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Ultrasonographic evaluation of subclinical atherosclerosis in the femoral and carotid arteries of patients with psoriasis

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Background: Psoriasis is a prevailing continual inflammatory affliction, carrying a considerable risk of cardiac diseases, sometimes even not traceable by conventional predisposing factors. Detection of subclinical atherosclerosis in psoriasis by ultrasonography is beneficial, and it has been solitarily explored in carotid arteries. It was found to have a weak predictive value, and so the femoral arteries have now been contemplated. This study aims to determine subclinical atherosclerosis occurrence by evaluating the femoral and carotid arteries' intima-media thickness (IMT) by ultrasonography in patients with psoriasis.

Methods: The study was carried out in the departments of dermatology and radiology at Dr. Pinnamaneni Siddhartha Institute of Medical Sciences & Research Foundation for eight months. The sample size consisted of 30 chronic plaque psoriasis cases and 30 controls, matched for age and sex. Patients with comorbidities were excluded. Femoral & carotid arteries were assessed for IMT by ultrasonography.

Results: In our study, the age range was 30–80 years, and a male (56.7%) preponderance was observed in cases and controls. The mean femoral artery and carotid artery IMTs were remarkably greater in cases than in controls, with *P*-values < 0.001 and 0.04, respectively. The mean femoral artery IMT was significantly more elevated (1.4 ± 0.63 mm) than the carotid artery IMT (1.0 ± 0.62 mm) in cases (*P* = 0.01).

Conclusion: Ultrasonographic screening of femoral artery IMT enhances the early discernment of subclinical atherosclerosis when compared with carotid artery IMT. Thereby, it helps in the early identification of cardiovascular disease in patients with psoriasis.

Keywords: femoral artery, carotid artery, intima-media thickness, psoriasis, atherosclerosis

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INTRODUCTION

Psoriasis is a continual inflammatory, immune-mediated, recurrent affliction affecting the skin and joints of individuals predisposed genetically ¹. This disorder is linked with a considerable risk of cardiovascular disease (CVD), which is sometimes

not traceable by conventional predisposing factors.

Augmented intima-media thickness (IMT) is an early anatomical change in atherosclerosis; the IMT of the large peripheral arteries correlates with the existence and development of atherosclerosis in minor arteries like the coronary arteries ². Early discernment of subclinical atherosclerosis

and addressing this condition in patients with psoriasis will reduce the probability of coronary artery disease. Henceforth, meticulous screening of patients for subclinical atherosclerosis is necessary, making it essential to have an easy but accurate, quantifiable measure of subclinical atherosclerosis. Among various diagnostic techniques, the B-ultrasonographic mode quantification of IMT has evolved as one of the finest practices for assessing subclinical atherosclerosis.

In various studies, subclinical atherosclerosis screening in psoriasis has solitarily been explored in carotid arteries. It was found to have a weak predictive value, so the femoral artery has now been contemplated for this purpose. Compared to carotid plaques, femoral plaques have been cited as a remarkable indicator of coronary atherosclerosis and coronary fatality in autopsy studies ^{3,4}. Research among normal adults has shown that femoral plaques are more common than carotid plaques and are more firmly correlated with conventional CVD predisposing factors and coronary calcium ⁵⁻⁷.

The present study aims to evaluate the IMT of the femoral and carotid arteries by ultrasonography in cases of psoriasis, thereby examining the existence of subclinical atherosclerosis.

MATERIAL AND METHODS

The study was conducted at the dermatology and radiology departments of Dr. Pinnamaneni Siddhartha Institute of Medical Sciences & Research Foundation after acquiring assent from the Institutional Ethics Committee. It was done for eight months, from July 2019 to February 2020. The sample consisted of 30 chronic plaque psoriasis cases and 30 controls, matched for age and sex. Patients with earlier diagnosis of or treatment for peripheral or coronary artery disease, acute coronary syndrome, transient ischemic attack or stroke, heart failure, and remarkable kidney or liver dysfunction were eliminated from the study.

After obtaining consent from cases and controls, the medical history and Psoriasis Area and Severity Index (PASI) were evaluated among cases, and ultrasonography (Philips model Affinity 50G, USA) of the common carotid arteries was done. After freezing the image, the IMT of the distal portion ⁸ of both arteries was measured. IMT measurement was taken from the lumen's leading-edge-intima

juncture to the contrary media-adventitia juncture at 2 cm beneath the bisection of the arteries on either side ^{9,10}, and the mean IMT of three readings was recorded. Similarly, both common femoral arteries were imaged sequentially, from just above the inguinal ligament to its bisection into the superficial femoral branches and profunda femoris. The IMT at the leading edges of the lumen-intima juncture and the media-adventitia juncture was measured twice ^{9,11,12} at a point 1–2 cm above the bisection of the common femoral arteries, and the mean was noted ^{9,12}. A detailed sonographic assessment of IMT was performed by an expert radiologist deprived of all clinical details. The radiologist was unaware whether the person being examined was a psoriasis patient or a healthy control, exempting when cutaneous lesions were apparent to the eye.

Statistical Analysis

The data obtained were tabulated and assessed using Statistical Package for the Social Sciences software version 21 (SPSS Inc). Frequency tables, means $\pm$ standard deviation, and percentages were used to summarize the age and sex distribution, mean duration, PASI score, and femoral and carotid arteries IMT among cases and controls after normality testing. A chi-squared test was used to test age and sex variables with respect to cases and controls. Independent t-tests and ANOVA tests were used to measure femoral artery intima-media thickness (FIMT) and carotid artery intima-media thickness (CINT) in cases and controls with respect to age and sex. An independent t-test at a 95% level of significance was used to compare FIMT and CINT between cases and controls. A Pearson correlation coefficient was used to assess the correlation of FIMT and CINT in cases with the PASI. Two-tailed *P*-values < 0.05 were contemplated as statistically significant.

RESULTS

Out of 60 study participants, 30 were cases (17 males and 13 females), and 30 were healthy controls (17 males & 13 females), aged from 30 to 80 years. The mean age was 51.23 ± 14.14 and 50.73 ± 13.67 years in the cases and controls, respectively. Male (56.7%) preponderance was observed in both groups. The mean duration of the disease was 3.4 ± 1.2 years, and the mean PASI score of the patients was 12.8 ± 5.2 . On comparison between

groups, no statistical difference was seen using the chi-squared test concerning age and gender.

No statistical differences were observed in the FIMT and CIMT of cases and controls with respect to age and sex, as shown in Tables 1 and 2.

The mean FIMT (mm) was remarkably higher in the cases (1.4 ± 0.63 mm) in comparison with controls (0.5 ± 0.09 mm), with a *P*-value < 0.001 . Similarly, the mean CIMT (mm) was also higher in the cases (1.0 ± 0.62 mm) in comparison with controls (0.8 ± 0.07 mm), with a *P*-value of 0.04 (Table 3).

All patients in the study group showed increased mean intima-media wall thickness (IMT) compared to controls. Among 30 patients, 16 (53.3%) patients had only increased FIMT, and 14 (46.7%) patients had both increased FIMT and CIMT. Out of these 14, 71.4% (10) had more pronounced changes in the FIMT than in the CIMT. No significant differences were observed in FIMT (0.132) and CIMT (0.15) in cases with respect to the PASI score, with *P*-values of 0.48 and 0.42, respectively.

Among psoriasis patients, the mean FIMT (1.4 ± 0.63 mm) was significantly higher than the mean CIMT (1.0 ± 0.62 mm), with a *P*-value of 0.01. Examples of IMT measurement are presented in Figures 1–4.

Table 3. Comparison of femoral artery intima-media thickness (FIMT) and carotid artery intima-media thickness (CIMT) between cases and controls

	FIMT (mm)		CIMT (mm)	
	Mean	SD	Mean	SD
Cases (30)	1.402	0.63	1.004	0.62
Controls (30)	0.5	0.09	0.8	0.07
<i>P</i> -value	< 0.001		0.04	

DISCUSSION

The link between psoriasis and the possibility of cardiac diseases is contentious, and a systematic review proposed that psoriasis is interrelated with ischemic heart disease but not with cerebrovascular diseases and cardiovascular fatality¹³. Our study also showed that patients with psoriasis are at greater risk of subclinical atherosclerosis.

The precise pathogenesis of psoriasis in aiding atherosclerosis remains ambiguous. Psoriasis is a chronic systemic inflammatory state connected to a hastening of atherosclerotic lesions. Chronic systemic inflammation stimulates endothelial dysfunction, glucose metabolism alteration, and insulin resistance, which play a remarkable role in atherosclerosis development^{14,15}. Various immunological factors with a dominant interleukin

Table 1. Comparison of femoral artery intima-media thickness (FIMT) in cases and controls with respect to age and sex

Variables	Cases		Controls	
	FIMT (mm)	<i>P</i> -value	FIMT (mm)	<i>P</i> -value
Age (years)				
30–40	1.01 ± 0.25	0.22	0.50 ± 0.09	0.57
41–50	1.63 ± 0.61		0.47 ± 0.05	
51–60	1.35 ± 0.73		0.55 ± 0.08	
61–70	1.4 ± 0.61		0.48 ± 0.12	
71–80	1.81 ± 0.89		0.49 ± 0.09	
Sex				
Male	1.57 ± 0.69	0.09	0.51 ± 0.10	0.54
Female	1.17 ± 0.46		0.48 ± 0.08	

Table 2. Comparison of carotid artery intima-media thickness (CIMT) in cases and controls with respect to age and sex

Variables	Cases		Controls	
	CIMT (mm)	<i>P</i> -value	CIMT (mm)	<i>P</i> -value
Age (years)				
30–40	0.73 ± 0.21	0.54	0.76 ± 0.05	0.53
41–50	1.05 ± 0.69		0.80 ± 0.11	
51–60	1.32 ± 0.81		0.78 ± 0.04	
61–70	0.95 ± 0.81		0.73 ± 0.05	
71–80	1.05 ± 0.90		0.80 ± 0.14	
Sex				
Male	1.12 ± 0.72	0.25	0.76 ± 0.07	0.23
Female	0.85 ± 0.45		0.79 ± 0.08	

