c-e) Immunohistochemistry technique showing an immunophenotype with a predominance of positive CD8 lymphocytes (CD3; 10x).

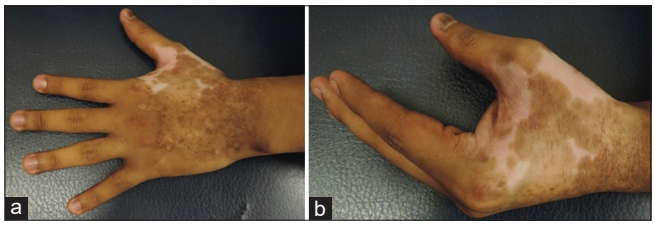
compatible with mycosis fungoides-variety pagetoid reticulosis CD3 (+), CD4 (+), and CD8 (-). In his first evaluation at our dermatology department, he presented dermatosis located on the left hand with erythematous and squamous plaques of psoriasiform appearance and perilesional achromic areas (Figs. 4a and 4b). The patient did not have extracutaneous activity. Regarding the treatment, surface radiation with electron beam therapy was performed. He received 12Gy in six fractions, presenting mild erythema after the sessions. The patient did not have evidence of recurrence after twenty-four months of follow-up.

DISCUSSION

Mycosis fungoides-variety pagetoid reticulosis has a benign behavior, with a high rate of healing and an adequate response to surgery and/or radiation therapy, yet it is advisable to follow these individuals since recurrences have been reported.



Figures 3: (a-b) Positron emission tomography without evidence of extracutaneous activity.



Figures 4: (a-b) Erythematous and squamous plaques of psoriasiform appearance and perilesional achromic areas.

Clinically, it behaves as a single asymptomatic lesion, distal to the extremities, with slow growth and well-defined edges, psoriasiform appearance, or keratose plaques [5,6]. Due to its indolent course and its unspecific clinical features, it may remain undiagnosed for years. Currently, some dermoscopy characteristics have been described and the main features have included dotted/glomerular vessels on a homogeneous pink background and white scales [7]. In a recent systematic review of 84 studies and 143 patients, 78.2% had a complete remission and 9.4% recurred [8].

For its diagnosis, it requires the sum of the clinical, histopathological, immunophenotypic, and genotypic correlation (demonstrating TCR monoclonality) [3]. More studies are needed to determine the prognosis and effective treatments for this disease [8].

CONCLUSION

Despite the low frequency of this type of mycosis fungoides, we should keep it in mind in our differential diagnoses since, despite its benign course, it presents different treatment options and requires long-term follow-up.

Consent

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

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

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Our Dermatology Online

Case Report

Transformed mycosis fungoides in an atypical location

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ABSTRACT

Mycosis fungoides is the most common variant of primary cutaneous T-cell lymphoma. Large cell transformation in mycosis fungoides is the histopathological transformation of neoplastic small lymphocytes to a clonally identical large cell phenotype. It is associated with a poor prognosis, although some patients have indolent disease. Clinically, it is manifested by ulcerated, tumoral lesions that may affect the entire body. The location in the external auditory canal has never been described before. Herein, we report the first case of transformed mycosis fungoides located in the external auditory canal.

Key words: External auditory canal; Large cell transformation; Mycosis fungoides

INTRODUCTION

Mycosis fungoides (MF), the most common form of cutaneous T-cell lymphoma, is mainly seen in older patients [1]. It generally follows an indolent course. However, a transformation of MF into large cell lymphoma occurs in 10% of cases in adults and is associated with an aggressive course and shortened overall survival. Herein, we report an original case of transformed MF located in the external auditory canal (EAC) never described before.

CASE REPORT

A 52-year-old Moroccan patient, with no pathological history, presented to the dermatology department for the appearance of multiple, ulcerative tumors as well as a papulous nodule on the trunk, back, all four limbs, and face with the involvement of the genitals mucosa. All had been evolving for one year. He also reported purulent otorrhea and hypoacusis of the left ear present for one month.

A clinical examination revealed three ulcerative tumors, one next to the right nipple, and the other two on the hypogastrium. He also presented multiple, erythematous papules and nodules on the face, trunk, back, and all four limbs and a multiple, ulcerative lesion on the scrotum (Figs. 1a – 1c). An auricular examination revealed an ulcerative tumor on the posterior wall of the EAC and erythematous papules on the helix (Fig. 1d).

An examination of the lymph node areas found mobile, painless inguinal adenopathy, firm on palpation. The rest of the clinical examination was normal. A skin biopsy and a biopsy of the auricular process with an immunohistochemistry study were in favor of transformed MF (Fig. 2a).

CT of the petrous bone revealed a heterogeneous filling of the EAC and the left eardrum, which was in favor of a tumoral process (Fig. 2b). An extended examination through imaging and a biological test was normal and showed no metastasis.

A diagnosis of MF with large cell transformation located in the EAC was established. It was classified as T3N1M0B0 IIB. He was transferred to the hematology department to receive polychemotherapy and, then, he was lost to sight.

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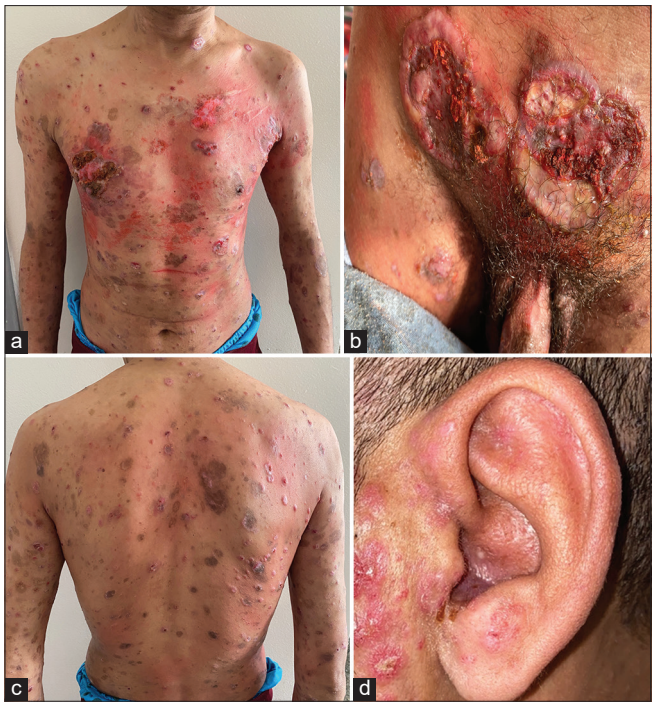

Figure 1: (a) Ulcerative tumor on the right nipple and erythematous papules on the trunk, abdomen, and arms.(b) Annular, ulcerative tumors localized in the hypogastrium.(c) Erythematous papule with cicatricial pigmentation of the back. (d) Erythematous papules of the helix and the tumoral process.

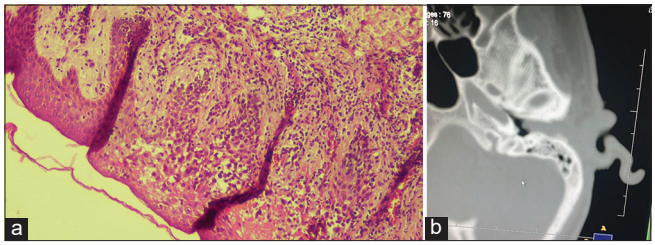

Figure 2: (a) Histology with epidermotropism and atypical lymphocyte. (b) CT of the petrous bone revealing a heterogeneous filling of the EAC and the left eardrum.

DISCUSSION

The incidence of malignant EAC tumors is low. The most common tumors are adenocarcinoma and squamous cell carcinoma. Seventeen cases of MF involving the external ear and EAC have been described so far [2]. Ours was the first case of MF with large cell transformation located in the external auditory canal.

The clinical presentation of MF at the CAE level is not specific. It may be manifested by otalgia, hypoacusis, or otorrhea [3]. The involvement of the EAC by MF portends a poor prognosis [2].

The main complications are essentially infection (otitis) and perforation of the eardrum [4].

Diagnosis is based on histology with an immunohistochemistry study. The biopsy should be deep, or even a complete excision of the process should be performed so as not to miss the diagnosis.

The diagnosis is histological and finds discreet epidermotropism, an atypical lymphocyte population (at least 25%), and significant mitotic activity. The phenotype of these cells may be CD30+ or CD30-.

Diffusion of the lesions to cutaneous, ganglionic, then all organs (spleen, liver, kidneys, lung, GI tract, oropharynx, MO, CNS, etc.) may occur.

The evolution is quick toward the aggressive form and the prognosis is poor. The MF is a great imitator of psoriasis, tinea, and syphilis especially if the lesions are annular [5]. This is why it is always necessary to consider the diagnosis of MF in front of any chronic dermatosis and not to hesitate to multiply the biopsies [6].

Dermoscopy may sometimes help to guide the diagnosis of MF if there is a lesion on the body. The main finding is short linear vessels, dotted vessels, and orangish-yellow, patchy areas [7].

The treatment is poorly codified and depends on the extent of the lesions: localized radiotherapy, monochemotherapy, or polychemotherapy.

In our patient, polychemotherapy treatment with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was prescribed.

CONCLUSION

The auricular location of the MF is exceptional. It will be necessary to perform a systematic ENT examination in front of any MF even if the clinical manifestations are not specific.

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

Case series of a varied spectrum of drug reactions

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ABSTRACT

Adverse drug reactions are an important cause of iatrogenic morbidity and mortality in the medical field across the globe. As newer drugs emerge into the market, newer adverse reactions are being reported. More than half of these new drugs have serious side effects. A distinction between numerous patterns of drug-induced reactions is potentially of critical importance because a delay even of several hours may make the difference between survival and death. Herein, we report five cases of severe cutaneous adverse drug reactions admitted at our dermatology ward.

Key words: Adverse drug reaction, Iatrogenic morbidity

INTRODUCTION

Adverse reactions to drugs are common in clinical practice, and reactions affecting the skin constitute a significant percentage of these reactions [1]. It is important to distinguish features of cutaneous drug reactions that help to classify the underlying mechanism, and likely prognosis, as both of these influence management decisions, some of which, necessarily, have to be taken immediately. Five cases of different morphological presentations of drug reactions will be reported here.

CASE REPORTS

Case 1

A 23-year-old male presented with complaints of fluid-filled lesions present for five days. The lesions appeared on the back, then progressed to involve the upper limbs, lower limbs, and abdomen, associated with itching and a burning sensation. He had been a known case of a seizure disorder since the age of eleven years and was on tablet phenobarbitone. He stopped tablet phenobarbitone and took sodium valproate fifteen days prior to the onset of these lesions. There was a history of five similar episodes, each lasting for 5–6 days. The fluid-filled lesions were present on the same site as in the past. A cutaneous examination revealed multiple well-defined flaccid bullae, erosions, and crusting involving the trunk, extremities, face, palms, and soles. Circumscribed areas of PIH were seen (Fig. 1). The Nikolsky sign and the bulla spread sign were negative. A diagnosis of generalized bullous fixed drug eruption (secondary to tablet sodium valproate) was established.

Case 2

A 42-year-old female presented with complaints of itchy, red, raised lesions over the entire body present for the last two days. There was a history of fever and joint pain one week previously, for which she took tablets and injections (unknown). Two days later, red, raised lesions appeared on the trunk initially, then progressed to involve the face, both upper limbs, and lower limbs. On examination, diffuse erythema and scaling were seen involving the entire body (Fig. 2). A diagnosis of erythroderma secondary to an adverse drug reaction was established.

Case 3

A 28-year-old female presented with complaints of red, raised lesions over the entire body associated with a severe burning sensation and itching present for the last two days. There was a history of fever five

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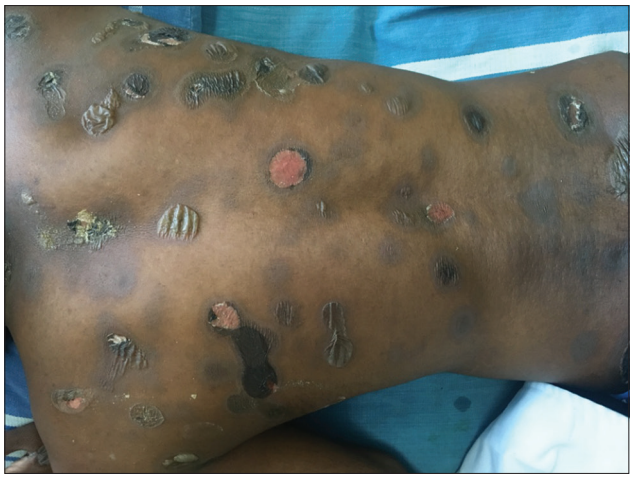

Figure 1: Multiple well-defined flaccid bullae, erosions, and crusting involving the trunk.

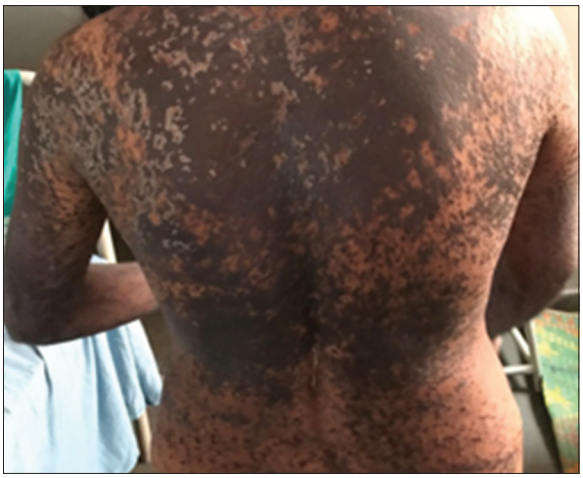

Figure 3: Multiple well-defined hyperpigmented maculopapular lesions with dusky erythema.

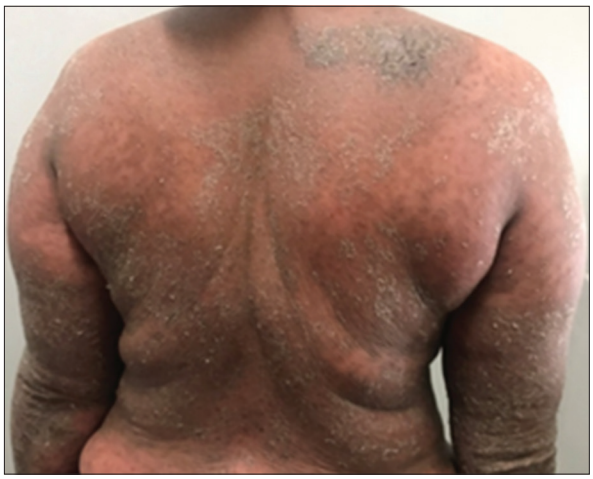

Figure 2: Diffuse erythema and scaling involving the entire body.

days previously, treated with tablet aceclofenac + chlorzoxazone at a local clinic. The following morning, redness and a burning sensation were initially on the forearms, then progressed to involve the entire body, including the face. On examination, multiple well-defined hyperpigmented maculopapular lesions with dusky erythema were seen over the entire body (Fig. 3). The Nikolsky sign was positive, and skin tenderness was present. Eighty percent of the body surface area was involved, with 20% epidermal detachment. On histopathology, the epidermis revealed full-thickness keratinocyte necrosis, Civatte bodies, and spongiosis. Eosinophils and lymphocytes were noted in the dermis. A diagnosis of SJS–TEN overlap syndrome secondary to aceclofenac and chlorzoxazone was established.