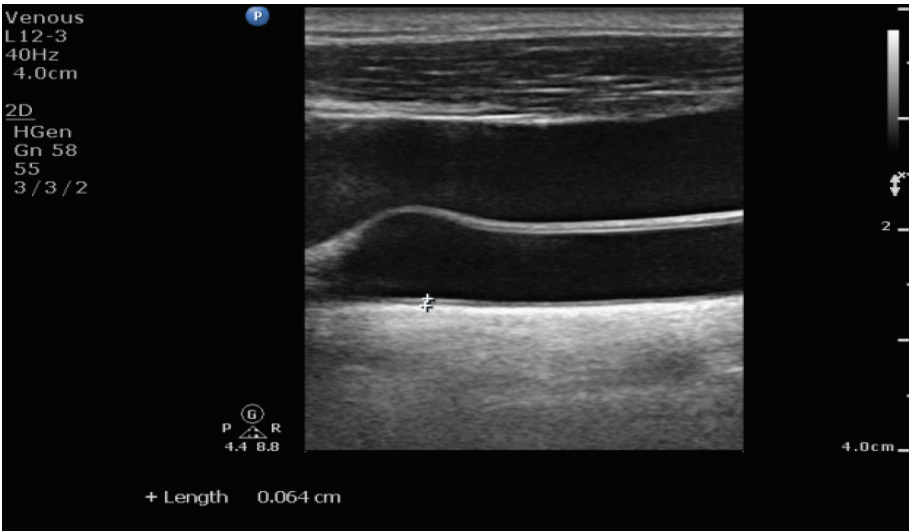


Figure 1. Carotid artery intima-media thickness in a patient with psoriasis

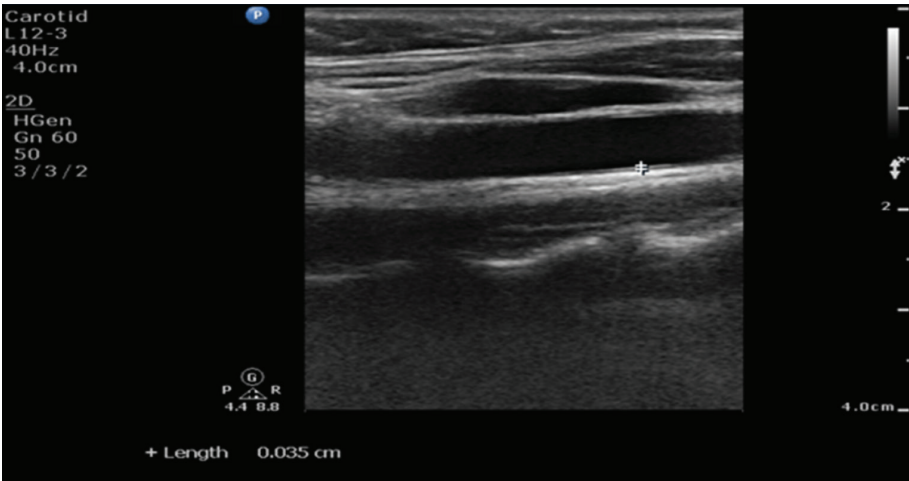


Figure 2. Carotid artery intima-media thickness in a participant from the control group

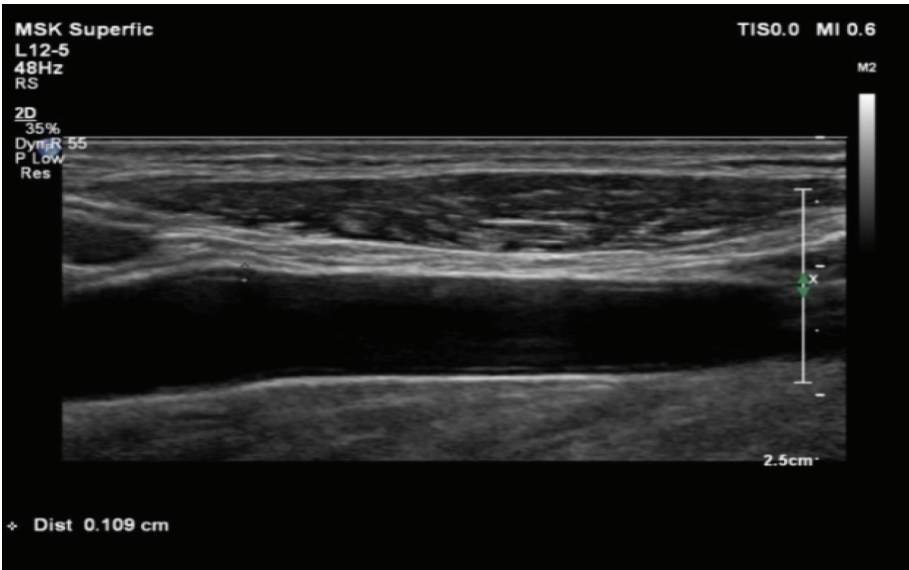


Figure 3. Femoral artery intima-media thickness in a participant from the control group

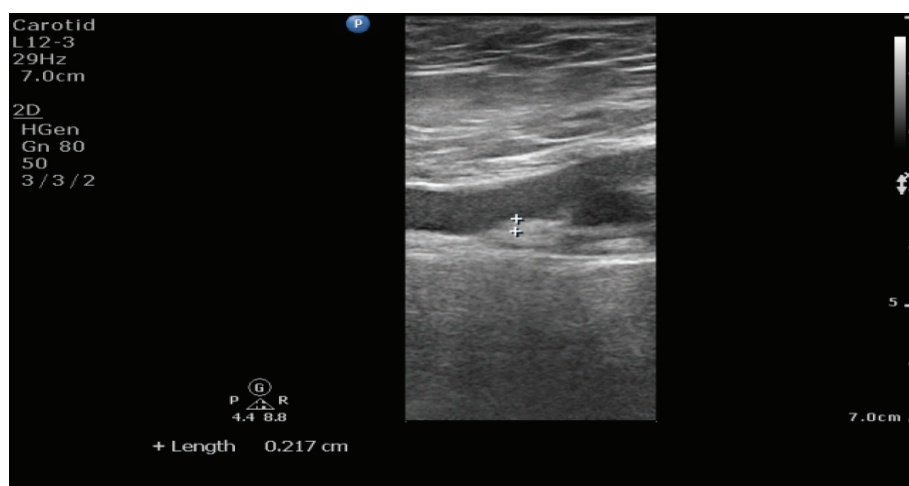


Figure 4. Femoral artery intima-media thickness in a patient with psoriasis

(IL)-23/Th17 axis and adipocytokines are involved in these processes, such as adiponectin, which suppresses the secretion of tumor necrosis factor (TNF)- α from keratinocytes. The inflammatory scene stimulates keratinocyte multiplication via TNF- α , interferon- γ , and IL-17. Factors, namely C-reactive protein & TNF- α , also contribute to atherosclerosis¹⁶. Compared with healthy controls, decreased adiponectin levels in normal-weight psoriasis patients were observed¹.

In psoriasis, evaluation of subclinical atherosclerosis by ultrasound in previous studies was carried out only on the carotid arteries. Nevertheless, contentious outcomes were seen, with one research done by Arias-Santiago *et al.* showing a greater prevalence of carotid plaques among cases with psoriasis compared with controls¹⁷. In contrast, the other two studies noted no remarkable between-group differences in the prevalence of carotid plaques^{18,19}. As the need to detect subclinical atherosclerosis early in patients with psoriasis persists, the FIMT has been contemplated.

Ultrasonography data of our study showed that the mean FIMT and CIMT were 1.4 ± 0.63 mm & 1.0 ± 0.62 mm, respectively, in patients with psoriasis. A comparison between both revealed a significant difference ($P = 0.01$), confirming that FIMT improved the discernment of subclinical atherosclerosis among cases with psoriasis compared to CIMT and was in accordance with various studies^{20,21}. In our study, no significant association was seen between IMT and PASI. So,

ultrasonography aids in assessing the cardiovascular risk in psoriasis patients without the overt disease, and the PASI does not play a significant role in such conditions.

The increased mean FIMT indicated an elevated risk of CVD in patients with psoriasis in comparison with controls. This may substantiate the postulation that the reason for the increased atherosclerosis risk in these cases is both diseases' common inflammatory pathways. The share of identical inflammatory mediators and similar cellular responses leads to endothelial dysfunction, oxidative stress, and angiogenesis. Auxiliary, genetic predisposition concedes searching for novel techniques of treatment and prevention.

CONCLUSION

Ultrasonographic screening of FIMT enhances the early discernment of subclinical atherosclerosis when compared with CIMT. Thereby, it helps in the early identification of cardiovascular disease in patients with psoriasis.

Conflict of Interest: None declared.

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Serum folic acid, vitamin B₁₂, vitamin D, and homocysteine levels in Iranian children with vitiligo

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Background: Hyperhomocysteinemia and vitamin D deficiency may be involved in the pathogenesis of vitiligo. This study compared the serum levels of vitamin D, homocysteine, vitamin B₁₂, and folic acid between vitiligo-affected children and healthy children.

Methods: Using a case-control design, 30 children with vitiligo and 30 age and sex-matched healthy children were enrolled from April 2018 to August 2020. Serum levels of vitamin D, homocysteine, vitamin B₁₂, and folic acid were analyzed in both groups during the same season of the year. Additionally, the association between serum levels of these factors with demographic and clinical features of the children (collected by interview and physical examination) was evaluated. Data were analyzed using the independent T-test, Fisher's exact test, and chi-squared test.

Results: The vitiligo group had significantly lower vitamin D and folic acid serum levels compared with the control group [95% CI -19.87 to -2.96 and -4.15 to -4.18, respectively]. Among patients, the vitamin D level was negatively correlated with age ($r = -0.459$, $P = 0.011$) and disease duration ($r = -0.373$, $P = 0.042$). Moreover, there was a significant association between vitiligo activity and serum homocysteine levels ($P = 0.027$).

Conclusion: Routine measurement of vitamin D and folic acid serum levels might be suggested, especially in children with long-standing disease. Monitoring the homocysteine level may be beneficial, particularly in children with progressive vitiligo.

Keywords: vitamin D, folic acid, homocysteine, vitiligo, children

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INTRODUCTION

Vitiligo is an acquired autoimmune dermatologic disorder that presents with depigmented lesions. The disease pathogenesis is not completely known, but several factors such as genetic background, autoimmunity, oxidative stress, neurohormonal etiology, and cytotoxicity of melanocytes may be involved ¹⁻³. Recently, the effect of hyperhomocysteinemia on impaired melanogenesis has been elucidated ⁴⁻⁶. Decreased activity of the catalase enzyme can lead to hyperhomocysteinemia

in vitiligo patients. Hyperhomocysteinemia results in an increased level of oxidative stress, cytokine activation (interleukin 6), nuclear factor $\kappa\beta$ activation, and tyrosinase inhibition, destroying melanocytes and impairing melanogenesis ⁵⁻⁸. On the other hand, low levels of B₁₂ and folic acid in serum, as co-factors for homocysteine methylenetetrahydrofolatereductase (MTHFR) in homocysteine to methionine conversion, have been demonstrated in hyperhomocysteinemic patients ⁸⁻¹⁰.