Case 4

A 64-year-old female presented with a rash over the entire body present for the last four days. There was a history of high-grade fever five days back, for which the patient was prescribed tablet Augmentin 1 gm. She developed a rash within two days, which was initially on the neck and arms and gradually spread to involve the entire body. A history of an allergy to penicillin had been present since 1987, documented on records (type of reaction unknown). On examination, generalized, discrete to confluent, tiny pustules were present on an erythematous background involving the entire body sparing the palms and soles (Fig. 4). A diagnosis of acute generalized exanthematous pustulosis to the penicillin group was established.

Case 5

A 19-year-old male patient presented with complaints of watering eyes, erosions on the lips and oral cavity, and fluid-filled lesions on the trunk present for the last four days. There was a history of fever with coughing one week earlier, for which he took over-the-counter medications (Syp. dextromethorphan, oral aceclofenac, and chlorzoxazone). The following morning, the patient developed a burning sensation, watering and difficulty in opening the eyes, difficulty in swallowing, and erosions on the entire lips and oral cavity. He went to a nearby local hospital, where he was admitted and treated with injections of ceftriaxone, tablet paracetamol, and aceclofenac. The following morning, dark red lesions on the trunk, face, both upper limbs, and buttocks appeared. There was a history of similar episodes in the past. The eyes and oral cavity were involved. On examination, target lesions were seen on the trunk (Fig. 5). White patches on the tongue, conjunctival congestion, and epiphora were also seen. A provisional diagnosis of

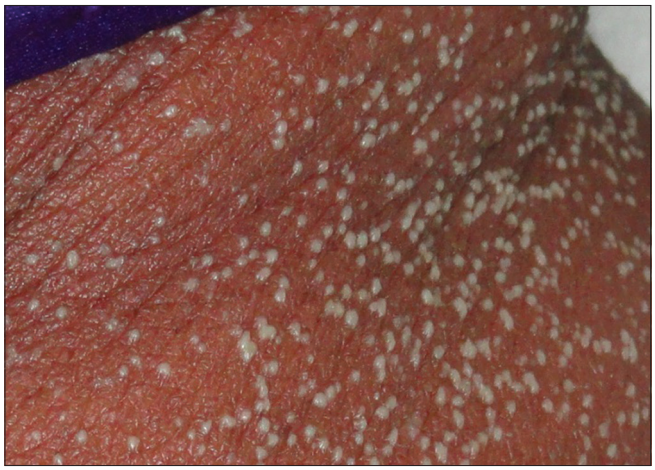

Figure 4: Discrete to confluent tiny pustules on an erythematous background.

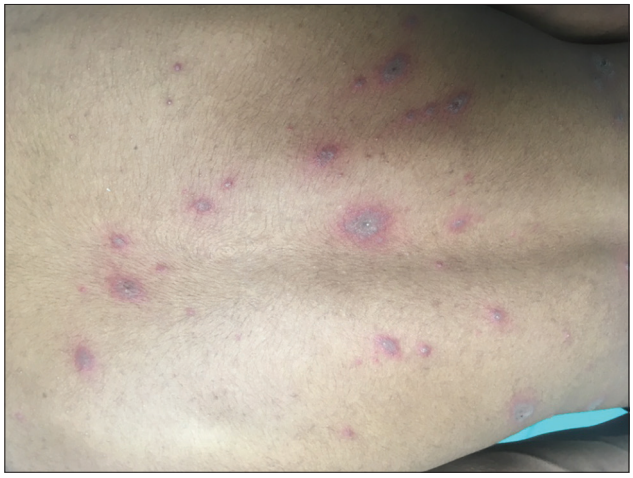

Figure 5: Target lesions on the trunk.

Steven–Johnson syndrome (secondary to aceclofenac and chlorzoxazone) or erythema multiforme was established. On histopathology, the epidermis revealed spongiosis, epidermal necrosis, and subepidermal bullae. The dermis showed a mixed inflammatory infiltrate composed of lymphocytes, neutrophils, histiocytes, and some eosinophils. A final diagnosis of Steven–Johnson syndrome was reached.

DISCUSSION

Drug reactions are unintended reactions that occur following the administration of drugs that are not characteristic of the desired pharmacodynamic effects of the drugs [2]. Cutaneous adverse drug reactions (CADRs) are common and account for 10–30% of all reported adverse drug reactions [3, 4], and their incidence in hospitalized patients is estimated to be 2–3%.

Drug reactions may be classified into two general categories: immunologic and non-immunologic [5]. Most adverse drug reactions are secondary to predictable, non-immunologic effects, while the residual adverse reactions are caused by unpredictable effects, some of which may be immune-mediated [6]. Only 5–10% of all adverse drug reactions are immune-mediated [7]. Immune-mediated reactions most commonly consist of either immediate or delayed immunologic mechanisms, mediated by cellular or humoral immune responses [8]. The presentation of cutaneous drug reactions may vary from localized and transient erythema to severe forms. The common CADRs are maculopapular skin rash, urticaria, fixed drug eruption (FDE), angioedema, and contact dermatitis. Serious CADRs endangering the patient's life are Steven–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) [9].

Once the diagnosis of CADR has been established, the most important part of the management includes the immediate discontinuation of the offending/suspected drug(s) and instituting relevant supportive and specific therapeutic measures [4]. IV corticosteroids, high dose IV IG (> 2 g/kg), appears to be a reasonable and relatively safe choice among the selective therapies currently available and previously tested. The role of steroids in the management of SJS–TEN and TEN has been controversial. Several studies have shown the possible benefit of corticosteroids. However, most of the studies have lately criticized the use of corticosteroids, stating that they not only prolong the hospital stay yet also make the patient susceptible to complications [10]. Other treatments such as cyclosporine, cyclophosphamide (100–300 mg/day), plasmapheresis, n-acetylcysteine (2 g/6 h), and TNF-α antagonists (e.g., etanercept, infliximab) have shown promising results [11].

CONCLUSION

After a cutaneous drug eruption has been diagnosed and treated, clear information must be provided to the patient regarding their drug rash. It is advisable that the patient carry a card of emergency identification that lists drug allergies and/or intolerances. The predisposition to some drug-induced eruptions may be genetic and family counseling is part of the care plan.

This may be important, especially in SJS, TEN, and drug hypersensitivity syndromes.

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

Special presentation of antiphospholipid syndrome

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ABSTRACT

Antiphospholipid antibody syndrome (APAS) is a condition of acquired thrombophilia due to autoantibodies directed against membrane phospholipids and/or their cofactors. It may be primary or part of a systemic autoimmune disease, such as systemic lupus erythematosus (SLE). Dermatological lesions during APS are frequent, although non-specific, sometimes inaugural, and may be the only clinical manifestation. However, extensive cutaneous necrosis is rare and treatment is based on anticoagulants and appropriate local care. Herein, we report a case of multiple extensive cutaneous necroses in a female with SLE. The particularity of our case is the presence of two types of lesions, necrotizing plaques surmounted by hemorrhagic bullae surrounded by a purpuric border specific to antiphospholipid syndrome and ecchymotic plaques evolving according to the color of the biligenesis, which may be consistent with coagulopathy, in particular, a protein C or S deficiency, hence the interest in good knowledge and semiological analysis.

Key words: Anti-phospholipid antibody syndrome; Extensive skin necrosis; Systemic lupus erythematosus

INTRODUCTION

Antiphospholipid antibody syndrome (APAS) is a condition of acquired thrombophilia due to autoantibodies directed against membrane phospholipids and/or their cofactors characterized by venous and arterial thrombosis and/or pregnancy morbidity.

It may be primary or part of a systemic autoimmune disease, notably systemic lupus erythematosus (SLE). It affects up to 36% of patients with SLE.

Dermatologic lesions during SLE are common, although nonspecific, and may be the only clinical manifestation.

Herein, we report a case of multiple extensive cutaneous necroses in a female with SLE revealing an unknown SAPL.

CASE REPORT

We report a 39-year-old patient followed since 2012 in internal medicine for systemic lupus with hematological (anemia, lymphopenia) and cardiac (pericarditis) tropism under corticosteroid therapy with initially negative antiphospholipid antibodies. Admitted for the management of diffuse, painful, purplish-red lesions of abrupt onset evolving for one week. A dermatological examination revealed ecchymotic plaques surrounded by a purpuric halo, well-limited, with irregular contours, with the largest 10 cm in length, topped by bullae with a hemorrhagic content in some places, located on the left arm and forearm (Figs. 1a and 1b), the back, the lower abdomen, and the posterior surface of the thigh. All plaques regressed according to the biligenesis shade, except for two, which became necrotic and surrounded by a purpuric border, surmounted by hemorrhagic bullae (Figs. 2a and 2b).

A biological workup revealed normocytic normochromic anemia at 10.9, lymphopenia at 780, thrombocytopenia at 122,000, sedimentation rate at 30 mm/1st hour, C-reactive protein at 0.05 (0.1–0.4), and normal proteins C and S.

The immunological workup was as follows: positive anti-nuclear antibodies of speckled appearance >1/160, negative anti-native DNA antibodies, positive

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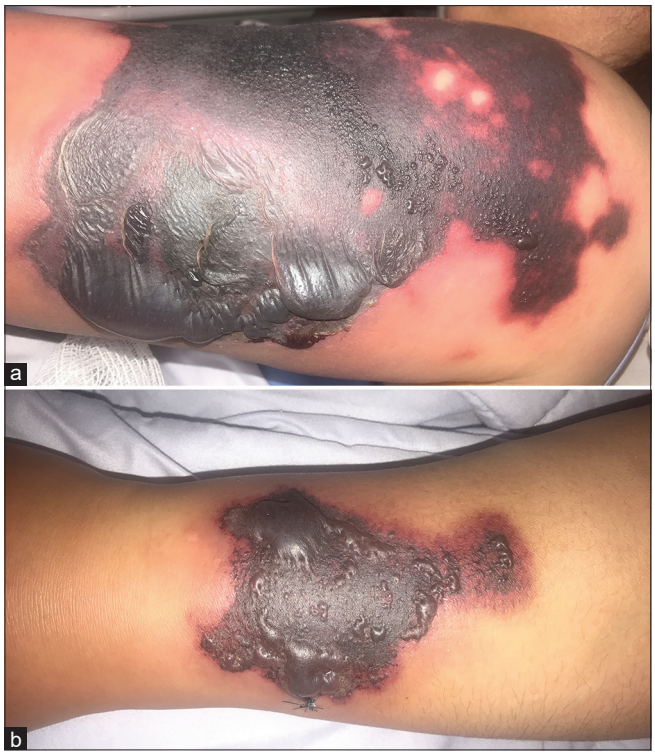

Figure 1: (a and b) Ecchymotic plaques surrounded by a purpuric halo, well-limited, with irregular contours, with the largest 10 cm in length, topped by bullae with a hemorrhagic content in some places, located on the left arm and forearm.

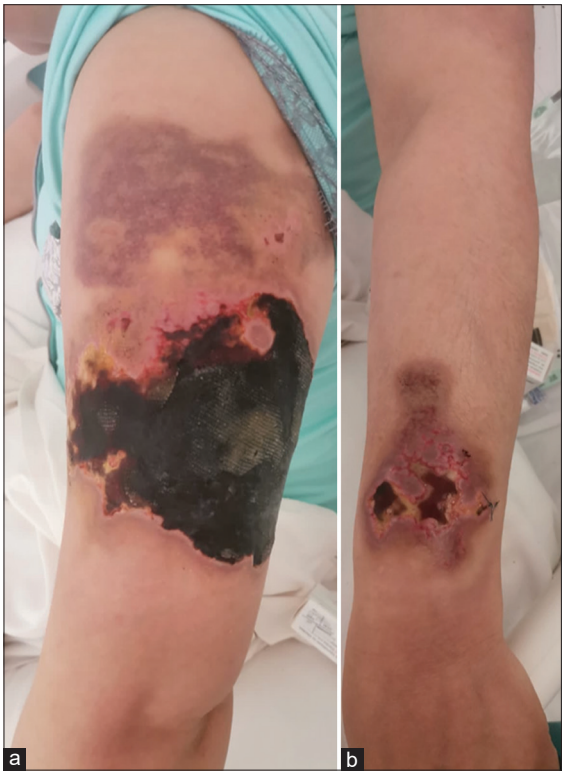

Figure 2: (a and b) Escharotic plaques, well-limited, with irregular contours, with the largest 10 cm in length, located on the left arm and forearm.

anti-histone and anti-SSA antibodies, and positive circulating lupus-type anti-coagulant antibodies.

A skin biopsy at the level of the purpuric border revealed leukocytoclastic vasculitis with fibrinoid necrosis and the presence of micro-thrombi.

The patient was administered corticosteroids and antiplatelet agents with the regression of the ecchymotic plaques and the necrosectomy of the necrotic ones (Figs. 3a and 3b).

DISCUSSION

Antiphospholipid antibody syndrome (APAS) is a condition of acquired thrombophilia due to the presence of at least one of the circulating antiphospholipid antibodies: anti-β2glycoprotein I IgG or IgM, anti-β2glycoprotein I IgG or IgM, and/or lupus-positive circulating anticoagulants.

Dermatologic lesions during SAPL are common, although nonspecific, sometimes inaugural, and may be the only clinical manifestation [1,2].

However, extensive superficial skin necrosis remains extremely rare, reported in only 2% of cases [2,3].

The onset is brutal with necrotic purpura evolving into a blackish, escharotic plaque bordered by a purpuric border and or necrotic bullae. They are located on the limbs, face (cheeks, nose, ears), or buttocks, as in our patient.

A skin biopsy of the purpuric border shows diffuse thrombosis of the dermal and hypodermal vessels with secondary skin necrosis.

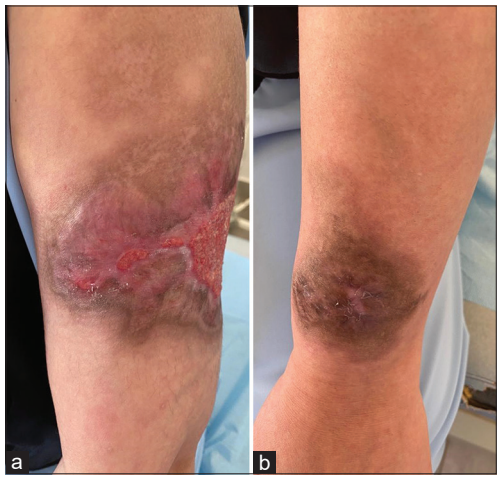

Figure 3: (a and b) Clinical images after necrosectomy, corticosteroids, and antiplatelet agents.

The diagnosis is based on the criteria by Myaskis et al. from 2006 [4]: the presence of at least one of the antiphospholipid antibodies and the histological confirmation of small vessel occlusion.

The particularity of our case was the presence of two types of lesions: necrotizing plaques surmounted by hemorrhagic bullae surrounded by a purpuric border specific to antiphospholipid syndrome and ecchymotic plaques evolving according to the hue of biligenesis, which may be consistent with coagulopathy, in particular a deficiency of protein C or S, hence the interest in good knowledge and semiological analysis.

The treatment is based on preventive and curative treatment with effective anticoagulation, possibly combined with corticosteroids, immunosuppressants, plasma exchange, or immunoglobulins [5-7].

Necrosectomy is essential to avoid superinfections. We must not forget to fight against other thrombotic risk factors, which are present in about 50% of patients [8] (hypertension, smoking, diabetes, obesity, vitamin D deficiency, pregnancy, postpartum, surgery, prolonged immobilization) [9].

CONCLUSION

This was a rare case of SAPL with necrotic lesions that evolved according to the color of the biligenesis, which had not yet been reported.

Hence is the interest in good semiological knowledge and analysis, which helped the diagnosis after the elimination of coagulopathies, in particular a deficiency of protein C or S.

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

Onychopapilloma: Report of two cases

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ABSTRACT

Onychopapilloma is a benign neoplasm of unknown etiopathogenesis of the distal nail matrix and proximal nail bed. It may have different clinical presentations, which constitute a diagnostic challenge. It is usually monodactyl and mainly affects the fingers. Despite that it is not uncommon, doctors outside of dermatology are unaware of this entity. Herein, we report two patients, with a median age of 67 years, who presented with monodactylous chromonychia, including longitudinal erythronychia and longitudinal leukonychia, associated with a subungual keratotic mass. With these clinical features, both patients were diagnosed with onychopapilloma.

Key words: Abnormal nail, Nail diseases, Nails

INTRODUCTION

Onychopapilloma is a benign tumor of the nail bed and distal matrix [1-7]. Although it is a common condition, there are currently few cases reported in the literature. It was first described by Baran and Perrin in 1995 as a localized longitudinal band of splinter hemorrhages associated with localized distal subungual keratosis. In 2000, the same authors introduced the term *onychopapilloma* [1-4]. Recent reports have described different clinical presentations, including longitudinal chromonychia, a subungual keratotic mass, splinter hemorrhages, distal fissuring, and other features, which makes it a diagnostic challenge [1-4]. It may be associated with non-specific symptoms such as pain and distal nail fragility [3,5,6].

CASE REPORT

A 62-year-old female patient consulted for contact dermatitis on the hands. During the examination, a longitudinal, white band on the right thumbnail was found (Figs. 1a and 1b). She reported a ten-year history of an asymptomatic subungual mass under the free edge of the nail plate, which had been clipping back. Dermoscopy revealed longitudinal leukonychia and a subungual keratotic mass (Figs. 2a and 2b). The rest of the physical examination revealed abdominal intertrigo and skin tags on the neck. She also referred a family history of type 2 diabetes.

The second case was a 72-year-old male who consulted for a fifteen-year history of an asymptomatic subungual mass under the free edge of the right ring fingernail. It had been diagnosed as a subungual wart and treated with topical creams with no relief. During the examination, a longitudinal, reddish band on the right ring fingernail plate was found (Fig. 3a and 3b). Dermoscopy revealed longitudinal erythronychia and a subungual keratotic mass (Fig. 4a and 4b). He also referred a personal and family history of high blood pressure.

DISCUSSION

Onychopapilloma is a benign nail tumor of the distal matrix and nail bed, yet malignancy has recently been reported. It was first described in 1995, as a localized distal subungual keratosis with multinucleated cells. In 2000, the term *onychopapilloma* was suggested by the same authors to refer to the condition [1-4]. Although its pathogenesis is unknown, some hypotheses have been suggested as a reactive hyperplasia of the nail bed epithelium due to chronic irritation or trauma,

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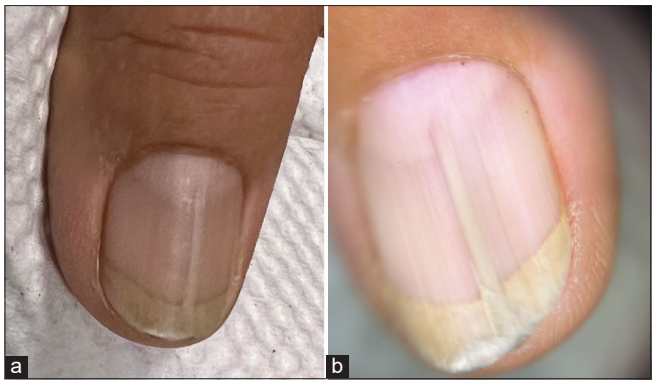


Figure 1: (a) Longitudinal leukonychia. (b) Dermatoscopy of longitudinal leukonychia on the right thumbnail.

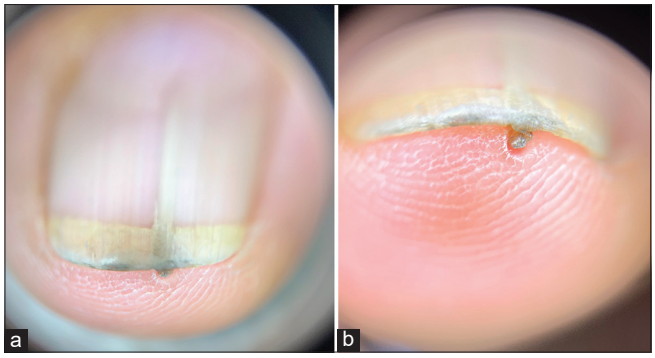


Figure 2: (a) Dermatoscopy of the subungual keratotic mass. (b) Dermatoscopy showing a close-up of the subungual keratotic mass.

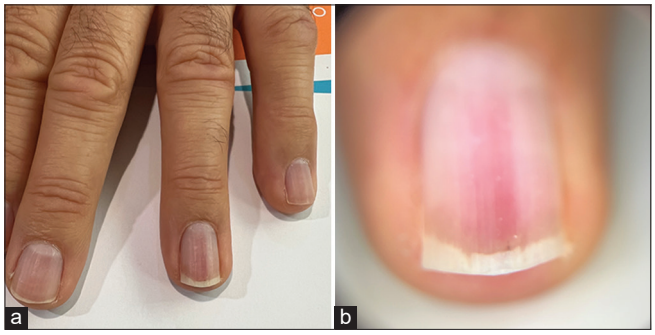
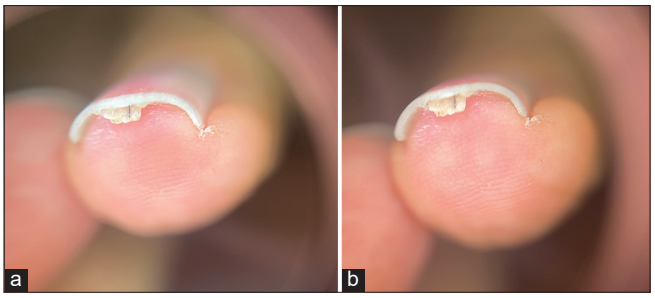


Figure 3: (a) Longitudinal erythronychia. (b) Dermatoscopy showing a close-up of longitudinal erythronychia.

neoplastic hyperplasia of the nail bed epithelium, and a concomitant response with other inflammatory nail diseases [3,6]. This neoplasm is commonly found in adults, with female predominance [1-7]. The clinical presentation of onychopapilloma is non-specific. The most common findings are longitudinal erythronychia, longitudinal leukonychia, distal uninterrupted or interrupted splinter hemorrhages, longitudinal melanonychia, yellowish-brown chromonychia, nail plate fissuring with or without a V-shaped notch, distal subungual keratotic papules, and onycholysis. The width of the bands ranges from 0.3 to 0.5 mm [1-4].



Figures 4: (a and b) Dermatoscopy of the subungual keratotic mass.

Most of the patients present associated symptoms, such as functional problems, as catching on fabrics, distal nail fragility, pain, tenderness, and cosmetic problems [3,5,6]. Onychopapilloma shows monodactylous involvement, principally, of the fingers. The most habitually affected digits are the thumbs, followed by the index, medium, and ring fingernails; the toes may also be affected, especially the halluces [1,2,4,5]. Dermoscopy usually reveals longitudinal erythronychia as a pale, whitish-pink band with sharp margins in the lunula continuing to extend to the nail bed as a pinkish-red band; splinter hemorrhages are visualized as a single or multiple, thin, interrupted, irregular lines; a yellowish-brown keratotic subungual mass in correspondence to the streak, in the distal margin; these features may be associated with distal onycholysis and nail plate fissuring [1,2].

The diagnosis is most readily made on an excision, yet transversal nail clipping may also be suggestive. The histological features of onychopapilloma involve acanthosis, papillomatosis, hyperplasia, metaplasia, hyperkeratosis, and hemorrhage of the distal nail matrix and nail bed [1-4,7]. Nail extraction of the hyperkeratotic lesions with curettage on the nail bed and an excisional biopsy may serve as a definitive treatment [2,3,6].

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.

Statement of Ethics

Verbal and photographic informed consent was obtained from the patient described in this article.

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Our Dermatology Online

Case Report

Diagnostic wandering of a case of giant pedicled lipoma of the left inguinal fold

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ABSTRACT

Lipomas are usually benign tumors formed from a proliferation of mature adipocytes, resulting in hypodermic, soft, compressible, and mobile nodular formations under the skin. In their subcutaneous location, superficial lipomas represent 16% to 50% of soft tissue tumors. They may be solitary or multiple. Solitary lipoma is usually seen in young adults between the ages of 30 and 50 years, regardless of sex, and is frequently asymptomatic. A lipoma is called giant when its weight exceeds 1 kg or its diameter exceeds 5 cm. The etiopathogenesis of lipomas is poorly understood. Herein, we report a case of giant pedunculated lipoma localized on the left inguinal fold being a distress for the patient.

Key words: Giant pedunculated lipoma, Diagnostic wandering, Ablation, Burkina Faso

INTRODUCTION

Lipomas are generally benign tumors formed from a proliferation of mature adipocytes, resulting in hypodermic, soft, compressible, and mobile nodular formations under the skin. They are most often encapsulated and slow-growing, reaching large dimensions. Usually sessile, in rare conditions, a lipoma is referred to as giant when its weight exceeds 1 kg or its diameter exceeds 5 cm [1-3]. Herein, we report a case of giant lipoma localized on the left inguinal fold being a distress for the patient.

CASE REPORT

This was a forty-year-old patient, farmer, residing in Djibo, Burkina Faso, monogamous, father of four children, with no known pathological history. He consulted for an asymptomatic mass localized on the left inguinal fold evolving for ten previous years and distressing the patient.

A physical examination revealed a tumor lesion, 5–12 cm in size, soft, non-depressible, mobile with respect to the deep plane, and superficial, localized on the left inguinal fold (Fig. 1a), pedunculated on a base of 4 cm, not painful on palpation. The skin in the front was normal. Another tumor lesion molasse (molluscum pendulum) of 1–2 cm was on the inner surface of the right buttock (Fig. 1b). An ultrasound examination confirmed that it was an avascular mass characteristic of a lipoma. For management, we performed a surgical excision (Fig. 1c), during which we, on gross examination, discovered encapsulated fatty lobules, confirming the diagnosis of giant pedunculated lipoma, whose weight was 830 g (Fig. 1d). Electrocoagulation of the small tumor (molluscum pendulum) was performed.

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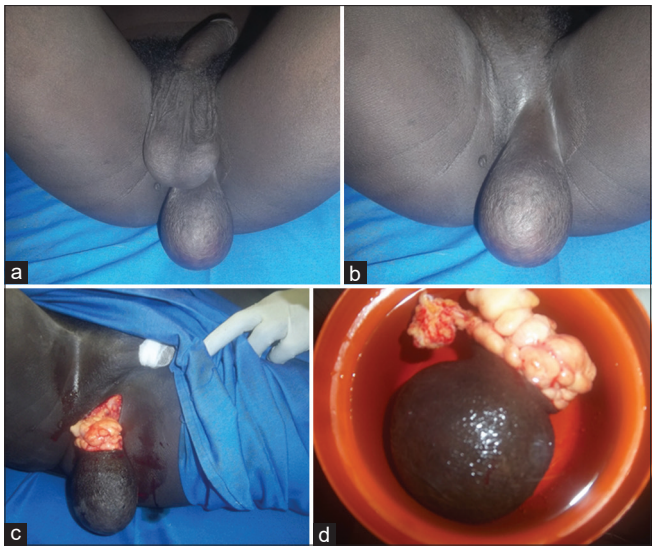

Figure 1: (a) Giant lipoma tumor, 5–12 cm in size, before ablation. (b) Molluscum pendulum tumor, 1–2 cm in size, on the inner surface of the right buttock. (c) Surgical excision of the giant lipoma tumor. (d) Giant lipoma tumor completely removed and deposited in a cup.

An anatomopathological examination of the room confirmed that it was a lipoma.

DISCUSSION

In their subcutaneous localization, superficial lipomas account for 16% to 50% of soft tissue tumors. They may be solitary or multiple. Solitary lipoma is generally seen in young adults between 30 and 50 years of age, regardless of sex, and is frequently asymptomatic [3,4], as in our patient, yet sometimes, it is painful [5]. The complaint in the latter was essentially functional discomfort and anxiety about the impact on his libido and fertility. The diagnosis is guided by clinical examination, as in our patient. Lipoma is often painless and usually results in a soft, regular, mobile tumor. It is located on the back in 15% to 20% of cases yet may be localized anywhere on the body [1,2,6]. The clinical presentation of the lesion in our patient (shape, size, pedunculated appearance, location) was not usual in lipomas and may be explained by the permanent pressure exerted by the inguinal fold and the action of gravity on the lesion. Posch described the clinical test of ice application to the tumor, which in the case of lipoma, results in the solidification of the mass. The usual course is slow growth, which may stabilize spontaneously [2,3]. The soft consistency and pedunculated appearance at first evoked molluscum pendulum, similarly to our daily practice, or inguinal hernia [2], yet the non-depressible aspect such as a hollowed out grape grain was not in favor. Differential diagnosis was also made with other soft tissue tumors such as angio-eccrine hamartoma [7] and hidradenoma [8].

Some authors opt for primary liposuction to reduce tumor volume, because the aesthetic result would be more satisfactory and post-operative morbidity would be decreased [3,6].

CONCLUSION

Our patient made a diagnostic wandering of ten years despite his numerous consultations. Abstention from treatment was the choice in previous consultations because of the location and the unusual clinical appearance of the lesion. This was a source of major anxiety and moral prejudice in our patient. Surgical treatment is of choice with total remission.

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

Acquired port-wine stain in an adult female: A rare entity

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ABSTRACT

The port-wine stain in adults, or acquired port-wine stain, is a rare entity. A fifty-year-old female presented with complaints of an asymptomatic erythematous patch affecting the right side of the face for the previous twenty years. The lesion gradually increased in size to involve the area below the eye, right nasolabial fold, cheek adjacent to the nasolabial fold, and area between the right nasolabial fold and the upper lip. On the basis of clinical and dermoscopic examinations, the diagnosis of a port-wine stain was established.

Key words: Acquired port-wine stain, Female sex, Congenital nevi, Dermoscopy

INTRODUCTION

Port-wine stains (PWS) are congenital, telangiectatic nevi consisting of ectatic dermal capillaries, affecting 0.3–1% of newborn infants. In contrast, acquired PWS develop later in life yet are morphologically identical to the congenital port-wine stain. Herein, we describe a case of acquired PWS.

CASE REPORT

A fifty-year-old female presented to the outpatient department of dermatology of a tertiary-care hospital with complaints of an asymptomatic erythematous patch affecting the right side of the face. She noticed it twenty years ago as a patch on the right side of the nose near the medial canthus of the eye (Fig. 1a). The lesion gradually increased in size to involve the area below the eye, right nasolabial fold (Fig. 1b), cheek adjacent to the nasolabial fold, and area between the right nasolabial fold and the upper lip. She denied having a history of a preceding birthmark. There was no history of antecedent mechanical or thermal trauma, drug intake, topical application, or excessive UV exposure.

On examination, the lesions were in the form of macular erythema. A dermoscopic examination revealed red, rounded, globular vessels (Fig. 2).

On the basis of clinical and dermoscopic examinations, the diagnosis of a port-wine stain was established. Laser therapy with pulse dye laser was discussed with the patient, yet she was reluctant to undergo any treatment at this age.