Vitamin D protects melanocytes from apoptosis

by its antioxidant effect, activation of T regulatory cells, and immunomodulatory effects via shifting the immune response from T-helper (Th) 1 to Th 2 and inhibiting the maturation of dendritic cells. It also augments tyrosinase activity and melanogenesis, affecting the vitamin D receptor (VDR) of melanocytes¹¹⁻¹⁵.

To date, few have evaluated the serum levels of vitamin D, homocysteine, vitamin B₁₂, and folate in vitiligo patients, with paradoxical results due to confounding factors such as genetic polymorphism on MTHFR, diet habits, age, and sun exposure. Some authors recommend regular measurements of these factors in patients suffering from vitiligo¹⁶⁻²⁰.

Regarding the relatively high cost of laboratory tests and confounding results, we decided to check these factors in Iranian children with vitiligo in comparison with healthy children.

MATERIAL AND METHODS

The current study was performed on a case-control basis, where 30 vitiligo-affected children and 30 sex- and age-matched healthy children referred to the Pediatric Dermatology Clinic of Afzalipour Hospital in Kerman, Iran, from April 2018 to August 2020 were enrolled. Inclusion criteria were children less than 18 years old diagnosed with new cases of vitiligo that received no treatment. The control group included healthy age- and sex-matched children with negative history of autoimmune diseases, recruited from children who came to our clinic complaining of minor skin problems such as impetigo, herpes simplex, or nevus. Exclusion criteria consisted of patients with other systemic or cutaneous diseases, smoking, taking folic acid, vitamin D, vitamin B₁₂, and vitamin B6 since six months ago, and unwillingness to participate in the study. The current research was approved by the Ethics Committee of Kerman University of Medical Sciences (IR-KMU.REC.1395.763). According to Atas *et al.*¹, serum levels of homocysteine in the case and control groups were 16.9 ± 8.4 and 9.10 ± 3.4 $\mu\text{mol/l}$, respectively; therefore, a minimum sample size of 15 participants in each group was calculated (power = 80%, $\alpha = 0.05$). However, to increase the study's power, the sample was expanded to 30 in each group.

Parents provided written informed consent if their child was less than 12 years old, while it was obtained

from both children and parents if children were older than 12. Vitiligo diagnosis was confirmed based on clinical examination and Wood's lamp assessment. Demographic features of the participants, including age, gender, and family history of vitiligo or other autoimmune disorders, were acquired by face-to-face interviews and questionnaires. Also, clinical features of vitiligo, including the site of the lesions, duration of the disease, and type of vitiligo, were recorded by history taking and physical examination. Based on the vitiligo disease activity (VIDA) score, the disease activity was classified using six points from -1 to +4. Furthermore, the area of involved skin was calculated using the vitiligo area scoring index (VASI) score (within the range of 10–100%) in five regions of the body according to the following equation (range: 0–100):

$$\text{VASI} = \sum \text{all body sites (hand units)} \times \text{depigmentation}^{20}.$$

After 12 hours of fasting, the serum level of vitamin D was assessed by a laboratory technician that was not aware of the two groups via the enzyme-linked fluorescence assay (ELFA) using Vidas kits (France), and homocysteine, vitamin B₁₂, and folic acid levels were assessed by chemiluminescence method using Siemens kits (Germany). The blood samples were obtained from all participants during the same season of the year to eliminate the confounding effect of weather on vitamin D serum levels. The analytical sensitivity for serum levels of vitamin D, homocysteine, vitamin B₁₂, and folic acid were 8.1 ng/ml, 0.5 $\mu\text{mol/l}$, 125 pg/ml, and 0.8 ng/ml, respectively. The normal ranges for vitamin D, homocysteine, vitamin B₁₂, and folic acid serum levels in pediatrics were 30–100 ng/ml, 0–15 $\mu\text{mol/l}$, 180–914 pg/ml, and 4.6–34.8 ng/ml, respectively.

Statistical analysis

SPSS 16 (software IBM, Armonk, NY, USA) was utilized for data analysis. Frequency and percentage were used to describe qualitative data, and mean $\pm$ standard deviation (SD) was used to describe quantitative data. Comparison of the two groups and association between clinical and demographic features of the case group with levels of vitamin B₁₂, homocysteine, folate, and vitamin D were evaluated using the independent T-test, Fisher's exact test, and chi-squared test.

RESULTS

Thirty children with vitiligo and 30 healthy age- and sex-matched children were enrolled in this study (Figure 1). Table 1 demonstrates the clinical features of children with vitiligo. The serum vitamin D in patients and controls were 19.34 ± 8.41 and 32.28 ± 15.41 ng/ml, respectively (95% CI -19.87 to -2.96, $P = 0.001$). The level of folic acid in the case and control groups was 12.62 ± 3.28 ng/ml and 14.60 ± 4.17 ng/ml, respectively (95% CI -4.15 to -4.18, $P = 0.046$).

A lower level of vitamin B₁₂ and a higher level of homocysteine were revealed in the vitiligo group, but the results were not significant [95% CI -85.30 to 19.40 and -1.41 to 2.68, respectively, $P > 0.05$] (Table 2). Moreover, a significant negative association between vitamin D and the age of the patients ($r = -0.459$, $P = 0.011$) as well as disease duration ($r = -0.373$, $P = 0.042$) was observed, but there was no association between other factors and

Table 1. Clinical features of children with vitiligo

Variable	Number	Percentage
Site of the lesions		
Head & neck	23	53.4
Extremity	12	40
Trunk	9	6.7
Type of the lesion		
Segmental	3	10
Generalized	7	23.3
Localized	20	66.7
VIDA score		
Active in past 1 year	7	23.3
Active in past 6 months	13	43.3
Active in past 3 months	9	30
Active in past 6 weeks	1	3.3
VASI score		
< 30	24	80
> 30	6	20

VIDA: Vitiligo Disease Activity Score; VASI: Vitiligo Area Scoring Index

age or disease duration. Moreover, there was no significant association of the levels of vitamin B₁₂,

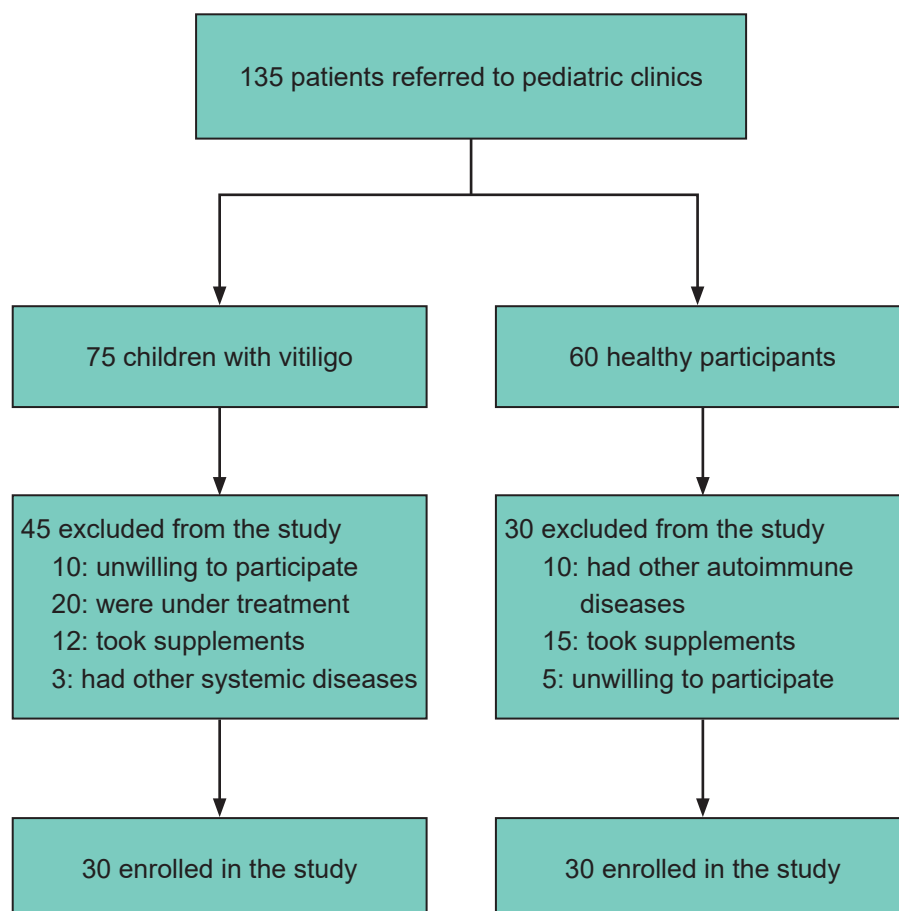


Figure 1. Flowchart of the study

Table 2. Demographic features and serum levels of homocysteine, vitamin B12, vitamin D, and folic acid in the two groups (mean $\pm$ SD, range)

Variable	Patients	Controls	P-value
Girls/boys (n)	16/14	15/15	0.796
Age (years)	6.90 $\pm$ 3.74 (2–15)	6.16 $\pm$ 2.98 (2–13)	0.4
Vitamin D (ng/ml)	19.34 $\pm$ 8.41 (5–35)	32.28 $\pm$ 15.41 11–66.6	0.001
Folic acid (ng/ml)	12.62 $\pm$ 3.28 (7.40–20.80)	14.60 $\pm$ 4.17 (5.12–19.91)	0.046
Vitamin B ₁₂ (pg/ml)	334.60 $\pm$ 108.56 (110–563.4)	373.19 $\pm$ 94.76 (171.4–536.8)	0.148
Homocysteine (μ mol/l)	10.26 $\pm$ 3.62 (5.12–20.50)	9.63 $\pm$ 4.14 (1–17.1)	0.536

homocysteine, vitamin D, and folic acid with the sex of the participants, as well as the VIDA and VASI scores, except a positive association between VIDA score and homocysteine level ($P = 0.027$).

DISCUSSION

In this study, vitamin D and folic acid levels were significantly lower in children with vitiligo than in healthy controls, but the serum levels of homocysteine and vitamin B₁₂ did not differ considerably between the two groups.

In a study by Singh and colleagues, folic acid/vitamin B₁₂ levels were inferior, while homocysteine levels were superior in patients with vitiligo relative to the control group. In the aforementioned study, no significant association of homocysteine and folic acid levels with the disease duration was reported, validating the results of our study. However, in the present investigation, in contrast to Singh *et al.*, there was a significant association between homocysteine and VIDA score¹⁶.