DISCUSSION

Port-wine stains are congenital, vascular malformations present at birth as pinkish-red to purple macules, which may become darker and nodular in adult life [1]. Biopsy specimens reveal an increase in vessel abnormalities with advancing age, which may be due to collagen degeneration and elastosis leading to the weakening of supporting dermal structures [2]. Rosen et al. implicated malformed sympathetic innervation in the pathogenesis of the port-wine stain and failure to regulate blood flow resulting the in progression of vascular injury [3]. Rydh et al. reported a lack of neural innervation in the port-wine stain, along with sympathetic innervation [4]. A study by Breugem et al. revealed the genetic inheritance of the port-wine stain as an autosomal dominant disorder, whose locus is mapped on chromosome 5q [5].

Unlike the congenital port-wine stain, the acquired port-wine stain occurs later in life. Various factors have been proposed for the occurrence of port-wine stains.

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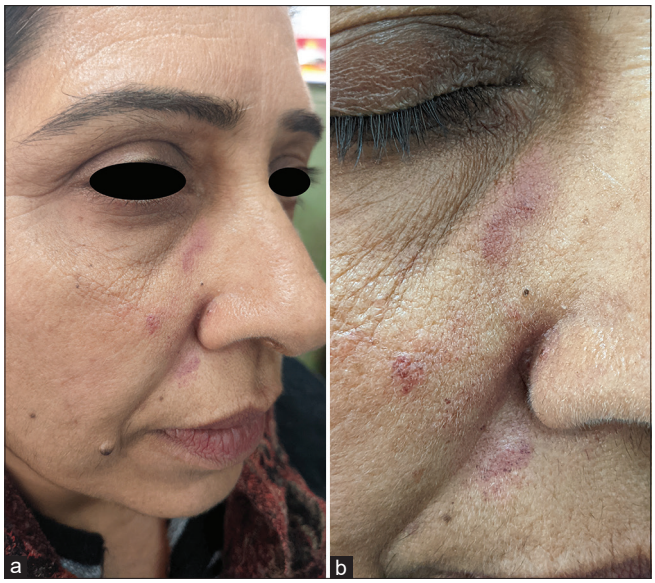

Figure 1: (a) Acquired port-wine stain in the fifty-year-old female involving the right side of the face. (b) Close-up view of the acquired port-wine stain.

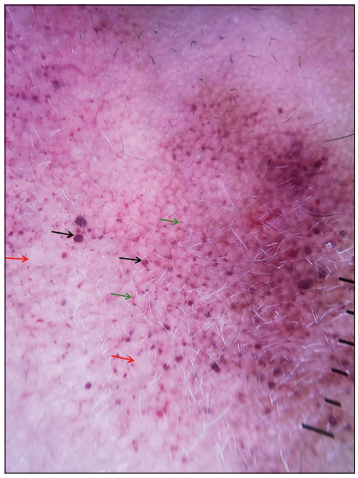

Figure 2: Dermoscopy of the acquired port-wine stain: white veils (*red arrows*), red dots (*green arrows*), globules (*black arrows*).

Post-traumatic capillary malformation may be seen, first described by Fegeler, and hence called Fegeler syndrome [6]. Other proposed etiologies are chronic sun exposure [7] and drugs such as isotretinoin [8] and OCPs [9].

On dermoscopy, findings such as dots, globules, linear vessels, reticular vessels, and whitish veils may be seen [10]. Dermoscopic features help to predict the response to laser therapy. Dots and globules represent the superficial or papillary form of the port-wine stain, which responds better to laser therapy when compared to a pattern showing linear vessels, which is the deep or subpapillary form.

Thus, dermoscopy serves as an important tool for assessing the depth of port-wine stains, as dotted or globular vessels indicate the superficial form and linear vessels indicate the deep form of the port-wine stain. Hence, the response to treatment may be assessed with dermoscopy. The acquired port-wine stain is rare and few cases have been reported in the literature so far.

Consent

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

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

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Our Dermatology Online

Review Article

Diet, sleep, and exercise in inflammatory skin diseases

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ABSTRACT

Inflammatory skin conditions are significantly impacted by lifestyle habits, particularly those related to diet, exercise, and sleep. Although ancient cultures emphasized the importance of lifestyle behaviors as both etiology and therapy in disease, modern medicine often overlooks nonpharmacological therapy. However, recent studies show that diet can have a significant impact on inflammatory skin diseases such as psoriasis, hidradenitis suppurativa, and atopic dermatitis. Foods high in glycemic index, advanced glycation end-products, and omega-6 polyunsaturated fatty acids are associated with obesity and systemic inflammation, which can exacerbate inflammatory skin diseases. In addition, lifestyle behaviors such as exercise and sleep have been shown to have positive effects on inflammatory skin diseases. This review aims to highlight the importance of lifestyle behaviors in the context of inflammation and inflammatory dermatoses.

Key words: Diet, Exercise, Sleep, Psoriasis, Inflammation, Skin

INTRODUCTION

Many ancient cultures place a strong emphasis on lifestyle behaviors as both an etiology and therapy in disease, whereas modern medicine focuses on scientific advancements often overlooking nonpharmacological therapy. Despite recent therapeutic advancements, the field of dermatology includes a myriad of heterogeneous, complex inflammatory diseases with which patients experience considerable morbidity and significant unmet need. The role of lifestyle behaviors in inflammatory processes and disease is not well-defined, and their evaluation, adjustment, or alteration is seldom recommended in dermatology. This review focuses on the function of lifestyle behaviors, such as diet, sleep, and exercise in the context of inflammation and inflammatory dermatoses.

PART I. DIET

Inflammatory skin conditions are the most common problem seen in dermatology practice [1]. Numerous studies have demonstrated a positive association between poor diet and worsening of inflammatory skin diseases, such as psoriasis, hidradenitis suppurativa (HS), and atopic dermatitis [BT1] [2-5]. More specifically, foods with a high glycemic index, advanced glycation end-products (AGEs), and omega-6 polyunsaturated fatty acids (PUFAs) are associated with obesity and systemic inflammation [6-9]. High glycemic index foods significantly increase blood glucose levels, stimulating insulin production [6]. Insulin promotes glucose uptake by adipocytes, promoting fat storage, leading to obesity and increased visceral adiposity. Visceral adipose tissue has a higher density of cells and is more biologically active than other forms of fat, producing inflammatory cytokines, such as leptin, resistin, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6 and monocyte chemoattractant protein-1 [6,10]. Additionally, increased visceral fat is associated with reduced levels of adiponectin and increased insulin resistance mediated through c-Jun N-terminal kinases (JNKs) phosphorylation in adipocytes [11-15]. These metabolic abnormalities

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lead to dysregulated lipolysis in the liver resulting in excessive delivery of fatty acids to hepatocytes [14,15]. With time, development of non- alcoholic fatty liver disease (NAFLD) and subsequent non-alcoholic steatohepatitis (NASH) occurs. These conditions are positively associated with increased serum concentrations of IL-1β, IL-6, TNF-α, c-reactive protein (CRP), and ICAM-1 [16]. Moreover, AGEs, formed by non-enzymatic glycation of macromolecules, bind to receptors for advanced glycation end products (RAGEs), increasing the transcription of IL-6, TNF-α, and CRP [5,8]. Lastly, PUFAs are metabolized into pro-inflammatory eicosanoids, such as prostaglandin E2 and leukotriene B4 [5,6,9,17]. Taken together, obesity, NAFLD, NASH, and specific dietary components promote a pro-inflammatory environment that is thought to exacerbate inflammatory skin disease. It should also be noted that insulin resistance leads to worsening of hyperglycemia and the development of type II diabetes mellitus, contributing to the vicious circle of obesity-related chronic inflammation [18,19].

In psoriasis, obesity and cardiovascular disease (CVD) are related to incidence, severity, and progression of the condition. The pathogenesis of psoriasis is driven by aberrant TNF-α/IL-23/IL-17 axis signaling, leading to hyperproliferation and increased differentiation of epidermal keratinocytes [20]. Specifically, TNF-α acts on dendritic cells to increase the transcription of IL-23, thereby stimulating T-helper 17 cells to release IL-17A. Through increased TNF-α production, obesity promotes T-helper 17 cell expansion, which also leads to increased IL-17A production, participating in the pathogenesis of psoriasis. Similarly, the link between psoriasis and CVD is thought to be due to shared pro-inflammatory pathways between the two conditions [21,22]. Akin to psoriasis, the pathogenesis of hidradenitis suppurativa (HS) involves hyperactivation of the TNF-α/IL-23/IL-17 axis, preceded by follicular occlusion of the follicular pilosebaceous unit [23]. The prevalence of obesity among HS patients was roughly 2.5 times that of non-HS patients [24]. The number of patients reporting HS symptoms after a 15% weight reduction decreased by 35%, with a statistically significant reduction in the number of body sites involved [25]. Interestingly, the prevalence of obesity and metabolic syndrome is thought to be higher in patients with HS relative to psoriasis with an OR of approximately 6.0 compared to 2.0 [26]. In addition to elevated TNF-α and IL-6 production, metabolic syndrome-induced androgen overproduction of sebum and overgrowth of the intra-ductal keratinocytes is thought to be the backbone of obesity-mediated HS exacerbation. In atopic dermatitis (AD), dietary factors such as cow's milk, egg, soybean, and wheat gluten contribute to symptom progression [27]. In a study by Breuer et al., the mentioned food allergens were administered to 106 pediatric patients with AD [28]. The food challenge triggered immediate onset exanthematous reactions in 46% of participants. Additionally, a cross-sectional study involving approximately 18,000 patients with or without AD identified a significant association between processed food, meat, and instant noodle consumption in those with a diagnosis [29]. Food allergens can trigger acute immunoglobulin E- mediated hypersensitivity reactions or food allergy related T-cell late eczematous reactions [27]. As such, patch testing and dietary modification via a predominantly plant based anti-inflammatory diet is recommended for those with AD [27-30]. The impact of poor diet and obesity on inflammatory skin disease is an important topic of discussion, as it is predicted 50% of adults will have obesity by 2030 [31]. As such, it is logical to assume an increase in the prevalence of inflammatory skin pathologies with time. Additional studies involving dietary intervention on disease remission are warranted.

PART II. SLEEP

The circadian rhythm is an essential internal clock synchronized with the environmental light-dark cycle present in all mammals. In humans, the circadian rhythm is under the control of the suprachiasmatic nucleus and retinohypothalamic tract, and it involves a molecular transcription- translation feedback loop present in most tissues and cell types [32,33]. Skin, an important immunological organ, exhibits a diurnal expression of various proteins within its layers, where the light-dark cycle- related alterations in gene expression are most prominent in the epidermis [34,35]. The immune function of the skin is regulated by circadian rhythms, and its proper function is important for suppression of autoimmune diseases [36,37]. Disturbances in circadian rhythms associated with shift work have been hypothesized to contribute to the development of psoriasis and other autoimmune conditions [33]. The possible contributing factors include decreased levels of melatonin and vitamin D, which are known for their anti-inflammatory effects [31-33]. Additionally, the light-dark cycle controls the function of γδ+ T cells and Langerhans cells within the epidermis, which are important for the immune functions of the skin.

The γδ+ T cells are controlled via a direct activation of the Interleukin-23 (IL-23) promoter by circadian rhythm CLOCK protein within the γδ+ T cell subset [38]. Similarly, macrophages and mast cells of the dermis layer are directly regulated by the circadian clock and mediate phagocytosis and cutaneous anaphylactic reactions, respectively [39]. Other diurnal immunologic skin patterns include circadian cycle-dependent T cell recruitment, which is implicated in nocturnal exaggeration of atopic dermatitis and overall fluctuations in chemoattractant levels throughout the skin layers [36,40].

Circadian cycle disturbances have been repeatedly linked to chronic inflammatory diseases [36,41-46]. Insufficient sleep is known to be associated with chronic inflammatory states seen in diabetes, obesity, and cardiovascular diseases, which are often comorbid with dermatologic autoimmune conditions [46]. Severity of several autoimmune skin conditions including psoriasis is inversely correlated with the amount of sleep and sleep difficulty [47,48]. Sleeping disturbances associated with disease state or pharmacological side effects negatively impact circadian cycle [49,50]. In psoriasis and atopic dermatitis, nocturnal pruritus disturbs sleep and further exacerbates severity of the autoimmune conditions, creating a positive feedback loop [50,51].

The effects of sleep on the immune system include a bidirectional regulation between the stages of the sleep cycle and levels of pro-inflammatory cytokines. Sufficient nighttime sleep is necessary for proper bimodal daily release of IL-6, which plays an important role in acute inflammation. IL-6 is a cytokine with context-dependent pro- and anti-inflammatory properties, and is implicated in cell differentiation, oncogenesis, and pathogenesis of inflammatory skin conditions including psoriasis, vitiligo, and atopic dermatitis [52-54]. Sleep deprivation is correlated with disproportional increase in daytime IL-6 accompanied by a decline in nocturnal IL-6 levels, as well as increased NF-κB activation [55,56]. Alterations of IL-6 and NF-κB functioning further support the role of sleep in the development of inflammatory states. Additionally, a variety of pro-inflammatory cytokines possess sleep-modifying properties [57,58]. For instance, elevated IL-1 and TNF-alpha levels have been associated with a reduction in rapid eye movement (REM) sleep and an increase in total non-REM [59]. Interestingly, sleep deprivation additionally skews the Th1/Th2 phenotypic ratio towards the Th2 dominance [60]. Increased prevalence of the Th2 phenotype, compared to Th1, is implicated in development of dermatologic conditions such as atopic dermatitis, highlighting the possible importance of sleep in autoimmune states. Further investigation is needed to elucidate the effects of molecular players of circadian cycles on the pathogenesis of autoimmune skin conditions.

PART III. EXERCISE

Both aerobic exercise and strength training produce a decrease in inflammation. Interestingly, exercise's true anti-inflammatory effects arise gradually, whereas short-term changes with exercise induce pro-inflammatory processes. The initial response is mediated by an increase in the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6, both during and immediately following exercise [61]. However, the transient inflammatory state is counteracted by release of anti-inflammatory hormones cortisol and adrenaline [62,63]. With frequent exercise, the anti-inflammatory effects predominate in a longer-term response.

Though the exact mechanism is unknown, several hypothesized pathways have been proposed. One proposed mechanism is that exercise's anti-inflammatory effects are due to a significant decrease in pro-inflammatory cytokines C-reactive protein (CRP), IL-6, and TNF [62]. Others suggest that exercise activates AMP-activated protein kinase (AMPK), thus increasing fatty acid oxidation and glucose metabolism [64]. Javaid, et al. suggest that beneficial effects of exercise may be explained by inhibition of NLRP3 inflammasome activation by the myokine Meteorin-like (METRNL) which is crucial for the onset of inflammation [65].

In support of exercise's downregulation of TNF-α, a clinical trial investigating exercise's pro-inflammatory effects showed that in participants infused with Escherichia coli, resting participants to have a two- to threefold increase in TNF-α compared to the participants who performed a cycling exercise earlier that day [66,67]. Furthermore, though the exact pathway is unknown, IL-6 appears to play a significant role [62,63,67-81]. IL-6 is commonly classified as a proinflammatory cytokine, much like TNF-α, however studies suggest it may have anti-inflammatory properties as well, due to its ability, via negative feedback, to decrease the body's levels of TNF-α and other proinflammatory cytokines [70,72,76,80]. Levels

of IL-6 may be increased up to 100-fold in long-term exercise [63,74-77]. In fact, participants who did not exercise but were given recombinant human IL-6 (rhIL-6), displayed a similar decrease in levels of TNF-α, as participants who rode a bike for three hours that same day [66]. As expected, the control group, who neither engaged in exercise nor received rhIL-6, showed elevated levels of TNF-α. Moreover, the increase of IL-6 further combats inflammation by increasing anti-inflammatory cytokines IL1ra and IL10. In turn, IL-10 down regulates pro-inflammatory cytokines TNF-a, IL-1b, IL-6, IL-1α, IL-8, and macrophage inflammatory protein-1α (MIP-1α) [63,74,76].

Further, varying exercise intensity may display different anti-inflammatory profiles in healthy individuals. For instance, Paoluccia et al. found that moderate intensity is optimal for reducing inflammation, while high-intensity training may be harmful due to perception of stress as unrecoverable [75]. In contrast, Schauer et al showed comparable anti-inflammatory effects among different intensity levels in healthy adults. However, breast cancer patients undergoing chemotherapy had decreased levels of pro-inflammatory CRP during high-intensity exercise compared to during low-to-moderate intensity exercise [79].

The few studies investigating exercise in skin diseases are limited to psoriasis and dermatomyositis (DM), where increased levels of TNF-alpha play a key role in disease progression. In psoriasis, keratinocytes proliferate in response to TNF-α, IL-17, and IFN-γ. Proliferating keratinocytes participate in a positive feedback loop, further secreting TNF-α and inducing neighboring cell proliferation [82]. Similarly, upregulation and promoter polymorphisms of TNF-alpha are associated with pathogenesis of DM [83,84]. Hence, beneficial effects of exercise seen in both psoriasis and DM may be mediated by reduction of TNF-alpha levels. Exercise is associated with reduced disease activity and improved functioning in patients with psoriasis [85]. Likewise, moderate intensity aerobic exercise is associated with improved muscle function, decreased disease activity, and higher quality of life among patients with DM [86].

CONCLUSION

This review highlights the major link between lifestyle factors and inflammatory skin disease. While there is no evidence that behavior modification should replace standard of care therapy, patients with inflammatory skin disorders may benefit from supplementing therapeutic regimens with non-pharmacological therapy in the form of altering diet, sleep, and exercise habits. Many mediators involved in pathogenesis of inflammatory disorders are those that are also shown to be downregulated during engagement in health behaviors. Of equal importance to incorporation into treatment regimens is the recognition of lifestyle behaviors as risk factors and potential screening tools for inflammatory disorders. Thus, thorough history-taking and a combination of traditional therapy with adjustment of practice in diet, sleep, and exercise will optimize holistic assessment and patient outcomes.

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Our Dermatology Online

Review Article

Recurrent pityriasis versicolor: A short review of clinical features and antifungal and non-antifungal treatment options

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ABSTRACT

Objective: We conducted a systematic review of the literature from the PubMed database from January 1, 2010, to December 31, 2021. The search criteria were "(pityriasis versicolor OR tinea versicolor) AND treatment," with the full text available and the English language required. This review focuses on the clinical evidence supporting the efficacy of antifungal and non-antifungal treatment for pityriasis versicolor. **Background:** Pityriasis versicolor is a chronic superficial mycosis caused by the *Malassezia* species. The condition is one of the most common infections worldwide, particularly in tropical climates. Although it is a superficial infection, recurrences are high due to the presence of *Malassezia* in the normal skin flora. **Summary:** Topical and oral antifungal treatments effectively reduce the recurrence, leading to a lasting clinical and mycological cure. In addition to antifungal therapies, non-antifungal treatments have shown efficacy in cases of recurrent pityriasis versicolor and could be used as maintenance or preventive therapy. Due to high recurrence rates, prophylactic treatment may be necessary.

Key words: Pityriasis versicolor, Superficial mycosis, Tinea versicolor, Treatment

INTRODUCTION

Pityriasis versicolor (PV) is a superficial chronic fungal infection caused by yeasts of the *Malassezia spp.* genus [1,2]. These species are commensals on human skin and warm-blooded animals, such as pigs, monkeys, goats, horses, dogs, cats, and others, developing skin diseases and systemic infections in humans and animals [3].

Malassezia yeasts have been classified into at least fourteen species; eight have been isolated from human skin. The frequency varies depending on country; *M. furfur* is the main species in Indonesia and Brazil, *M. sympodialis* in Canada, and *M. sympodialis* and *M. globosa* in Argentina. The isolation of *M. slooffiae* and *M. restricta* is less frequent [1].

M. sympodialis is the predominant species in human skin, healthy or diseased, and is usually found on the trunk, while *M. globosa* is found in PV scales and healthy skin and *M. restricta* seems to be associated with pityriasis capitis [4]. *M. pachydermatis*, an agent of external otitis in cats and dogs, has also been considered responsible for some cases of systemic infection, mainly in premature children [1].

Malassezia-related skin diseases include head and neck dermatitis, seborrheic dermatitis, PV, and *Malassezia*

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folliculitis [5]. *M. japonica*, a recently described species was isolated mainly in the Japanese and Chinese populations with psoriasis, atopic dermatitis, seborrheic dermatitis, and healthy individuals [6]. Romero-Sandoval et al. [7] reported the isolation of *M. japonica* from patients with PV refractory to treatment. *M. globose* in the mycelial phase is the causative agent of typical and disseminated PV [8].

EPIDEMIOLOGY

Pityriasis versicolor has a worldwide distribution, affects all races, and is most prevalent in tropical and subtropical regions, where high humidity and temperature increase disease prevalence [9]. It may affect 40–50% of individuals from specific geographic regions (temperate climates) and ethnic groups [4]. It may occur at any age yet is more common in adolescents and young adults, with a peak incidence between the second and fourth decades of life. In most series, both sexes are equally affected, although there may be a slight male predominance depending on the series studied [1,4].

Numerous epidemiological studies have been conducted globally, with *M. globosa* being the principal etiological agent in regions with a temperate climate; in tropical and subtropical climate regions, the most common species are *M. sympodialis*, *M. furfur*, and *M. globose* [9-11].

PATHOGENESIS

The factors involved in transforming the yeast into its pathogenic mycelial form are uncertain. Endogenous and exogenous factors include genetic inheritance, congenital or acquired immunosuppression, malnutrition, oral contraceptives and corticosteroids, hyperhidrosis, endocrine disorders, elevated temperature, humidity, occlusive clothing, use of oil or moisturizers on the skin, as well as the chemical sebum composition [12].

Malassezia yeasts are lipophilic fungi with a high dependence on a lipid-rich microenvironment, and these microorganisms are part of the skin microbiome [13]. Under certain conditions, the yeasts become a pathogenic agent and produce various skin diseases, even systemic diseases. These fungi are mainly found in the infundibulum of the sebaceous glands, where lipids are widely available. It often requires peptone-rich media to grow, containing short-chain fatty acids (*M. pachydermatis*, *M. furfur*) [14,15].

The virulence factors of these yeasts, intrinsic factors of the host, and extrinsic environmental factors are involved in the pathogenesis of PV. The *Malassezia* cell wall represents the initial point of interaction between the host and pathogen. Its composition is strongly associated with adherence and penetration to tissues, helping it evade host defenses. The cell wall of *M. furfur* and *M. pachydermatis* is mostly galactomannans (galactose and mannose) and glucose [14,15].

Adhesion to host cells is necessary for colonization and infection. In addition to the cell wall characteristics, it also exhibits hydrophobic cell surface characteristics, which promote biofilm formation on biological surfaces and inert surfaces in approx. forty-eight hours in polyurethane catheters. This property gives it increased virulence, resistance to antifungal penetration, and drug resistance, which seems to be associated with the production of systemic infections. Numerous microorganisms generate hydrolytic enzymes that help them in their pathogenicity [13-15]. *Malassezia* species may produce proteinases, lipases, phospholipases, hyaluronidases, and chondroitinsulfatases, which promote the formation of pores in cell membranes, dismantling cell function, and promoting tissue invasion, with the subsequent dispersal of organisms. These lipases destroy triglycerides in the sebaceous glands and produce numerous unsaturated free fatty acids, local irritants, and immunostimulants [12-15]. Complex interaction begins once the yeasts encounter the stratum corneum and colonize it. It has been seen that the *Malassezia* species, under normal conditions, favor the production of transforming growth factor β1 and interleukin (IL) 10, which are powerful immunomodulatory and immunosuppressants decreasing the local response against these yeasts and facilitate the colonization of the skin [12,15].

Once the yeasts penetrate the stratum corneum, these are recognized and phagocytosed by local dendritic cells or Langerhans cells, which recognize and process mannose receptors and present to B and T cells in lymph nodes [1,7,12]. The importance of this T response is reflected in patients with HIV, in whom there is a significant proliferation of *Malassezia* and, in addition, the appearance of seborrheic dermatitis that is difficult to control, related to lymphopenia. It has also been seen that a specific group of patients may have an idiosyncratic response to the *Malassezia* species that favor a type IV hypersensitivity reaction, resulting in a TH1-type response, in addition to increased activity of metalloproteinases, which are potent inhibitors

of elastic fiber synthesis, resulting in atrophic skin lesions [1,16,17].

Malassezia is able to convert tryptophan to a wide variety of indole compounds associated with some of the clinical features of PV, such as the hypopigmentation seen in some lesions. This has been linked to the induction of melanocyte apoptosis, mediated by the activation of the aryl hydrocarbon receptor, which results in the transcription of cytochrome p450 proteins and the stimulation of the caspase pathway [18]. This clinical phenomenon (hypopigmentation) is also explained by the production of azelaic acid, which inhibits the synthesis of tyrosinase, an enzyme that mediates the conversion of L-DOPA to melanin [14]. On the other hand, in ultrastructural studies, it has been observed that some lesions exhibit a decrease in the number, size, and distribution of melanosomes, which would also explain the hypochromic described above. Although indeed, the exact cause of the hyperpigmented variant is unknown, it is suspected to be due to an increase in the thickness of the epidermis, as well as a more remarkable lesional inflammatory infiltrate, which would stimulate the melanocytes to produce more pigment and culminate with an increase in the number, size, and distribution of melanosomes [14].

CLINICAL MANIFESTATION

The lesions include round or oval macules, papules, or isolated plaques that may coalesce and cover large body areas separated by normal skin, leading to pigmentary changes from hypochromic macules (mainly related to the increased production of *Malassezia*-derived dicarboxylic acids, including azelaic acid with the competitive inhibition of tyrosinase) to erythematous or hyperchromic lesions (due to abnormally large melanosomes) [14,17]. Patches of PV have a brown or yellowish color and, if scraped with the fingernail, furfuraceous scaling is observed (Besnier's sign or scratch sign). Zireli's sign is characterized by scaling when the skin is stretched, and it is pathognomonic of PV [1] (Figs. 1 and 2).

DIAGNOSIS

The diagnosis is based on typical clinical manifestations combined with bright yellow fluorescence under Wood's light and direct mycological examination. The methods of lesion scraping or adhesive tape may be employed for material collection and observation under an optical microscope [5]. Potassium hydroxide (10% to 20%) with methylene blue 1% or Albert solution (toluidine blue and malachite green) is used for better visualization of fungal structures. On direct examination, yeast cells and hyphae are easily identified [19]. Vitiligo,

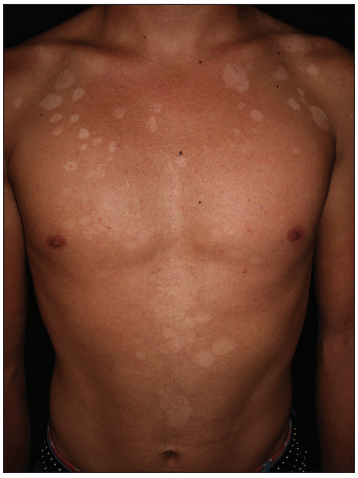

Figure 1: Extensive hypochrominant pityriasis versicolor.

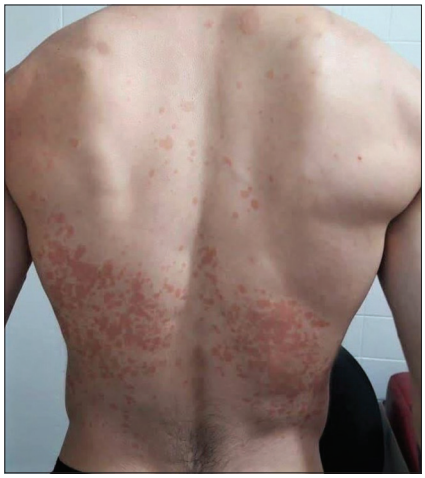

Figure 2: Extensive hypercromiant and recidivant pityriasis versicolor.

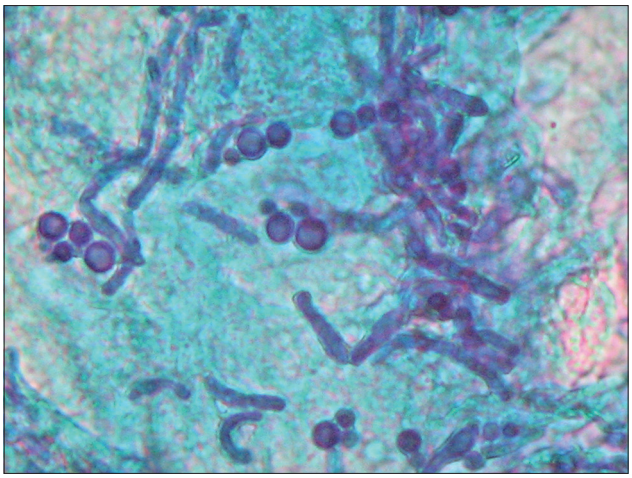

Figure 3: Direct examination: yeasts and short filaments (Albert's solution; 40×).

Table 1: Studies published between 2011 and 2021 on topical and systemic antifungal and non-antifungal treatments.

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
				Topical antifungal thera Romero py				
Dylag M [1]/2020/Poland/1	CR	50	Male	Ciclopirox 1% cream once daily and terbinafine 1% emulsion gel once daily	*M.furfur and M. sympodialis*	14/7 respectively	Direct microscopy examination Two weeks after completed treatment, still revealed fragments of pseudohyphae and single degenerated cells, while the cultures on modified Leeming-Notman agar (MLNA) was negative	No relapse during 8-month follow-up
Abdollahimajd F [2]/2019/Iran/2	CR	Eight months	Female	1% clotrimazole lotion (twice a day)	--	28	Lesions still present and less severity and KOH smears showed negative results for fungal elements	ND
	CR	Four months	Female	1% clotrimazole lotion (twice a day)	--	28	Lesions still present and less severity and KOH smears showed negative results for fungal elements	ND
Gobbato AA [3]/2015/Brazil/60	R, DB, CT	32.5	20/10	Dapaconazole tosylate cream 2%	--	28	Clinical and mycological cure *** (92.6%/84.6%, respectively)	ND
		34.5	15/15	Ketoconazole 2% cream				
Sharma J [4]/2018/India/60	O, R, CT	Comparable	Comparable	Eberconazole 1% cream once daily Terbinafine 1% cream once daily	--	14	Completely healed *** (80/63.33); mild residual disease (20/33.33). Considerable residual disease (0/3.33), respectively	Relapse in 1 patient (terbinafine) at eight weeks.
Ryu HW [5]/2011/Korea/1	CR	29	Male	Topical fluconazole and isoconazole	--	ND	Good clinical results.	ND
Romano C [6]/2015/Italy/1	CR	27	Female	Topical imidazole antimycotic	*M globosa*	28	Clinical and mycological recovery	ND
Marinello E [7]/2017/Italy/1	CR	42	Female	Topical ketoconazole 2% cream	--	42	Skin lesions and the atrophy completely resolved	No recurrence after Three months.
Dioussé P [8]/2017/Senegal/2	CR	18 months	Male	Topical ketoconazole once daily	--	56	Macules had regressed entirely, leaving hypochromia	ND
		12 months	Male	Topical ketoconazole once daily				
Sarkar S [9]/2016/India/80	CT	42 (52.5%) between 21 and 40 years of age	55/25	Ketoconazole 2% cream twice daily Topical luliconazole 1% cream twice daily	--	28	Mycological cure *** (72.50%/92.50%, respectively)	ND
Day T [10]/2014/Australia/1	CR	24	Female	Topical ketoconazole twice daily	--	21	Tan color faded gradually, disappearing by four months	No recurrence to date
Rad F [11]/2014/Iran/90	R, SB, CT	27.25 ± 8.46	56/34	Terbinafine hydrochloride 1% cream twice daily	--	14	Cure rates: *** 81.2/69 (4 weeks);. 70.8/61.9 (8 weeks), respectively.	The recurrence rate at the end of the eighth week: 1.3%/2.4%, respectively
		26.26 ± 8.6		Ketoconazole 2% cream twice daily				

(Contd...)