Zaki *et al.*, similar to this study, demonstrated a higher level of homocysteine in the serum of patients with vitiligo than in healthy individuals. But, in that study, a positive association between age and homocysteine level was reported, in contrast to our study. The lower age of our participants, higher level of serum homocysteine in older ages, and different genetic backgrounds can explain this difference¹⁷.

Ghalamkarpour *et al.* revealed a significantly higher percentage of hyperhomocysteinemia in adults with vitiligo (64.2%) in comparison with healthy controls (36%). In the present study, hyperhomocysteinemia was evident in 13.3% and 6.7% of the children with vitiligo and healthy ones,

respectively. But in contrast to Ghalamkarpour's study, the difference was not significant¹⁸. Several factors such as age, sex, lifestyle, genetic background, duration of disease, disease activity (VIDA score), and percentage of involvement (VASI) may have a role in modulating the serum levels of homocysteine, vitamin B₁₂, and folic acid. So, dissimilarity in the results between different studies can be due to differences in these factors⁴⁻¹¹.

Karaguzel *et al.* demonstrated higher vitamin D serum levels in children with vitiligo than in controls, contradicting our results¹⁹. Singla *et al.* reported significantly lower serum levels of vitamin D among individuals suffering from vitiligo compared to the healthy group, similar to the present study. Furthermore, there was no significant relationship between serum levels of vitamin D and VIDA and VASI scores, again compatible with the present study. In contrast to Singla *et al.*, our study indicated that the vitamin D level was negatively correlated with age and duration of disease²⁰. Factors such as age, sex, body mass index (BMI), Fitzpatrick skin type, lifestyle, ethnicity, genetics, and sunscreen application affect the serum vitamin D level. This can explain the difference in results between the studies²¹⁻²³.

Lajevardi *et al.* revealed lower serum levels of vitamin D in male vitiligo patients than in male controls; nevertheless, the difference was insignificant in females. This can be explained by the type of dressing in females in Iran, an Islamic country, which can lead to lower serum vitamin D levels in both vitiligo and control groups. In the current investigation, there was no discernible association between sex and serum vitamin D level, which may be explained by the lower age of our patients than in Lajevardi *et al.*'s study and the

Table 3. Comparison of serum levels of homocysteine, vitamin B12, vitamin D, and folic acid in other studies

First author	Groups	Homocysteine (μmol/l)	Folic acid (ng/ml)	Vitamin B ₁₂ (pg/ml)	Vitamin D (ng/ml)
Singh ¹⁴	Vitiligo	28.8 ± 7.7	4.88 ± 1.52	428.46 ± 133.52	NP
	Control	23.1 ± 1.9	6.25 ± 0.69	536.63 ± 111.43	NP
	P-value	< 0.01	< 0.01	< 0.01	NP
Zaki ¹⁵	Vitiligo	11.35 ± 3.14	NP	NP	NP
	Control	10.49 ± 1.68	NP	NP	NP
	P-value	0.19	NP	NP	NP
Ghalamkarpour ¹⁶	Vitiligo	12.5	883.38 ± 304.14	340.5	NP
	Control	17	939.87 ± 256.56	345	NP
	P-value	0.001	0.31	0.61	NP
Karaguzel ¹⁷	Vitiligo	NP	NP	NP	26.6 ± 18.3
	Control	NP	NP	NP	22.8 ± 13.5
	P-value	NP	NP	NP	NS
Singla ¹⁸	Vitiligo	NP	NP	NP	24.07 ± 3.79
	Control	NP	NP	NP	38.17 ± 9.54
	P-value	NP	NP	NP	< 0.001
Lajevardi ¹⁹	Vitiligo	NP	NP	NP	10.24 ± 1.72
	Control	NP	NP	NP	18.31 ± 7.39
	P-value	NP	NP	NP	NS

NP: Not Performed

difference in the type of dressing between adults and children ²¹. A comparison of the folic acid, vitamin D, vitamin B₁₂, and homocysteine levels in other studies is conveyed in Table 3.

Confounding factors such as dietary habits, socioeconomic status, lifestyle, physical activity level, culture, skin type, genetic background, and duration of outdoor activities can affect folic acid, vitamin D, vitamin B₁₂, and homocysteine serum levels ^{4-11,21-23}. The limitation of this study was the matching of case and control groups for only sex and age. Nonetheless, to eliminate the effect of sun exposure on the serum level of vitamin D, all subjects were sampled on the same day. Also, participants were recruited from a single center with the same socioeconomic status and skin type.

CONCLUSION

In this study, vitamin D and folic acid serum levels were significantly lower in children with vitiligo than in healthy ones. Furthermore, lower vitamin D serum levels were observed in pediatric vitiligo patients with longer disease duration and older age. Also, a higher homocysteine level was demonstrated in progressive vitiligo. Therefore, it might be suggested to regularly measure serum levels of these micronutrients in these children, especially in those with progressive and long-

standing vitiligo.

Conflict of interest: None declared.

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Prevalence of metabolic syndrome and its relationship with mucosal involvement in lichen planus: an observational study

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Background: Lichen planus (LP) is a chronic inflammatory disorder involving the skin, mucosa, hair, and nails. Previous reports have shown a possible association between LP and metabolic derangement, leading to increased cardiovascular risk among these patients. Our study aimed to assess the prevalence of metabolic syndrome (MetS) and its components in LP patients and to study their relationship with mucosal involvement in LP.

Methods: We conducted a cross-sectional observational study of 123 LP patients. Demographic and clinical data were obtained, and evaluation was done for the presence of abdominal obesity, hypertension, hyperglycemia, and dyslipidemia. MetS was diagnosed according to the modified National Cholesterol Education Program: Adult Treatment Panel III (NCEP-ATP III) criteria for the South Asian population. Data analysis was done using appropriate statistical methods.

Results: The prevalence of MetS in LP patients was 31%. The mean age of LP patients having MetS was considerably higher than those without MetS (44.8 ± 13.6 vs. 33.3 ± 15.9 years; $P = 0.0002$). Although statistically insignificant, female patients and patients with mucosal involvement showed a higher prevalence of MetS. Central obesity, hypertension, hyperglycemia, and hypertriglyceridemia were more prevalent in mucosal LP patients than in those without mucosal lesions, with hyperglycemia having a significantly higher prevalence in mucosal LP (41% vs. 18%; $P = 0.015$).

Conclusion: Increased age, female gender, and mucosal involvement are important predictors of concurrent metabolic derangement in LP patients. Thus, these patients should be screened for the presence of MetS and its components.

Keywords: metabolic syndrome, hyperglycemia, obesity, hypertension, lichen planus, India

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INTRODUCTION

Lichenoid disorders are inflammatory dermatoses characterized clinically by papules and plaques and histologically by a band-like lymphocytic infiltrate in the papillary dermis ¹. Lichen planus (LP), the

prototype of lichenoid dermatoses, is a chronic disorder of unknown etiology involving the skin, mucosa, and appendages. It affects about 0.5–1% of the population worldwide and is characterized by pruritic, violaceous, flat-topped papules and plaques ^{2,3}. It is believed to represent a T-cell-

mediated inflammatory response. This chronic inflammatory process and oxidative stress induction seen in LP may be linked to the development of metabolic derangement⁴⁻⁶. An association between LP and metabolic disorders has been reported in multiple studies worldwide⁷⁻¹⁹.

Metabolic syndrome (MetS) refers to a cluster of abnormalities that increase the risk of morbidity and mortality from cardiovascular disease and diabetes²⁰. The prevalence of MetS and its relationship with LP varies widely in published studies. In India, data on metabolic derangement in LP patients are scarce, with only a few of the related studies originating from eastern India. Our study was designed to assess the prevalence of MetS and its components in LP patients and to study their relationship with mucosal involvement in LP.

MATERIALS AND METHODS

This was a hospital-based cross-sectional observational study conducted at a tertiary care center in eastern India. All consecutive patients with a clinical diagnosis of LP, confirmed by histopathological examination wherever necessary, were selected from patients attending the dermatology outpatient department over a period of one year, starting from 1st March 2018. Based on the inclusion and exclusion criteria, a total of 123 patients were enrolled in the study after informed consent. The inclusion criteria for cases included new patients with clinical and/or histopathological diagnosis of classical or any morphological variant of LP. Patients on treatment or previously treated for LP, pregnant patients, and severely ill patients were excluded from the study.

Demographic and clinical data pertaining to age, gender, duration of illness, sites of involvement, and known history of hypertension, diabetes, or hyperlipidemia were obtained from the enrolled

patients using an interviewer-administered questionnaire. The patients were clinically examined for morphological type of LP and mucosal involvement, including oral as well as genital lesions. Hair and nail involvement was also noted. Waist circumference was measured at the level of the umbilicus using a tape measure. Blood pressure (BP) was measured in the arm using a sphygmomanometer at least 15 minutes after rest in the sitting posture. Venous blood samples were collected after overnight fasting for 12 hours for estimation of fasting blood sugar (FBS) by the hexokinase method and serum triglyceride (TG) and serum high-density lipoprotein cholesterol (HDL-C) by enzymatic methods. MetS was diagnosed based on National Cholesterol Education Program: Adult Treatment Panel III (NCEP-ATP III) criteria with a modification in the criteria for central obesity for the South Asian population (including Indians), as shown in Table 1^{21,22}. Patients satisfying three or more of these criteria were diagnosed with MetS.

All data were tabulated in a Microsoft Excel sheet and statistically analyzed using the same software. Numerical variables were computed as mean and standard deviation, while categorical data were described through frequencies and percentages. For inferential statistics, we used t-tests and chi-squared tests for intergroup comparisons of continuous and categorical variables, respectively. *P*-values of less than 0.05 were taken as statistically significant.

The details of the study were discussed with all patients, and written informed consent was obtained from the participants. Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the institution.

RESULTS

One hundred and twenty-three patients participated in this study. There were 57 (46%)

Table 1. Modified National Cholesterol Education Program: Adult Treatment Panel III criteria for diagnosis of metabolic syndrome

Central obesity	Waist circumference
	≥ 90 cm for men ≥ 80 cm for women
Hypertension	Blood Pressure ≥ 130/85 mmHg or specific medication
Fasting blood sugar	≥ 100 mg/dl or specific medication or previously diagnosed type 2 diabetes
Serum triglyceride	≥ 150 mg/dl or specific medication
Serum high-density lipoprotein cholesterol	< 40 mg/dl in men < 50 mg/dl in women or specific medication

males and 66 (54%) females, with a male-to-female ratio of 1:1.16. The mean age of the patients was 36.9 ± 16.1 years. Most patients (41%; $n = 51$) were in the age group of 40–59 years. The duration of LP in the patients ranged from 1 to 144 months, with an average duration of 18.3 ± 25.7 months.

Among the study subjects, 89 patients (72%) had skin LP, 19 (16%) had mucosal LP, and 15 (12%) had both skin and mucosal involvement. Also, 13 patients (11%) showed nail involvement. The most common morphological was classical LP in 75 patients, followed by hypertrophic LP in 9 patients. Among the 28 patients with oral lesions, 23 had reticular, 4 had erosive, and 1 had plaque-like oral LP. Seven out of the eight patients with genital lesions had erosive LP, while one had annular LP.

Thirty-eight (31%) of the patients enrolled were found to have MetS. The prevalence among females was 35% as compared to 26% among

males ($P = 0.410$). Table 2 compares various characteristics between LP patients with and without MetS. The mean age of LP patients having MetS was substantially higher than those lacking MetS (44.8 ± 13.6 vs. 33.3 ± 15.9 years; $P = 0.0002$). Prevalence was maximum in the age group of 50–59 years, while none of the patients below 20 years of age had MetS (Figure 1). Also, 41% of the patients with mucosal involvement had MetS as compared to 27% of those without any mucosal lesions ($P = 0.191$).

The LP patients with MetS showed a shorter mean duration of lesions and a higher prevalence of mucosal and nail involvement as compared to those without MetS. However, the P values were not significant in any of these cases.

Among the patients with MetS, the most common morphology of skin lesions was classical LP, followed by LP pigmentosus (Table 3). The

Table 2. Comparison of characteristics between lichen planus (LP) patients with and without metabolic syndrome (MetS)

	MetS Present ($n = 38$)	MetS Absent ($n = 85$)	<i>P</i> -value
Mean age $\pm$ SD (years)	44.8 ± 13.6	33.3 ± 15.9	0.0002
Mean duration of LP $\pm$ SD (months)	13.0 ± 15.2	20.7 ± 29.0	0.129
Oral lesions	13 (34%)	15 (18%)	0.073
Genital lesions	3 (8%)	5 (6%)	0.702
Nail involvement	6 (16%)	7 (8%)	0.346

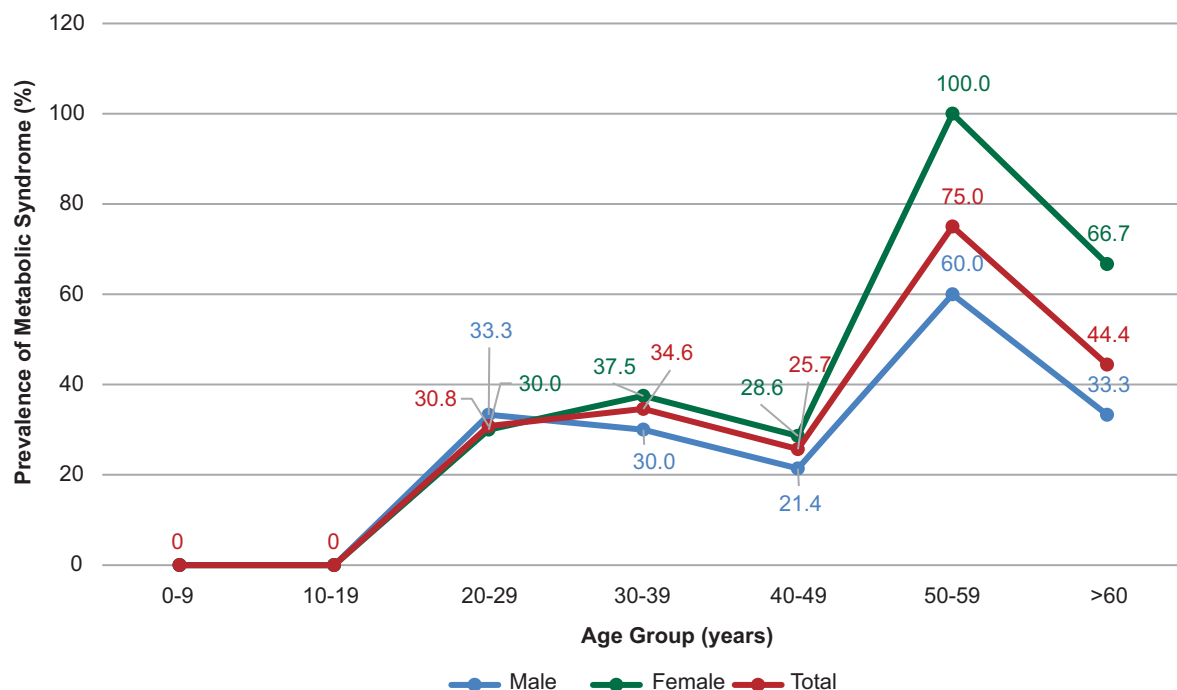


Figure 1. Line chart showing the age-specific prevalence of metabolic syndrome in the study population.

Table 3. Types of lichen planus (LP) in patients with metabolic syndrome

Type	Frequency (%)
Skin lesions (n = 32)	
Classic	27 (84)
Hypertrophic	1 (3)
LP Pigmentosus	3 (9)
Linear	0
Actinic	0
Bullous	1 (3)
Annular	0
Follicular	0
Oral lesions (n = 13)	
Reticular	10 (77)
Erosive	2 (15)
Plaque-like	1 (8)
Genital lesions (n = 3)	
Erosive	3 (100)
Annular	0

predominant type of oral LP in this group was the reticular type. Three patients with MetS had genital lesions, and all three had erosive LP.

The most prevalent component of MetS observed was central obesity in 77 patients (63%), followed by hypertension in 39 patients (32%). Central obesity, hypertension, elevated FBS, and low HDL-C were more prevalent in females, with the latter showing statistical significance ($P = 0.007$) (Figure 2). All the parameters of MetS, except low HDL-C, were more prevalent in LP patients

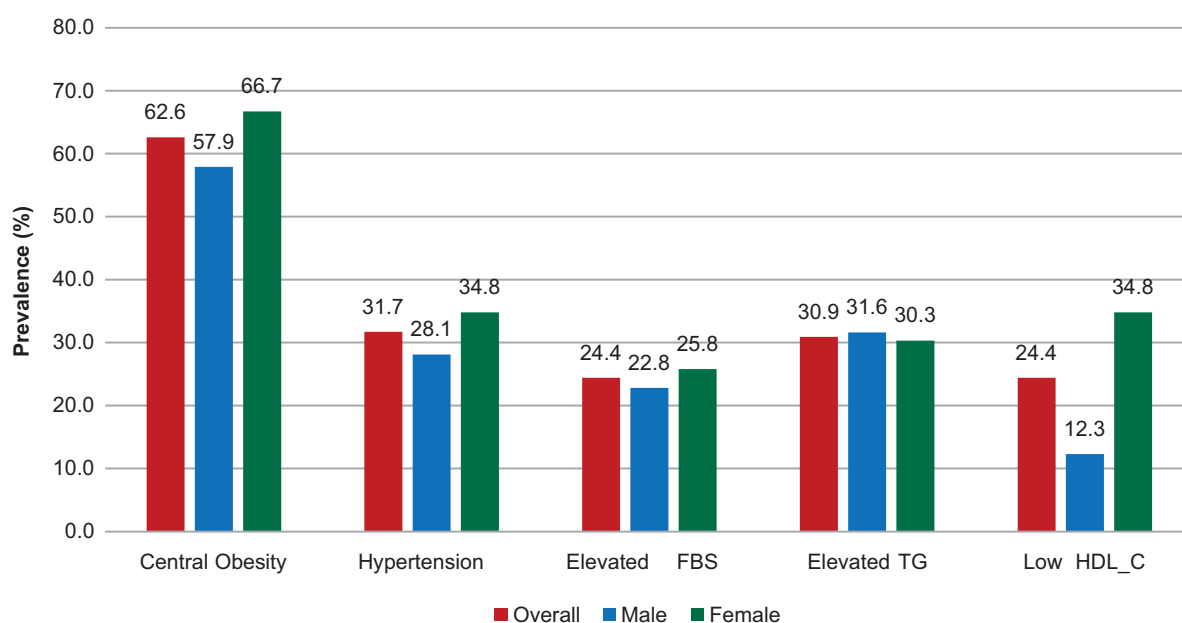
with mucosal involvement than in those without mucosal lesions. The prevalence of elevated FBS was notably higher in patients with mucosal involvement (41% vs. 18%; $P = 0.015$) (Figure 3).

DISCUSSION

LP is a common, chronic inflammatory papulo-squamous disorder encountered in dermatological practice. Although its etiopathogenesis is not well understood, several potential pathogenetic mechanisms have been proposed, indicating that LP may serve as a reliable external marker of underlying immune and metabolic dysfunction^{4,6,23,24}.

Our study was conducted on 123 patients of LP attending the outpatient department in a tertiary care hospital in eastern India. Females outnumbered males to a small extent, with the maximum number of patients aged 40–59 years. These findings were comparable to most other Indian studies, such as those by Garg *et al.* and Ireddy *et al.*^{3,23}. Morphologically, the predominant type of skin lesion was classical LP, and the predominant type of oral lesion was the reticular type. Similar findings have been reported by other authors^{15,17}.