Table 1: *(Continued)*

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
				Systemic Antifungal				
Helou J [12]/2014/France/1	CR	52	Male	Itraconazole 200 mg/day one week but not cured Fluconazole 300 mg/week with partial improvement at two weeks Fluconazole 300 mg/week for one month combined with terbinafine twice daily for two weeks	--	49	Total clearance after three treatment schemes.	Relapse after one year
Brandi N [13]/2019/Italy/10	CR	18–38	2/8	Fluconazole 200 mg/day¸ ketoconazole shampoo and a topical antifungal in cream	--	14	Reddish-brown plaques gradually faded within 3-4 weeks, while the pink-white ones remained clinically stable, with negative mycology after one month.	ND
Alam HS [14]/2021/US/1	CR	52	Male	Fluconazole 300 mg/ weekly and ketoconazole 2% shampoo	--	14	At the 6-month follow-up, the tinea versicolor was resolved.	No relapse after six months.
Badri T [15]/2016/Tunisia/71	CT	29.1	20/16 19/16	Fluconazole and ketoconazole shampoo Fluconazole	--	14,28,56	*** 14 days (83/70), 28 days (63/86), 56 days (75/100), respectively.	The highest reinfection rate at the follow-up evaluation occurred in the fluconazole group. Relapse in 18/35 and 15/36, respectively
Balestri R [16]/2012/Italy/7	CR	52.3	5/2	Miconazole nitrate cream twice daily; fluconazole, 300 mg/week	--	28-21	Complete resolution in only 1 patient; complete resolution, respectively.	ND
Sharma M [17]/2014/India/1	CR	22	Male	Fluconazole 400 mg single dose; clotrimazole 1% cream twice a day	--	21	No change in the hypopigmented skin color was noted, but the mycological cure	ND
Jubert E [18]/2015/India/1	CR	32 + 3 weeks of gestational age	Male	Intravenous fluconazole	--	14	Total resolution of the lesions on follow-up after three months with no post-inflammatory hypopigmentation.	ND
Li [19]/2021/US/1	CR	58	Male	Fluconazole 200 mg daily on day 1, followed by 100 mg daily for six additional days	--	7	The rashes resolved within days.	No relapse after 1-year follow-up.
El-Housiny S [20]/2018/Egypt/30	R, CT	--	30/0	Gel 2 (1% Carpobol gel containing: solid lipid nanoparticles of 10% Compritol 888ATO 0.5%, Cremophor RH40, 1% fluconazole) twice daily	--	28	Clinical and mycological cure rates against marketed cream ranged from 40 to 98/36 to 99/22 to 80.	ND

(Contd...)

Table 1: *(Continued)*

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
				Gel 3 (1% Carpobol gel containing: solid lipid nanoparticles of 10%PrecirolATO5,0.5% Ploxamer 407,1% fluconazole) twice daily Clotrimazole 1% cream twice daily				
Romero-Sandoval K [21]/2017/ Brazil/16	CT	--	11/5	Itraconazole 100 mg daily for 28 days Itraconazole 200 mg daily for 7 days Itraconazole 200 mg daily for 28 days Ketoconazole 200 mg daily for 28 days	*M. japonica (30), M. furfur (30), M. sympodialis (20), M. sloofiae 10), and M. obtuse (10).*	7-28	Clinical improvement (0/0/28.5/50); No response (93.7/100/42.9/20); clinical and mycological cure (6.3/0/28.5/30), respectively.	ND
Choi E [22]/2020/Singapore/1	CR	24	Male	Itraconazole 200 mg for one week, followed by 100 mg for three weeks	--	28	Successful eradication of disease	ND
Allegue F [23]/2017/Spain/1	CR	28	Male	Itraconazole 200 mg daily for one week, topical flutrimazole for four weeks	--	28	Complete resolution after six months	No relapse one year follow up
Cam [24]/2019/Italy/240	CT	--	156/84	Fluconazole 300 mg a week and 2% ketoconazole foam twice a week for two weeks Itraconazole 200 mg daily for one week Ketoconazole 2% foam daily for two weeks	--	28	Clinical cure *** (62.4/36.3/37.5). Negative mycological examination (81.3/66.3/60.0), respectively	ND
Wahab MA [25]/2020/Bangladesh/200	O, R, CT	--	150/50	Itraconazole 200 mg daily Preventive treatment: Itraconazole 200 mg twice daily monthly for six consecutive months Preventive treatment: Placebo monthly for six consecutive months	--	7	Open treatment with itraconazole: Clinical improvement: 90%; negative Wood's lamp examination: 86.5%; mycological cure: 85.5%.	Preventive treatment versus placebo: 81(90%)/ 44(55%); 76(84.4%)/ 41(51.3%); 75(83.3%)/ 42(52.5%), respectively.
Bossini B [26]/2022/Italy/1	CR	15	Female	Oral fluconazole	--	14	Cure	--
Cantrell WC [27]/ 2014/USA/10	O, CT	21 and older		Ketoconazole 2% foam twice daily	--	14	Three out of ten evaluable subjects had negative skin samples. Four additional subjects tested negative at week 4.	1 of 3 relapsed at the week four follow-up visit

(Contd...)

Table 1: *(Continued)*

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
Dehghan M [28]/2010/Iran/105	R, DB, CT	24.9 5.1	20/30	Fluconazole 400mg single dose.	*M. furfur*	14	Complete clinical response: *** 30% and 49.1; Incomplete response: 66% and 47.3%. No response 4% and 3.6%.	Recurrence or no clinical response was seen in three cases (6%).
		24.1 5.9	21/34	Clotrimazole cream twice daily				
				Non-antifungal treatment				
Carmo ES [29]/2013/Brazil/48	R, CT	32.8	10/20	Cymbopogon citratus essential oil	*M. sympodialis* (33/33); *M. furfur* (26.7/11.1); *M.obtusa (3.3/-); M. globose (-/5.5); M. sloofiae (-/5.5)*	40	Mycological cure *** (60/90, respectively)	None
		33.5	10/8	Ketoconazole 2%				
Bakr E [30]/2020/Egypt/90	R, CT	29.9	22/8	Ketoconazole cream 2%	ND	28	Significantly improved (83.3/70/93.3); improved (13.3/16.7/6.7); Slightly improved (3.3, 13.3/0), respectively; no unchanged or aggravated cases were seen	ND
		29.8	19/11	Adapalene gel 0.1%				
		29.1	26/4	Combined treatment				
Balevi A [31]/2018/Turkey/38	CT	30.63 ± 12.03	26/12	Narrow-band UVB phototherapy 3x/weekly	--	Until complete clearing or to a maximum of 56 days	66.7% achieved excellent results; 14% had the mild residual disease; In 20% had improved lesions were <50%, and the KOH test was positive	16.6% of the good responders relapsed two months after the end of phototherapy.
Shi TW [32]/2015/China/95	R, CT	25.8 ± 6.5/2	56/44	Adapalene 0.1% gel and ketoconazole 2% cream once daily	--	14	Total improvement rate (92% significantly improved/72% improved)	ND
		28.5 ± 7.3		Ketoconazole 2% cream twice daily				
Khattab FM [33]/2021/Egypt/26 unresponsive	R, CT	29 ± 903	14/10	Excimer laser (308 nm three times weekly)	*Malassezia furfur* (61), *M. globose* (19), *M. sympodialis (16), M. restricta (4)*	56	Total improvement rate (91.6)	Follow-up for ten months: 8.3% of recurrence rate
				Topical placebo				
Nashwa RK [34]/2020/ Egypt/120	CT	Range 12-40	52/68	Weekly tea tree oil-saturated human amniotic membrane	--	56	Clinically healed *** (78.3/55)	No relapse three months post healing
				Tioconazole 1% cream daily				
Sepaskhah M [35]/2016/Iran/50	DB, R	30± 8.9	--	Tacrolimus 0.03% ointment twice daily	--	21	Complete global cure (14 [56]/ 14 [56]); Partial cure (3 [12]/ 1 [4]); Failure (8 [32]/ 10 [40]), respectively.	ND
		30±9.6		Clotrimazole 1% cream twice daily				
Alberdi E [36]/2020/Spain/4	CR	43.2 ± 10.7	0/4	Photodynamic therapy with methylene blue	--	28	Complete clinical and mycological cures were observed in all patients.	Relapse was not seen in the 6month follow-up

(Contd...)

Table 1: *(Continued)*

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
Lone AH [37]/2012/India/40	SB, R	30.2	34/6	Polyherbal formulation topically twice daily	--	30	Effective treatment: 19 (95)/18(90); mycological cure: 20 (100)/20(100); Not cured: 1(5)/2(10), respectively	After the completion of treatment (30 days), all became negative for KOH examination on the 30th-day assessment
		31.3		Sodium thiosulphate lotion (20%) locally twice a day				
Jowkar F [38]/2010/Iran/64	DB, CT	21 (13–28)	31/33	3% sodium nitrite (nitric oxide-liberating) cream with 3% salicylic acid, twice daily 3% salicylic acid cream (placebo)	--	10	Cured: 87.5% and 43.8% *** Uncured: 12.5% and 56.2%	ND

*Disseminated pityriasis versicolor with more than four relapsing episodes in twelve months.
**DB: double-blind; SB: single-blind; O: open; R: randomized; CT: clinical trial; CR: case report.
***Statistically significant: $p < .05$.
ND: Not determined.

pityriasis alba, hypochromic mycosis fungoides, and postinflammatory hypopigmentation should be considered in the differential diagnosis [20] (Fig. 3).

TREATMENT

We detected several systematic reviews focused on the different topical and systemic treatment options in the management of PV (Table 1). The four most important reviews in the search parameters focus on the efficacy of topical ketoconazole, and in cases that require systemic management, the best options are itraconazole and fluconazole [21-24]. The lesions may be recurrent or recalcitrant to antifungal treatments [21,25]. Recurrent cases include extensive or disseminated cases with atypical variants related to infectious agents such as *M. japonica* and elevated IgE levels [7,26].

Pityriasis versicolor may persist chronically if left untreated. Numerous topical and oral antifungal treatments effectively alleviate clinical symptoms and lead to mycological cure. First-line treatment includes topical antifungal therapy [27]. Topical azole antifungals are effective for PV, and no significant difference in the efficacy of different azoles is observed. Ketoconazole shampoo, selenium sulfide, or zinc pyrithione are recommended in hairy areas; due to the difficulty of applying the antifungal cream, these are applied to the skin in a shower and washed off after 3 to 4 minutes for 2–3 weeks [28]. Terbinafine 1% cream and ketoconazole 2% cream are adequate, similar to new antifungals such as topical fluconazole. The usual treatment time is 2 to 3 weeks [29].

Based on evidence, treatment once or twice daily for fourteen days with topical ketoconazole cream or foam and once-weekly ketoconazole shampoo may be effective for PV with long-term efficacy. Similarly, terbinafine 1% cream should be applied twice daily for seven days [21]. Keratolytic soaps, such as sulfur-salicylic acid soaps, demonstrated a 62% cure rate and had the best results with extended duration of application, yet when compared to 1% clotrimazole, the latter had better results [30].

Shi et al. [31] compared ketoconazole 1% cream as monotherapy with ketoconazole cream combined with adapalene 1% gel. Adapalene is a naphthoic acid derivative indicated for treating acne vulgaris, because it binds to retinoic acid receptors (RAR) located mainly in the skin and epidermis (RARb and RARg, respectively), inhibiting cell differentiation. This study defined the

total improvement rate as negative direct microscopy and a clinical improvement of 50% four weeks after treatment. The combined treatment significantly improved (92% vs. 72%, respectively; $p = 0.0009$). In a study by Bakr et al. [32], the response to treatment was significantly different when the combined treatment of ketoconazole 2% cream and adapalene 0.1% gel was administered as compared to the treatments as monotherapy at seven weeks (93.3/70/83.3, respectively).

Regardless of the medication administered, the normalization of pigmentation may take several months after the completion of treatment [1,2].

RECURRENT PV

Although the infection does not represent a significant health risk to the affected individual, the psychological and social implications may be profound. The disease becomes chronic without treatment. A relapsing disease tends to recur in around 60% of the cases within a year after treatment. Spontaneous remissions are rare [3].

It is also described as recurrent, recalcitrant, or relapsing PV. The disease evolves in outbreaks, with the improvement and aggravation of the symptoms, leading to relapse. Due to several predisposing factors, relapse is a significant problem. PV may recur after incomplete antifungal treatments [2,3]. Faergemann reported a relapse rate of 60% after one year and 80% after two years of treatment [33]. Relapse probably occurs due to the presence of yeasts in the sebaceous follicles and several predisposing factors that allow the multiplication and filamentation (hyphae formation) of yeasts. During the twenty-month follow-up, relapse was observed in periods of excessive sweating caused by physical exercise or after spending time at the beach, pool, and farm. The patients also associated relapses with higher temperatures (summer) or the application of oily products to the body (moisturizers, sunscreens). The patients with PV with one to four relapsing episodes in twelve months were classified as having relapsing PV [3].

Drug resistance is another increasing problem affecting all antifungal agents [34]. Azole resistance may be primary (intrinsic) or secondary (acquired). The former is found naturally without prior (known) antifungal exposure. The latter results from a previously susceptible strain exposed to antifungals or other selective pressure and may result from altered gene expression, point mutations, or allelic variations. Both may be attributed to an increase in 1) the prophylactic use of azole drugs, 2) prolonged treatment regimens, 3) agricultural use of azole fungicides, or 4) the broad-spectrum, long-term, and low-dose use of azoles in consumer care. As an example, azole resistance has been extensively studied for *Aspergillus fumigatus*. It develops either during treatment at the hospital or following intensive agricultural practice [35]. The environmental route of resistance development has been reported since 2007 [35]. *Malassezia* azole resistance is associated mainly with mutations in the ERG11 gene, identified from clinical isolates [36].

TREATMENT OF RECURRENT PV

In recurrent, disseminated, or recalcitrant cases with topical therapy or patients who experience multiple relapses, oral itraconazole 100 mg daily for fourteen days may be a practical option [37]. Oral fluconazole is also effective and safe [38,39]. The cure rate ranged from 78% to 98% when fluconazole was started once weekly for two weeks [38]. A randomized controlled trial on adults demonstrated that a single high-dose (400 mg) fluconazole treatment may be more effective than itraconazole (65% vs. 20%, respectively); the relapse rate was 35% in the fluconazole group and 60% in the itraconazole group at the end of eight-weeks follow-up [39].

Other treatment options, including adapalene gel with ketoconazole cream [31,32], increase the success rate of topical ketoconazole cream from 72% to 92% [31].

Ali Balevi et al [40] showed that narrow-band UV-B is an effective and safe alternative for managing extensive and recurrent PV. It is suggested for PV cases, unresponsive to conventional treatments or not suitable for systemic antifungal treatments.