The prevalence of MetS in the general population in various parts of India ranges from 11% to 41%²⁵. A large community-based survey from eastern India reported the prevalence to be 33.5%

**Figure 2.** Bar graph showing the prevalence of metabolic syndrome parameters in the study population (FBS: Fasting Blood Sugar; TG: Triglyceride; HDL-C: High-Density Lipoprotein Cholesterol)

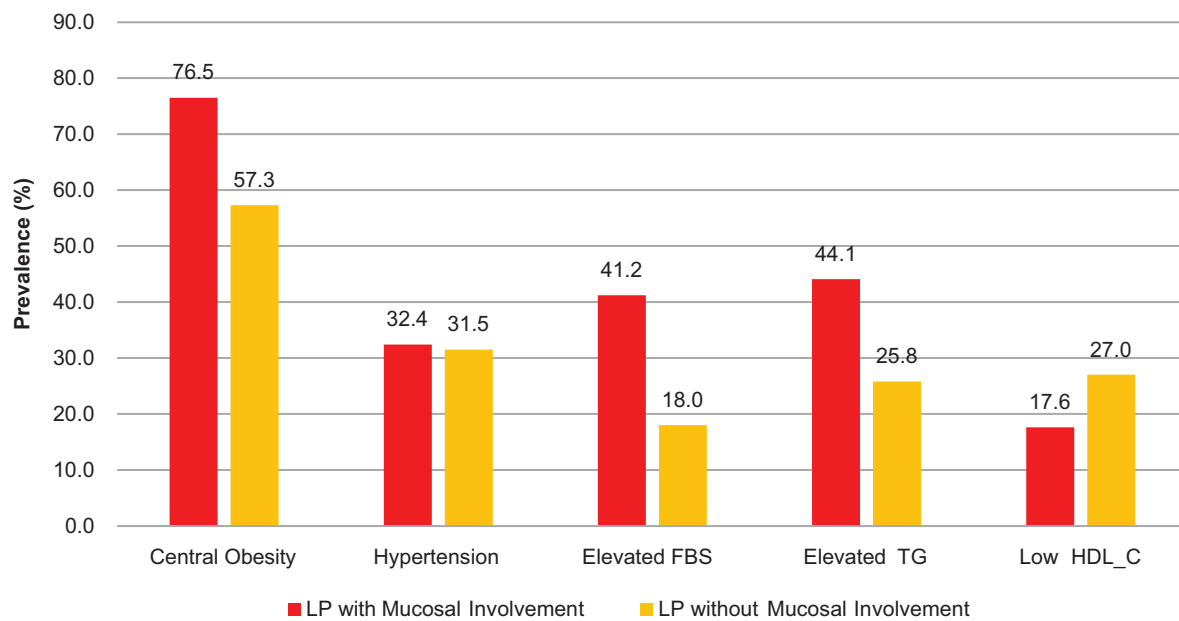


Figure 3. Bar graph showing prevalence of metabolic syndrome parameters based on mucosal involvement (FBS: Fasting Blood Sugar; TG: Triglyceride; HDL-C: High-Density Lipoprotein Cholesterol LP: Lichen Planus)

overall²⁶. Interestingly, the prevalence of MetS among LP patients in our study was in the same range as that reported in the general population. However, according to a recent systematic review, LP patients have a significantly higher prevalence of MetS (approximately twice) compared with the general population²⁷.

As mentioned in Table 4, studies from across the world have reported variable prevalence of MetS in LP, ranging from 6% to 48%^{4,9,10,14-19}. The observed variation may be due to differences in study settings, sample sizes, patient selection, population genetics, dietary habits, physical activity levels, and MetS diagnostic criteria. The sample size in our study was more than most similar studies

from our country, making our observations more significant.

In our study, the mean age of LP patients with MetS was significantly higher than that in those without MetS. A Nigerian study by Okpala *et al.* reported similar findings, showing participants with LP and MetS to be significantly older than LP patients without MetS¹⁶.

Krishnamoorthy *et al.* found the prevalence of MetS in patients of oral LP to be 27.27%¹¹. A significantly higher prevalence of MetS was reported in LP patients with mucosal involvement by Baykal *et al.* (34.5 vs. 8.3%; $P = 0.032$)¹⁰. Hashba *et al.* and Daye *et al.* also reported a higher frequency of MetS in patients with oral involvement than those with isolated cutaneous lesions, although not statistically significant^{15,19}. This was corroborated by the findings in our patients, with the prevalence of MetS being higher in patients with mucosal involvement than those without it, although insignificantly. Similarly, we found oral, genital, and nail involvement to be more common among LP patients with MetS. Contrary to this, Okpala *et al.* reported oral involvement to be more common in patients without MetS¹⁶.

Baykal *et al.* reported a significantly longer duration of LP in patients with insulin resistance—a primary feature of MetS¹⁰. Similarly, in the study by Hashba *et al.*, the mean duration of LP in patients

Table 4. Comparison of prevalence of metabolic syndrome in lichen planus (LP) patients in previous studies

Study	Sample Size	Metabolic Syndrome (%)
Arias-Santiago <i>et al.</i> , 2011 ⁴	100	27
Baykal <i>et al.</i> , 2015 ¹⁰	79	26.6
Kuntoji <i>et al.</i> , 2016 ⁹	50	6
Kurian <i>et al.</i> , 2017 ¹⁴	40	45
Hashba <i>et al.</i> , 2018 ¹⁵	70	35.7
Okpala <i>et al.</i> , 2019 ¹⁶	90	18.9
Geetharani <i>et al.</i> , 2019 ¹⁷	113	19
Singla <i>et al.</i> , 2019 ¹⁸	100	43
Daye <i>et al.</i> , 2020 ¹⁹	98	48
Present study	123	31

with MetS was slightly higher than those without it¹⁵. Conversely, in our study, the mean duration of LP in patients with MetS was lower than those without it. This may be due to the fact that only newly diagnosed LP patients were taken into account, while relapsing and treatment-resistant chronic cases, in whom chronic inflammation and the associated metabolic derangement are likely to exist more frequently, were excluded from our study.

The high prevalence of central obesity and hypertension noted in our study can be explained by similar findings from a community-based survey done in eastern India by Prasad *et al.*, suggesting an overall high prevalence of these abnormalities in the general population²⁶. Central obesity showed a consistently high prevalence among LP patients in other similar studies from our country^{14,15}. The frequencies of hypertension and hypertriglyceridemia in our patients were also comparable with those reported by Singla *et al.* and Hashba *et al.*, respectively^{15,18}. However, compared to both these studies, hyperglycemia and low HDL-C were relatively less common in our patients^{15,18}.

Out of 62 patients suffering from oral LP, 17 (27.4%) had type 2 diabetes mellitus, and 11 (17.7%) had impaired fasting glucose levels in a study by Romero *et al.*²⁸. Lopez-Jornet *et al.* also reported a high prevalence of diabetes in oral LP²⁹. Hashba *et al.* found increased FBS in 59% of patients with oral LP, compared to 52.6% of patients with skin LP¹⁵. In keeping with these findings, our study revealed a significant association between elevated FBS and the presence of mucosal lesions. This implies that underlying pathomechanisms may link mucosal involvement in LP to the occurrence of insulin resistance in these patients.

Our study had a few limitations. There was no control group, so the strength of the association between LP and MetS could not be determined. Also, as it was a cross-sectional study, so the directionality of the association could not be assessed, for which long-term prospective studies are required. Although the sample size was larger than most similar studies from our country, it could not be increased further due to limited time and resources, resulting in very few statistically significant correlations. Therefore, larger case-control studies are recommended to determine

any association of MetS with LP and its various types, including mucosal LP.

CONCLUSION

Based on our study findings, routine screening for metabolic derangement should be considered in LP patients, especially in older patients and females. The presence of mucosal lesions could also serve as a guide to indicate the presence of metabolic abnormalities, especially hyperglycemia. Early detection and prompt treatment of these risk factors may go a long way in preventing such patients' subsequent development of cardiovascular disorders and diabetes mellitus.

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Conflict of interest: None declared.

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Predictive factors associated with antimony treatment failure in anthroponotic cutaneous leishmaniasis in Kerman: a case-control study

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Background: Treatment failure of antimony drugs for anthroponotic cutaneous leishmaniasis (ACL) is rising. Recognizing predictive factors of unresponsiveness to treatment can substantially influence better ACL management. The goal of this study was to investigate predictive factors associated with treatment failure in ACL in Kerman, southeast Iran.

Methods: This case-control study was conducted retrospectively on 2,128 ACL cases in Kerman over ten years from 2011 to 2020. The case group included patients whose lesions failed to resolve after one treatment course. The control group included those whose lesions were cured after one treatment course.

Results: Treatment failure was observed in 13.5% of cases (10.7% of systemic therapy and 16.7% of local therapy). No significant difference was reported between the type of treatment and treatment failure. The association of treatment failure with winter-onset ($P = 0.001$, OR = 1.39, CI = 1.23–1.56), face ($P = 0.001$, OR = 1.86, CI = 1.38–2.49), ulceration ($P = 0.01$, OR = 0.51, CI = 0.30–0.85), small diameter ($P = 0.005$, OR = 0.57, CI = 0.38–0.84) and long duration of lesions ($P = 0.01$, OR = 1.57, CI = 1.11–2.21) was validated by multivariate logistic regression analysis.

Conclusion: Efficient detection and timely management of ACL cases are essential to reduce resistant cases, as lesions lasting longer than four months show poor response to treatment. Furthermore, early treatment of facial lesions with systemic therapy is suggested to optimize results and reduce the risk of disfiguring scars. Further surveys are required to determine the reason behind more treatment failure in winter-onset lesions.

Keywords: leishmaniasis, treatment failure, glucantime

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INTRODUCTION

Leishmaniasis is one of the most neglected infectious diseases with widespread clinical spectrums from the fatal type, visceral leishmaniasis (VL), to the less threatening type, cutaneous leishmaniasis (CL). CL is the most prevalent type

of leishmaniasis, accounting for three-quarters of cases. Although CL is not a life-threatening disease, permanent disfiguring scars may lead to lower quality of life ¹⁻⁴. Iran is one of the endemic regions of CL, with an estimated annual incidence of approximately 20,000 cases ^{4,5}.

Two main types of CL are recognized:

anthroponotic CL (ACL) and zoonotic CL (ZCL), caused by *Leishmania tropica* and *Leishmania major*, respectively. In old-world CL, ACL or urban type and ZCL or rural type are transmitted to the host by the bite of the female sandfly (*Phlebotomus sergenti* and *Phlebotomus papatasi*, respectively) ^{6,7}.

Based on a previous survey, Kerman is an endemic region for ACL ⁸. According to the World Health Organization (WHO) and national leishmaniasis treatment guidelines, early detection and efficient treatment are recommended to prevent the spread of ACL. First-line therapy for ACL is pentavalent antimonials, including meglumine antimonate (Glucantime) and sodium stibogluconate (Pentostam) administered intralesionally (IL) or parenterally as intravenous (IV) or intramuscular (IM) depending upon the *Leishmania* species, clinical features of the lesions (site, size, and the number of lesions), and host's immune system status. Both methods of drug administration can result in noticeable adverse effects. Local administration is painful and can lead to erythema, edema, and swelling. Parenteral administration can have toxic effects on the heart, pancreas, kidney, and liver, leading to elevated pancreas and liver enzyme levels, cardiac arrhythmia, leukopenia, thrombocytopenia, myalgia, and abdominal pain ⁸⁻¹⁰.

Considerable numbers of recalcitrant cases have been reported in recent years. Several factors, such as the type of *Leishmania* species, demographic features of patients, clinical features of lesions, and host's immune system status, can influence treatment failure or success ¹¹. In this study, we investigated predictive factors associated with treatment failure in ACL in Kerman, southeast Iran.

PARTICIPANTS AND METHODS

Study design

This case-control study was conducted retrospectively at Shahid Davari Health Center in Kerman, Iran, for ten years (2011 to 2020). This study was approved by the Ethics Committee of the Kerman University of Medical Sciences (IR.KMU.AH.REC.1399.173).

Study population

Inclusion criteria were patients suffering from

ACL referred to this center from 2011 to 2020, those who have completed records of demographic characteristics and clinical features of lesions, received a complete treatment course, and were followed for three months afterward. Only patients who lived in Kerman city and presented with new leishmaniasis lesions were enrolled. Exclusion criteria were patients with either an incomplete treatment course or incomplete data.

The case group included patients whose lesions failed to resolve after one treatment course. The control group included those whose lesions were cured after one treatment course. Complete cure was described as complete re-epithelialization of the lesion and absence of any induration or inflammation. The treatment course consisted of weekly IL administration of meglumine antimonate (0.1 ml/cm², maximum 5 ml) and biweekly cryotherapy with liquid nitrogen for a maximum of 12 weeks or until complete healing of the lesions. A 21-day treatment course of IM administration of meglumine antimonate (20 mg/kg/day, maximum 3 ampoules) with biweekly cryotherapy was prescribed for those with lesions on the face, digits, genitalia, and joints, > 4 lesions, or ≥ 3 cm lesion diameter. Demographic characteristics (age, sex, nationality, job, and history of chronic disease), clinical features of lesions (date of onset, site, number, diameter, duration, and type of lesion), type of treatment, and response to therapy were recorded and statistically analyzed with SPSS.

Statistical analysis

Data were analyzed by SPSS 16 (IBM, Armonk, NY, USA). Quantitative and qualitative data were described by mean ± standard deviation and frequency, respectively. Initially, univariate logistic regression analysis was used to assess the correlation of lesions' diameter or number as well as treatment response with the patients' demographic characteristics and clinical features. Subsequently, multivariate logistic regression analysis was performed to omit confounding factors and confirm the results. P-values of less than 0.05 were regarded as significant.

RESULTS

From 3,765 cases, 2,128 ACL cases were enrolled

in the study. The highest rates of infection occurred in 2015 (20.3%), March (12.3%), and the autumn season (28.4%) (Table 1).

Demographic features

The mean age of patients was 27 ± 20.7 years (range 8 months to 92 years). The mean age of females was higher than that of males (30.06 ± 21 and 24.61 ± 18.7 years, respectively). Male and female cases were roughly equal (49.8% and 50.2%, respectively). Children and adolescents (19 years old or younger) constituted 43.9% of cases. Most patients had Iranian nationality (87.6%), and the remaining were Afghan. Most patients were students (26.7%) (Table 1).

Clinical features of the lesions

The mean number of lesions was 1.81 ± 0.73 (range 1–30), and most were single (63.5%). The mean diameter of lesions was 13.06 ± 9.40 mm, and most lesions had a diameter of 10 mm or less (82.8%). The vast majority of the lesions were ulcerated (95.7%) and located on body areas other than the face (71%, Table 1).

Association between clinical features of lesions and the number of lesions

Univariate analysis revealed that most of the single lesions were spring-onset, while the majority of multiple lesions occurred in the autumn season ($P = 0.031$, OR = 1.09, CI = 1–1.8). Most face lesions were single ($P = 0.001$, OR = 0.644, CI = -0.52–0.78). Moreover, most of the multiple lesions were ulcerated ($P = 0.014$, OR = 0.737, CI = -0.57–0.94), had a duration longer than four months ($P = 0.001$, OR = 1.69, CI = 1.34–2.14), and were 1 cm or less in diameter ($P = 0.001$, OR = 1.55, CI = -1.23–1.95). Multiple lesions were observed most frequently in patients younger than nine years old ($P = 0.001$, OR = 1.13, CI = -1.08–1.18) (Table 2).

Multivariate analysis confirmed that single lesions were mostly spring-onset ($P = 0.018$, OR = 1.10, CI = 1.01–1.19) and in the face area ($P = 0.018$, OR = 0.77, CI = 0.62–0.95). Predictive factors of multiple lesions included age of younger than nine years ($P = 0.001$, OR = 1.08, CI = 1.03–1.14), autumn-onset ($P = 0.018$, OR = 1.10, CI = 1.01–1.19),

Table 1. Demographic and clinical features of patients with anthroponotic cutaneous leishmaniasis

Variables	Number	Percentage
Sex		
Female	1068	50.2
Male	1060	49.8
Age (years)		
0-4	193	9.1
5-9	345	16.2
10-19	398	18.7
20-29	270	12.7
30-39	343	16.1
40-49	210	9.9
50-59	188	8.8
60-69	116	5.5
70-79	45	2.1
≥80	20	0.9
Nationality		
Iranian	1864	87.6
Afghan	267	12.4
Occupation		
Student	564	26.7
Others	555	26.3
Housewife	532	25.2
Child	355	16.8
Worker	62	2.9
Employee	32	1.3
Farmer	11	0.5
History of chronic disease		
Yes	70	3.3
No	2058	96.7
Season of onset		
Spring	579	27.2
Summer	448	21.1
Autumn	604	28.4
Winter	497	23.4
Type of treatment		
IL + cryotherapy	1969	92.5
IM + cryotherapy	159	7.5
Site		
Face	614	28.9
Body	1511	71.1
Type of lesion		
Ulcerated	2033	95.7
Non-ulcerated	91	4.3
Treatment response		
Cure	1841	86.5
Failure	287	13.5
Duration (months)		
≤ 4	440	20.7
> 4	1688	79.3
Size (mm)		
≤ 10	1761	82.8
> 10	367	17.2

Abbreviations: IL, intralesional; IM, intramuscular

Table 2. Association of demographic and clinical features of patients with the number of lesions

Variables	Single lesion	Multiple lesions	P-value	Univariate OR (CI)	Multivariate OR (CI)	P-value
Sex						
Male	670 (49.4)	390 (50.2)	0.79	0.976 (-0.81-1.16)		
Female	681 (50.4)	387 (49.8)				
Age (years)						
0-9	385 (28.5)	153 (19.7)	0.001	1.71 (-1.42-2.05)	1.08 (1.03-1.14)	0.001
10-19	277 (20.5)	121 (15.6)				
20-29	144 (10.7)	126 (16.2)				
30-39	219 (16.2)	124 (16)				
40-49	133 (9.8)	77 (9.9)				
50-59	107 (7.9)	81 (10.4)				
60-69	51 (3.8)	65 (8.4)				
70-79	23 (1.7)	22 (2.8)				
≥ 80	12 (0.9)	8 (1)				
Season of onset						
Spring	401 (29.7)	178 (22.9)	0.031	1.09 (1-1.18)	1.10 (1.01-1.19)	0.018
Summer	277 (20.5)	171 (22)				
Autumn	352 (26.1)	252 (32.4)				
Winter	321 (23.8)	176 (22.7)				
Face lesions	433 (70.5)	181 (29.5)	0.001	0.644 (-0.52-0.78)	0.77 (0.62-0.95)	0.018
Type of lesion						
Ulcerated	1281 (94.9)	752 (97.2)	0.014	0.737 (-0.57-0.94)	0.75 (0.58-0.96)	0.024
Non-ulcerated	69 (5.1)	22 (2.8)				
Duration of disease (months)						
≤ 4	320 (23.7)	120 (15.4)	0.001	1.69 (1.34-2.14)	1.66 (1.31-2.11)	0.001
> 4	1031 (76.3)	657 (84.6)				
Size of lesion (mm)						
≤ 10	1150 (85.1)	611 (78.6)	0.001	1.55 (-1.23-1.95)	1.30 (1.03-1.65)	0.027
> 10	201 (14.9)	166 (21.4)				

ulceration ($P = 0.024$, OR = 0.75, CI = 0.58–0.96), longer duration ($P = 0.001$, OR = 1.66, CI = 1.31–2.11), 1 cm or less in diameter ($P = 0.027$, OR = 1.30, CI = 1.03–1.65) (Table 2).

Association between demographics and clinical features of lesions

Univariate analysis revealed that larger lesions (diameter > 1 cm) were observed more commonly in men ($P = 0.011$, OR = 0.746, CI = -0.59–0.93) and had a longer duration ($P = 0.008$, OR = 1.51, CI = -1.11–2.04). Furthermore, larger lesions were frequently ulcerated ($P = 0.003$, OR = 0.46, CI = -0.27–0.76), single ($P = 0.001$, OR = 1.55, CI = -1.23–1.95), and located most commonly in body areas other than the face ($P = 0.001$, OR = 0.62, CI = -0.49–0.78). Patients younger than nine had a significantly higher number of smaller lesions ($P = 0.001$, OR = 2.03, CI = -1.59–2.59) (Table 3).

Multivariate analysis confirmed the association

of larger lesions with the male gender ($P = 0.021$, OR = 0.73, CI = 0.57–0.95), longer duration of lesions ($P = 0.013$, OR = 1.49, CI = 1.08–2.05), ulcerated lesions ($P = 0.003$, OR = 0.46, CI = 0.27–0.76), single lesions ($P = 0.018$, OR = 1.33, CI = 1.05–1.69), and body lesions ($P = 0.008$, OR = 0.69, CI = 0.53–0.91). Patients younger than nine years old demonstrated a significantly higher number of smaller lesions ($P = 0.001$, OR = 1.12, CI = 1.04–1.2) (Table 3).