Other reported options include topical tacrolimus 0.03%, showing similar clinical and mycological cure rates to clotrimazole 1% cream in cases of PV [41]. Bartell et al. [42] reported the case of a fourteen-year-old male with recurrent PV, who was treated with isotretinoin for acne vulgaris and had complete remission of the mycosis. This favorable response was probably due to the excessive sebum production in the pathogenesis of PV, allowing for novel therapies.

A prophylactic regimen may delay or avoid PV recurrence. Prophylactic regimens using ketoconazole include 200 mg given on three consecutive days every month or a single dose of 400 mg taken once a month; itraconazole is also a reliable option for prophylaxis [43].

CONCLUSION

The prevention of the recurrence of infections is essential, including superficial infections such as PV. There are currently numerous topical and oral antifungal treatments that effectively reduce the recurrence, leading to clinical and mycological cure. Topical therapy is the first line of treatment for PV in uncomplicated cases of PV. When topical treatment is not feasible or practical, itraconazole and fluconazole are viable options, with pramiconazole as a potential new therapy. In addition to antifungal therapies, non-antifungal treatments have shown efficacy in cases of recurrent PV and could be employed as maintenance or preventive therapy.

The advantages of topical treatment include fast acting, well toleration, smaller risk of severe adverse effects, and limited drug interactions. This is especially evident with the use of ketoconazole. Multiple applications of topical medications may increase adverse events and limit patient compliance, especially in cases of PV in which large body areas are affected. In these cases, oral antifungal may be preferable for many patients, and short courses of oral treatments are the most reliable option. Relapse is common, and thus prophylactic treatment may be necessary to relieve symptoms, especially in recurrent PV.

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Our Dermatology Online

Clinical Image

Koplik's spots

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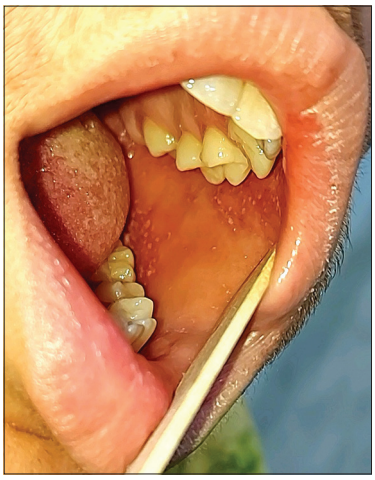

Figure 1: Koplik's spots of the oral cavity

Koplik's spots are pathognomonic features of measles in its prodromal phase. They are named after American pediatrician Dr. Henry Koplik, who first described them in 1896. They appear 2–3 days before the onset of a measles rash as small, bluish-white, slightly elevated papules on erythematous bases on the buccal mucosa, usually opposite the first and second lower molar teeth. Because of their characteristic appearance, they are described as "grains of salt on a reddish background." They may spread to involve other parts of the buccal cavity, pharynx, and soft palate. Occasionally, they occur on the conjunctiva and the vaginal and gastrointestinal mucosae. The white color of the spots may result from the destruction of cells of the glandular epithelium. They persist for 12 hours to 4 days and fade on the rash appearance. When the skin rash appears and progresses, the spots lose their characteristic appearance, and after several days, the mucosa returns to its normal appearance [1,2].

A fifteen-year-old child presented with high fever, tiredness, conjunctival congestion, and upper respiratory tract symptoms persisting for the past two days. On examination of the mouth, there were multiple, white spots on erythematous bases facing the upper and lower molar teeth (Fig. 1). The patient was diagnosed with a case of measles and admitted to the hospital for further investigations and 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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Research Letter

Epidemiological and clinical profile of vascular malformations: Experience of the Dermatology Department of CHU Hassan II in Fes, Morocco

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Sir,

In contrast to vascular tumors, particularly infantile hemangiomas, few publications have addressed the epidemiology of vascular malformations.

The diagnosis and management of these cutaneous vascular anomalies require a well-equipped technical platform and a wide variety of treatments. The objective of this study was to describe the epidemiological and therapeutic profiles of cutaneous vascular malformations seen in our training.

This was a cross-sectional study of patients who consulted for a cutaneous vascular malformation at University Hospital Hassan 2 in Fez, Morocco, over a period of five years (2016–2021).

A total of 134 patients, adults and children, were included in the study. The age of the patients ranged from 1 month to 58 years, with an average of 16.95 years. The adult population constituted 38.5% of the sample, and the sex ratio (M/F) was 0.48 with a clear female predominance (67.16%). 125 patients were from the Fes region (Fes, Meknes, Taza, Taounate) and nine from the oriental region (Nador, El Hoceima, Oujda, Figuigue, Errachidia). 50.7% of the patients had a low socioeconomic level, and 49.3% had a medium level. The symptomatology began at birth in 92.5% of the patients, with a maximum age of onset of twenty years. Seventy-six percent of the malformations were in the head and neck, and 24% in the limbs and trunk. Radiological explorations (echo Doppler, scanner, MRI) performed in all patients allowed the confirmation of doubtful cases. The most common vascular anomalies were plan angiomas in 55.9% (75 cases), venous malformations in 23.13% (31 cases), lymphatic malformations in 5.2% (7 cases), and arteriovenous malformations in 1.4% (2 cases). The four cases of complex vascular anomalies were Klippel–Trénaunay syndrome (3 cases) and one case of Proteus syndrome. We opted for sclerotherapy in fifteen patients with venous malformations, laser in 77 with planar angiomas, and surgery in two superficial venous malformations. A combination of sclerotherapy and rapamycin was employed for lymphatic malformations.

Venous malformations are more frequent than arteriovenous malformations [1,2].

Female involvement was predominant in our series, which could be explained by a greater therapeutic demand because of the aesthetic damage.

It is necessary to differentiate plane angiomas with nodules on the surface from tuberous hemangiomas with a nipple aspect. Plane angiomas, unlike hemangiomas, are present at birth and worsen with age.

Note that two venous malformations in our series were wrongly diagnosed and treated as subcutaneous hemangiomas. Venous malformations, unlike subcutaneous hemangiomas, are characterized by an increase in size during the Valsalva maneuver. They are present at birth and the evolution is toward aggravation with age and does not improve under propranolol.

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The diagnosis of lymphatic malformations is easy when they are associated with superficial lesions, although the main differential diagnosis in hyperkeratotic papular forms is condyloma acuminata. Dermoscopy is an essential tool for diagnosis. Lymphatic malformations are composed of vesicles with translucent, hemorrhagic, or yellowish content separated by whitish septa. Note that, if lymphangioma is completely hemorrhagic, the dermoscopic appearance becomes indistinguishable from that of tuberous hemangioma, which is why it is important to search for a specific sign of lymphangioma, which is the Hypopyon-like appearance that corresponds to the precipitation of red blood cells at the bottom of vesicles.

The criteria for selecting a Klippel–Trénaunay syndrome are extensive cutaneous vascular malformation of a limb, congenital or acquired varicosities of the same limb, and tissue or bone hypertrophy of the same limb [3].

A Tunisian series on ninety-nine patients with venous malformation revealed the predominance of this type of malformation in females [4]. Cephalic localization was predominant in the Tunisian series and all patients benefited from ethibloc or alcohol sclerotherapy, while the patients in our series benefited from aetoxisclerol sclerotherapy due to its safety compared to alcohol. Skin necrosis occurred in nine Tunisian patients and one patient in our series.

To conclude, capillary malformations followed by venous malformations were the most frequent vascular malformations in our series. Capillary malformations are present from birth, unlike infantile hemangiomas, which are characterized by a free interval, and venous malformations appear during early childhood or adolescence and have a differential diagnosis with deep microcystic and macrocystic lymphatic malformations.

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

Peculiar cutaneous manifestation in a Japanese patient with COVID-19 infection

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Sir,

Patients with coronavirus disease 2019 (COVID-19) are reported to present with various cutaneous manifestations, with frequencies up to over 20% [1]. Skin symptoms associated with COVID-19 are classified into maculopapular lesions, vesicular lesions, urticarial lesions, and livedoid/necrotic lesions [2,3]. We, herein, report the case of a patient presenting with an uncommon rash associated with COVID-19 infection.

A 66-year-old Japanese male with a history of diabetes mellitus, who was diagnosed with moderate COVID-19 pneumonia two months previously, was referred to our department complaining of cutaneous manifestations on both lower limbs that had appeared one month earlier. A physical examination showed brownish livedo reticularis on both lower limbs (Fig. 1). He had been taking ursodeoxycholic acid for nine days prior to the appearance of the cutaneous manifestations; thus drug eruption was suspected. A biopsy was taken to exclude drug eruption. Histological features revealed lymphocytic and histiocytic infiltration of the perivascular area within the dermis (Fig. 2). We did not observe any liquefaction degeneration. Also, vascular involvement was not observed in the dermis. A drug-induced lymphocyte transformation test for ursodeoxycholic acid was negative. We diagnosed the patient as having livedo reticularis related to COVID-19. A patch test was not performed due to a lack of consent.

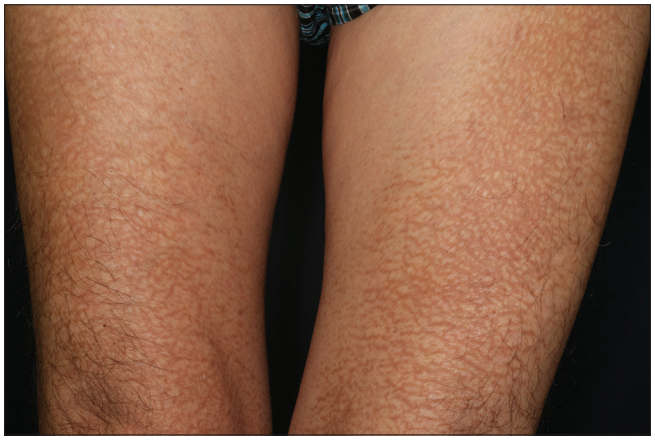

Figure 1: Brownish livedo reticularis on both lower limbs.

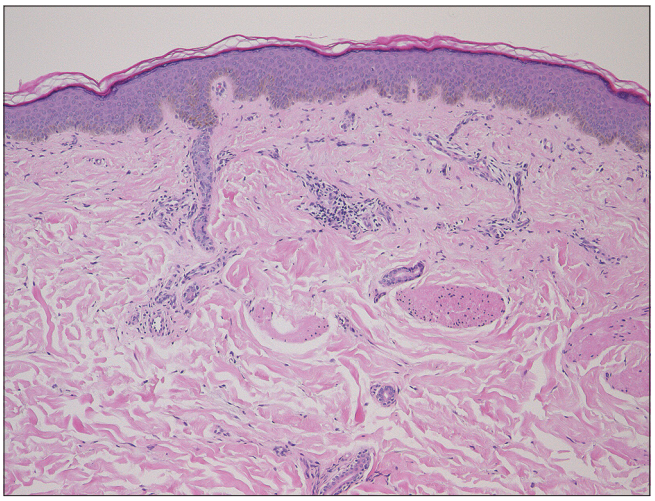

Figure 2: Lymphocytic and histiocytic infiltration of the perivascular area in the dermis (H&E, 100×).

According to the analysis of COVID-19 cases with cutaneous manifestations in nine countries ($n = 998$), skin lesions were classified into five major groups. The most commonly reported skin finding was chilblain-like lesions (40.1%), followed by maculopapular lesions (23.1%), vesicular lesions (10.1%), urticarial lesions (8.7%), livedoid/necrotic lesions (2.3%), and other/

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non-descript rashes/skin lesions (19.8%) [4]. Galvan et al. reported that livedoid or necrotic lesions were more frequently seen in elderly or patients with severe disease, and their mortality rate was as high as 10% [5]. Livedo reticularis is an uncommon cutaneous feature associated with COVID-19 [3], and there is a small number of cases that present with livedo reticularis [6]. In a report on 738 Japanese patients with COVID-19 by Tamai et al. [7], 21 patients (2.8%) presented with COVID-19-related rash, 19 had erythematous papular lesions, and two had an urticarial rash. No patient presented with reticular eruption. There are racial differences in the frequency and type of skin symptoms in COVID-19 patients, and the frequency of occurrence and the proportion of each type of skin symptom may vary depending on race and country. However, reticular eruption is a rare type of skin symptom, and the number of global cases is small, thus further accumulation of cases is desired in the future.

Consent

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

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Our Dermatology Online

Case Letter

Cutaneous localization of Waldenström's macroglobulinemia

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Sir,

Waldenström's macroglobulinemia (WM) is a rare B-type lymphoproliferative disease of unknown etiology characterized by lymphoplasmacytic proliferation in the bone marrow and a peak of monoclonal IgM in peripheral blood [1]. Cutaneous manifestations remain rare, being manifested in only 5% of the patients. It is divided into two subtypes: neoplastic and non-neoplastic. Non-neoplastic lesions or secondary to paraproteinemia are more frequently non-specific, such as purpura, ulcers, and urticarial lesions. These lesions are caused by hyperviscosity of the blood, immune complex-mediated vascular damage, paraprotein deposition, and amyloid deposition. A cutaneous neoplastic attack or a result of direct cutaneous infiltration of lymphoplasmacytic cells are rarer [2]. Clinically, the cutaneous localization of WM of the neoplastic type presents as firm, erythematopurple papulo-nodules embedded in the dermis and hypodermis, rarely ulcerated, or as a cutaneous infiltration in reddish-brown plaques. More rarely, they are non-infiltrated lesions, such as brownish macules, rounded or oval, and of variable size [2]. Its lesions are located more frequently on the face and ears in a symmetrical manner. Localizations at the level of the thorax, the flanks, and the back are also described [3]. Skin biopsies show a normal epidermis, a dermal infiltrate composed of small lymphocytes and plasma cells or lymphoplasmocytoid cells with a nodular, diffuse, or interstitial pattern, sometimes perivascular or periadnexal; the cutaneous lymphoplasmacytic infiltrate is positive for CD19, CD20, and CD22 and negative for CD38 and CD138 (plasma cell markers)s [2]. The treatment of cutaneous localizations of WM is, therefore, justified in the absence of a general indication only in the cases of aesthetic or functional damage, especially since these cutaneous localizations have no prognostic value and do not change the course of the disease [1]. Herein, we report the case of a patient followed for WM with a cutaneous localization presented afterward.

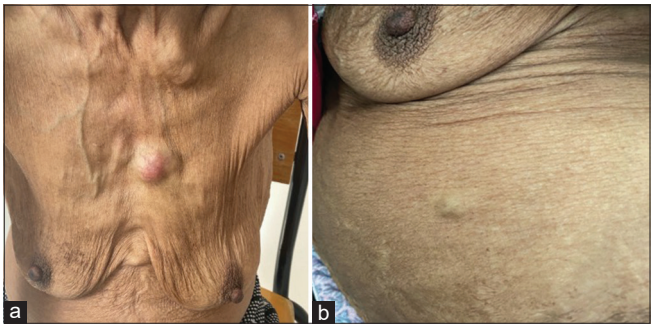

Figure 1: (a) An erythematous plate in regards to the sternum. (b) Cutaneous and subcutaneous nodules at the level of the trunk.

A 75-year-old patient without a pathological history followed for WM for three years consulted for asymptomatic, cutaneous nodules, which appeared two months earlier. On examination, we found cutaneous and subcutaneous nodules at the level of the trunk with an erythematous plate in regards to the sternum (Figs. 1a and 1b). In this context, we suggested a cutaneous localization of WM, cutaneous metastases of solid tumors, and amyloidosis. A skin biopsy was performed revealing a dermal and hypodermic infiltrate consisting of plasma cells and lymphocytes. Immunohistochemistry revealed CD20

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to be intensely positive, in favor of a subcutaneous localization of lymphocytic lymphoma. We did not indicate a specific treatment for the cutaneous 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 Letter

Syringocystadenoma papilliferum associated with apocrine gland hyperplasia arising from nevus sebaceous

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Sir,

A 22-year-old male with essential endocranial hypertension and hyperaldosteronism consulted for a lesion on the scalp that appeared four years prior to consultation. The patient reported a hairless, yellowish plaque present since childhood at the place of the actual lesion. A clinical examination revealed a soft, erythematous mass, 4 x 4 cm in size, with hyperkeratotic, exophytic horns (Fig. 1). From the medical history, suspicion of a tumor that developed from nevus sebaceous was raised. The patient was referred to the Plastic Surgery Department where the lesion was excised. A histological examination confirmed the clinical suspicion of nevus sebaceous (Fig. 2a). In addition, under areas of epidermal papillomatosis, cystic invaginations were found extending down the dermis. In the lower portion of the cystic invaginations, numerous papillary projections extended into the lumina of the invaginations. The inner row of the papillary projections consisted of columnar cells, while the outer row consisted of small cuboidal cells. This was compatible with the diagnosis of syringocystadenoma papilliferum (Fig. 2b). Another interesting histological finding was apocrine gland hyperplasia (Fig. 2c). Syringocystadenoma papilliferum, likewise apocrine gland hyperplasia, stains positive for cytokeratin CK7, an immunomarker for epithelial cells (Fig. 2d). Nevus sebaceous of Jadassohn manifests in childhood as a hairless, yellowish plaque usually solitary, yet its linear variety may

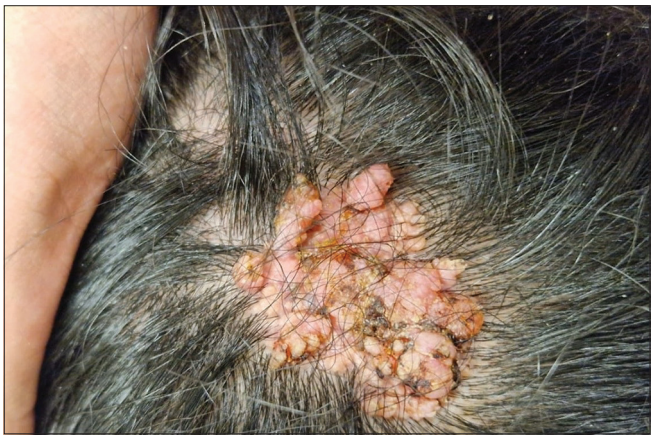

Figure 1: Lesion on the scalp.

be a component of Schimmelpenning–Feuerstein–Mims syndrome associated with multisystemic complications. Histologically, no or little hair is associated with sebaceous glands that mature with age. Nevus sebaceous is derived from primary epithelial germ cells, which under the influence of external factors, leading to the mutation of different genes (HRAS, KRAS, etc.), may give rise to a variety of neoplasms, both benign and malignant [1]. Syringocystadenoma papilliferum, sebaceoma, trichoblastoma, and trichilemmoma may develop from nevus sebaceous [2]. Basal cell carcinomas, squamous cell carcinomas, and microcystic adnexal carcinomas have also been reported. Rarely, multiple tumors may develop from a single lesion [3]. Ectopic apocrine glands, which are abundant at the breasts, anogenital area, and axilla, may be found in nevus

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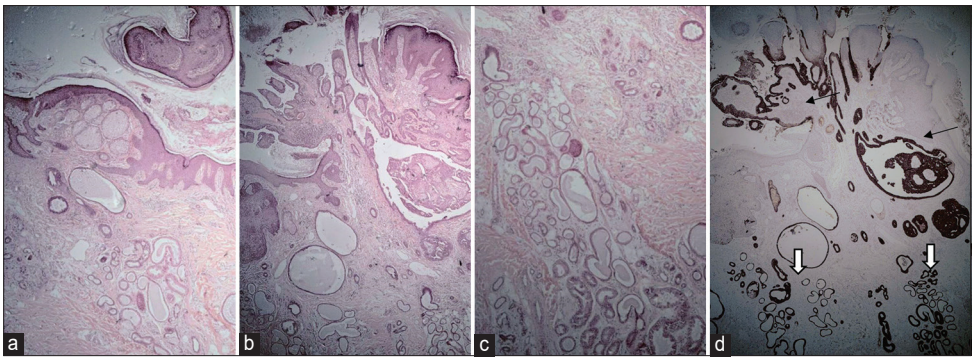

Figure 2: (a) Nevus sebaceous.(b) Syringocystadenoma papilliferum. (c) Apocrine glands hyperplasia. (d) CK7 staining of both syringocystadenoma papilliferum and apocrine gland hyperplasia.

sebaceous, yet the presence of apocrine gland hyperplasia has been considered as a precursor of cancer by some authors [4]. This case is being reported because it is the first case associating syringocystadenoma papilliferum with apocrine gland hyperplasia originating in nevus sebaceous.

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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Conflict of Interest: The authors have no conflict of interest to declare.

Our Dermatology Online

Case Letter

Nifuroxazide and erythema pigmentosa: A side effect to be aware of

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Sir,

Erythema pigmentosa fixata (EPF) is a delayed-type toxidermia. It manifests itself within forty-eight hours after the reintroduction of a drug by the appearance of a recurrent rash, leaving a residual hyperpigmentation [1]. Herein, we report the first case of erythema pigmentosa fixed to nifuroxazide.

A 48-year-old male, a chronic smoker, with a history of type 1 diabetes under insulin, having four limbs amputated five years previously for ischemia of the limbs secondary to Shepherd's disease, suffering from a functional colopathy, for which the patient often received symptomatic treatments, including nifuroxazide. A drug investigation revealed the ingestion of nifuroxazide for a digestive episode, after which the patient presented a rash composed of pruritic, erythematous macules of the trunk and limbs with a 48-hour delay, evolving into post-inflammatory hyperpigmentation (Figs. 1 and 2). A biopsy showed an interface dermatitis consisting of a predominantly lymphocytic infiltrate. A pharmaco-vigilance report accused nifuroxazide. All data allowed us to conclude the diagnosis of erythema pigmentosa fixata. The patient presented no recurrences after the eviction of the molecule.

Nifuroxazide is widely prescribed for its analgesic and anti-bacterial properties in various digestive diseases, including functional colopathy. Nifuroxazide, identified as a STAT3 inhibitor, has also proven to be effective in the treatment of certain tumor pathologies, due to its anti-tumor properties and ability to induce apoptosis [2]. Numerous adverse effects have been reported with nifuroxazide, particularly in the skin: urticaria, allergic reactions, angioedema, and anaphylactic shock.

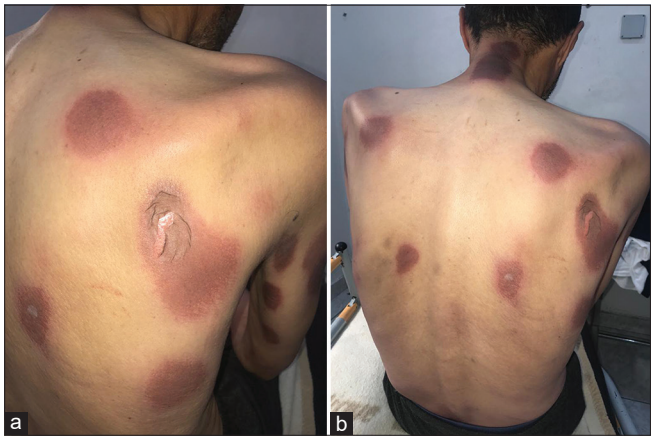

Figure 1: (a) Rounded, erythemato-cellular plaques on the back and neck. (b) Rounded, erythemato-cellular plaques on the back and neck.

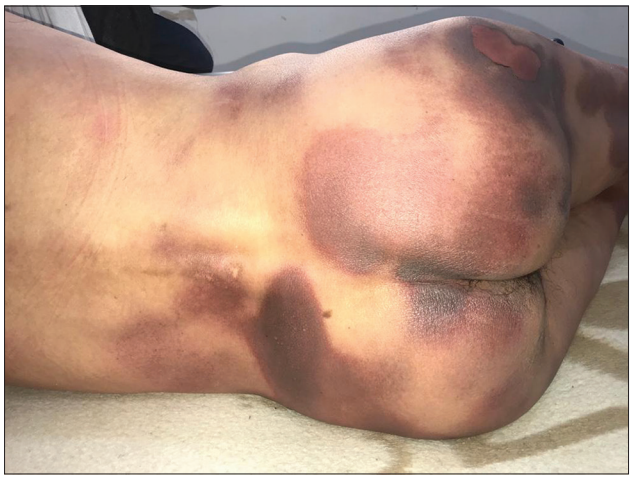

Figure 2: Rounded, erythemato-cellular plaques on the buttocks and lower back.

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EPF is most often benign. More rarely, it may be bullous and extend to the oral and genital mucosas. A pharmacovigilance investigation is necessary to establish the causal link between the EPF and the responsible drug. The diagnosis of EPF is clinical, characterized by the reappearance of lesions on the same site of the initial outbreak after the reintroduction of the offending drug [3].

The discontinuation of the offending drug must be formally and permanently indicated [3].

Usually, the drugs most frequently responsible for EPF are sulfonamides, non-steroidal anti-inflammatory drugs, and tetracyclines, although this frequency may vary depending on consumption habits and the emergence of new drugs [4].

It is recommended to perform patch tests on the site previously affected by EPF, and this seems to be more appropriate when several molecules are attributable [4].

Indeed, our observation is the first case of EPF induced by nifuroxazide reported 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

Case Letter

Atypical distribution of lichen planus pigmentosus: Pigmentation of the nose and ears

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Sir,

Lichen planus pigmentosus (LPP) is considered a rare variant of lichen planus (LP). It typically presents with a symmetrical distribution of dark brown to grayish-blue macules and blotches, which eventually enlarge and coalesce. Usually localized on the face, it has a predilection for the temporal areas, whereas on the neck, it affects all sides [1]. There are some reported cases of a linear pattern, a zosteriform pattern over the trunk, the involvement of non-sun exposed areas, such as the thighs, and a band-like distribution of LPP on the abdomen [2]. Dermoscopy in LPP demonstrates pigmented globules, whose color ranges from dark brown to bluish-gray, arranged in diffuse, dotted, annular, hem-like, arcuate, speckled, and perifollicular patterns. Wickham striae and vascular features are absent, unlike in classical lichen planus [3,4]. Histopathology reveals a vacuolar interface dermatitis with band-like lichenoid or perivascular lymphocytic infiltrates in the papillary dermis, as well as superficial pigmentary incontinence and melanophages [3,5]. The differential diagnoses are melasma, ashy dermatoses, often present on the trunk and limbs, ochronosis, and post-inflammatory hyperpigmentation. The treatment of LPP has had limited success and there is no clear consensus. Topical treatment includes corticosteroids, tacrolimus, hydroquinone, and retinoids. One of the most commonly employed topical treatments is tacrolimus. Refractory forms may be treated with systemic corticosteroids with gradual tapering, as well as dapsone or isotretinoin [5]. Herein, we report a case of an atypical clinical distribution of LPP with a typical dermoscopic pattern.

A 71-year-old male patient visited our department for a hyperpigmentation of the nose and the auricles of the ears evolving for a month. He had no history of medication or the application of hydroquinone or other topical ointments. A clinical examination revealed well-limited hyperpigmented macules with irregular borders located on the tip of the nose and the auricle of both ears (Figs. 1a and 1b). This atypical clinical distribution of lesions along cartilaginous zones was initially suggestive of alkaptonuria. The diagnosis was less likely, given the absence of black discoloration of the urines and the absence of pigmentation of the sclera. Dermoscopy revealed brown and gray globules arranged in a granular,

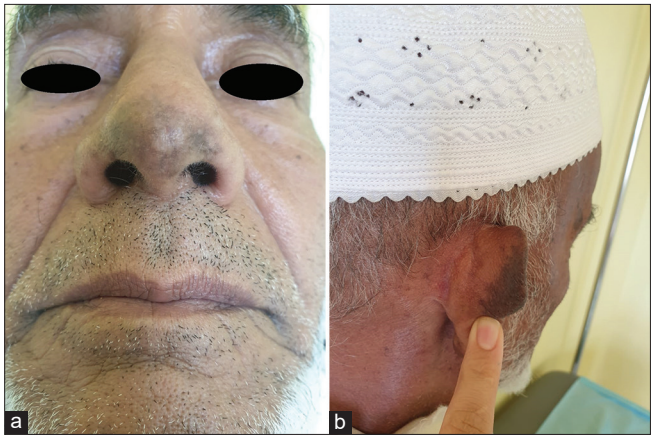

Figure 1: (a) Clinical presentation: well-limited, hyperpigmented macules with irregular borders located on the tip of the nose. (b) Clinical presentation: well-limited, hyperpigmented macules with irregular borders located on the tip of the auricle of the ear.

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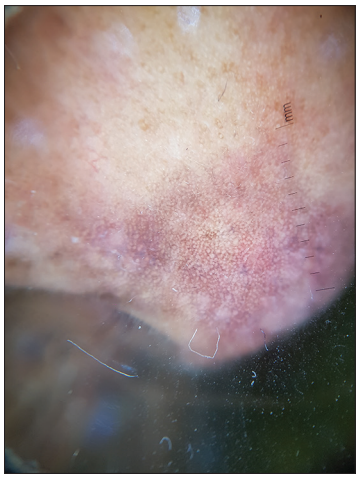

Figure 2: Dermoscopy of the nose: brown and gray globules arranged in a granular, annular, perifollicular pattern.

annular, perifollicular pattern, which was more suggestive of LPP despite the atypical topography (Fig. 2). The diagnosis of LPP was confirmed by histopathology, which showed an interface dermatitis with a lichenoid infiltrate of the dermis consisting of lymphocytes and plasma cells with numerous melanophages. The atypical distribution on the ears might have be related to the Koebner's phenomenon as the patient tended to wear glasses. Yet, this does not explain the location on the tip of the nose. The patient was treated with topical steroids with good evolution.

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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Obituary

Prof. Ramiro Jordán Rodriguez (1950-2022)

Piotr Brzeziński

Department of Physiotherapy and Medical Emergency, Faculty of Health Sciences, Pomeranian University, Slupsk, Poland

Corresponding author: Piotr Brzeziński, MD, PhD, E-mail: brzezoo77@yahoo.com

Figure 1: Prof. Ramiro Jordán Rodriguez (1950-2022).

Prof. Dr. Ramiro Jordán Rodriguez was a member of the scientific board of the journal Our Dermatology Online (Fig. 1).

Had taken the undergraduated medical Course a thet Federal Fluminense Faculty of medicine Rio Brasil. After, Post Graduate Course in Infectious diseases and tropical Medicine in the same University Rio Brasil. Former post graduate student of the Dermatology Diploma Course From de University of London at the St Johns Hospital for diseases of the Skin and the Diploma of Venereal Diseases from the Society of Aphotecaries London, Former Lecturer in Dermatology in the Faculty of Medicine, University of San Simon Cochabamba Bolivia. Member of CILAD- Society Iberolatinoamerican of Dermatology. At present doing private practice in Dermatology in Cochabamba Bolivia.

Activities and societies:

Socio de la Sociedad Boliviana de Dermatologi Past Presidente de la Sociedad Boloviana de Dermatologia Coichabamba, Socio de la Sociedad Iberolatinoamericana de Dermatología CILAD)

Postgrado en Dermatologia, St. Johns Hospita for Diseases of the Skin and University of London, Venereology Society of Aphotecaries University of London,

Former Lecturer of Deñatology Facultad de Medicina UMSS Cochabamba,

Private Consultant in Dermatology and Cosmetology Center Torres Sofer of. 402 Cochabamba

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

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