Type of treatment

Most patients received IL Glucantime combined with cryotherapy (92.5%), and the remaining received IM Glucantime combined with cryotherapy. Treatment was mostly initiated treatment after four months of lesion onset (79.3%). Most patients were cured after one treatment course (86.5%), and treatment failure was observed in 13.5% of cases (Table 1). Treatment failure was observed in 10.7% and 16.7% of cases treated with IM or IL Glucantime

Table 3. Association of demographic and clinical features of patients with the size of the lesion

Variables	≤ 10 mm	> 10 mm	P-value	Univariate OR (CI)	Multivariate OR (CI)	P-value
Sex						
Male	855 (48.6)	205 (55.9)	0.011	0.746 (-0.59-0.93)	0.73 (0.57-0.95)	0.021
Female	906 (51.4)	162 (44.1)				
Age (years)						
0-9	486 (27.6)	52 (14.2)	0.001	2.03 (-1.59-2.59)	1.12 (1.04-1.2)	0.001
10-19	340 (19.3)	58 (15.8)				
20-29	223 (12.7)	47 (12.8)				
30-39	276 (15.7)	67 (18.3)				
40-49	163 (9.3)	47 (12.8)				
50-59	139 (7.9)	49 (13.4)				
60-69	89 (5.1)	27 (7.4)				
70-79	32 (1.8)	13 (3.5)				
≥ 80	13 (0.7)	7 (1.9)				
Duration of disease (months)						
≤ 4	383 (21.7)	57 (15.5)	0.008	1.51 (-1.11-2.04)	1.49 (1.08-2.05)	0.013
> 4	1378 (78.3)	310 (84.5)				
Site of the lesion						
Face	540 (87.9)	74 (12.1)	0.001	0.571 (-0.43-0.75)	0.92 (0.67-1.27)	0.630
Body	1282 (84.8)	229 (15.2)	0.001	0.62 (-0.49-0.78)	0.69 (0.53-0.91)	0.008
Type of lesion						
Ulcerated	1670 (95)	363 (98.9)	0.003	0.46 (-0.27-0.76)	0.46 (0.27-0.76)	0.003
Non-ulcerated	87 (5)	4 (1.1)				
Number of lesions						
Single	1150 (65.3)	201 (54.8)	0.0001	1.55 (-1.23-1.95)	1.33 (1.05-1.69)	0.018
Multiple	611 (34.7)	166 (45.2)				
Failure	254 (14.4)	33 (9)				

combined with cryotherapy, respectively. No significant difference was reported between the type of treatment and treatment failure ($P = 0.09$) (Table 4).

Association between clinical features of the lesions and treatment failure

Univariate analysis revealed that treatment failure was most common in winter-onset ($P = 0.001$, OR = 1.37, CI = -1.22-1.54), face ($P = 0.001$, OR = 1.89, CI = -1.46-2.44), ulcerated ($P = 0.015$, OR = 0.533, CI = -0.32-0.88), smaller ($P = 0.006$, OR = 0.586, CI = 0.4-0.85), and long-lasting lesions ($P = 0.037$, OR = 1.42, CI = -1.02-1.99) (Table 4).

The association of treatment failure with winter-onset ($P = 0.001$, OR = 1.39, CI = 1.23-1.56), face ($P = 0.001$, OR = 1.86, CI = 1.38-2.49), ulceration ($P = 0.01$, OR = 0.51, CI = 0.30-0.85), small diameter ($P = 0.005$, OR = 0.57, CI = 0.38-0.84) and long-lasting lesions ($P = 0.01$, OR = 1.57, CI = 1.11-2.21) were validated by multivariate logistic regression analysis (Table 4).

DISCUSSION

This study revealed that overall treatment success and failure percentages were 86.5% and 13.5%, respectively. Furthermore, there was no significant difference between the type of treatment (IL or IM) and treatment failure, somewhat similar to the previous study in Kerman and dissimilar to a study in Yazd^{12,13}. The treatment failure rate in different regions of Iran varies from 7% to 59%¹⁴. Two studies in Pakistan demonstrated treatment failure of 19% and 45%^{15,16}.

In this study, most spring-onset lesions were solitary and responded better to treatment. In contrast, winter and autumn lesions demonstrated the highest percentage of treatment failure. These lesions usually are caused by sandflies at the highest levels of their activities in late spring or summer. Thus, they may be associated with the highest parasite load levels and greater diversity in *Leishmania* species, leading to less response to treatment¹².

In the current study, face lesions had a significantly

Table 4. Demographic and clinical features of patients associated with treatment failure

Variables	Cure	Failure	P-value	Univariate OR (CI)	Multivariate OR (CI)	P-value
Sex						
Male	911 (49.5)	149 (51.9)	0.443	0.907 (-0.70-1.16)		
Female	930 (50.5)	138 (48.1)				
Age (year)						
0-9	444 (24.2)	94 (32.8)	0.418	0.902 (-0.70-1.15)		
10-19	355 (19.3)	43 (15)				
20-29	226 (12.3)	44 (15.3)				
30-39	305 (16.6)	38 (13.2)				
40-49	191 (10.4)	19 (6.6)				
50-59	163 (8.9)	25 (8.7)				
60-69	101 (5.5)	15 (5.2)				
70-79	39 (2.1)	6 (2.1)				
≥ 80	17 (0.9)	3 (1)				
Season of onset						
Spring	529 (28.7)	50 (17.4)	0.001	1.37 (-1.22-1.54)	1.39 (1.23-1.56)	0.001
Summer	392 (21.3)	56 (19.5)				
Autumn	526 (28.6)	78 (27.2)				
Winter	394 (21.4)	103 (35.9)				
Site of the lesion						
Face	496 (80.8)	118 (19.2)	0.001	1.89 (-1.46-2.44)	1.86 (1.38-2.49)	0.001
Body	1293 (85.6)	218 (14.4)	0.047	1.33 (1-1.78)	0.95 (0.68-1.32)	0.77
Type of lesion						
Ulcerated	1750 (95.3)	283 (98.6)	0.015	0.533 (-0.32-0.88)	0.51 (0.30-0.85)	0.01
Non-ulcerated	87 (4.7)	4 (1.4)				
Size of the lesion (mm)						
≤ 10	1507 (81.9)	254 (88.5)	0.0006	0.586 (0.4-0.85)	0.57 (0.38-0.84)	0.005
> 10	1334 (18.1)	33 (11.5)				
Duration of disease (months)						
≤ 4	394 (21.4)	46 (16)	0.037	1.42 (-1.02-1.99)	1.57 (1.11-2.21)	0.01
> 4	1447 (78.6)	241 (84)				
Number of lesions						
Single	1178 (64)	173 (60.3)	0.22	1.17 (-0.90-1.15)		
Multiple	663 (36)	114 (39.7)				
Type of treatment						
Local treatment	270 (92.3)	1699 (94.1)	0.09	0.837 (-0.68-1.02)		
Systemic treatment	142 (7.7)	17 (5.9)				

higher rate of treatment failure than body lesions, similar to other studies¹². Previous studies revealed that most lupoid leishmaniasis cases were located in the face area. Regarding the chronic course of this type of leishmaniasis and higher resistance to therapy, less response of facial lesions can be expected¹². On the other hand, this study shows a higher percentage of larger lesions in the body area than in the face area.

In the present study, a higher percentage of treatment failure was observed in smaller lesions, probably due to early treatment of these lesions¹². Previous surveys hypothesized a positive correlation between lesions' diameter and immune

response activation. As a result, larger lesions are associated with more release of pro-inflammatory cytokines related to the T-helper 1 (Th1) immune pathway [tumor necrosis factor (TNF)- α , interferon (IFN)-gamma, and interleukin (IL)-2], resulting in phagocytosis and killing of *Leishmania* parasites. In contrast, smaller lesions may relate to less activation of the immune system and inflammatory cytokines; thus, a higher percentage of treatment failure can be expected with smaller lesions and facial lesions¹⁷.

Studies indicated higher treatment failure in early ulcerated lesions than in classic ulcerative ones. Furthermore, they showed less activation of the

immune system and production of inflammatory cytokines in early ulcerative lesions^{17,18}. The present study showed a higher percentage of treatment failure in ulcerated lesions than in non-ulcerated ones. On the other hand, most of the multiple lesions were ulcerated, which can lead to a higher percentage of treatment resistance.

The current study indicated that longer durations of lesions (> 4 months) had a significant association with treatment failure. Previous studies showed a higher percentage of resistance to therapy in patients who had delayed treatment^{7,12,18,19}. On the other hand, evidence shows a higher percentage of treatment resistance with early treatment of lesions (duration of less than 5 weeks)²⁰. It is assumed that early lesions are accompanied by less activation of the immune system against the parasite and less production of cytokines associated with Th1; therefore, early-developed lesions result in more resistance to treatment²⁰. This emphasizes the importance of choosing the right time to commence therapy post-lesion onset, probably after five weeks and definitely before four months.

Research revealed patients of younger age are associated with a significantly higher percentage of treatment failure^{17,21,22}. The current study demonstrated no significant difference between the age of the patients and treatment failure; however, patients younger than nine years old had a higher percentage of treatment failure than other age groups. Factors including less exposure to the parasite, lower serum concentration of antimony drug, administration of an inadequate amount of drug, and low compliance and adherence to treatment in children might contribute to more treatment failure in this age group^{20,23,24}.

Our study showed no significant difference between males and females in treatment response. Treatment failure was only slightly higher in males compared to females. Few studies indicated a higher rate of treatment failure in the male gender, probably due to differences in pharmacokinetics, hormonal issues, immune system response, and treatment adherence¹².

Although our study was performed retrospectively, it included many patients with ACL and attempted to determine factors leading to poor response to antimony treatment. The results of this study emphasize the importance of commencing therapy at an appropriate time. Furthermore, growing

numbers of ACL cases resistant to antimony therapy warrants seeking alternative treatments for recalcitrant cases.

CONCLUSION

Our study indicates that factors including winter onset, facial lesions, ulceration, small size, and long duration of leishmaniasis may predict poor treatment response. Multivariate logistic regression analysis confirmed predictive risk factors of large lesions including the male gender, longer duration of disease, ulcerated lesions, single lesions, and body lesions. Smaller lesions were observed more prevalently in patients younger than nine years old. Single lesions were observed mostly in spring-onset lesions and in the face. Multivariate logistic regression analysis confirmed predictive risk factors of multiple lesions as an age of younger than nine years, autumn onset, ulcerated lesions, longer duration of disease, and smaller lesions.

Conflict of interest: None declared.

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Epidemiological study of malignant melanoma in Kermanshah province of Iran in 2010-2016 based on the geographic information system

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Background: Malignant melanoma is a prevalent, offensive, and fatal cancer in developed countries. Most of our information is related to studies conducted in western countries. This study aims to evaluate demographic and clinical data of melanoma in the Kermanshah province of Iran.

Method: This was a descriptive study on data available in the Cancer Registry Center of Kermanshah, which includes 70 patients during eight years from 2010–2017. Clinical recognition of melanoma was based on American Joint Committee on Cancer criteria. Data were analyzed by SPSS 20 software and shown in ArcGIS (Version 10.7).

Results: Patients included 46 men (65.7%) and 24 women (34.3%) with a mean age of 60.49 ± 16.08 . The general prevalence of melanoma was 4.4 in every 1,000,000 persons annually. Most patients had skin type III (65.7%), indoor jobs (61.4%), and lived in the city (67.1%). Also, 35.7% had a trauma history, 2.8% had familial melanoma history, and 17.1% had other types of skin cancer. Extremities (51.4%), acral lentiginous melanoma (50.1%), Clark IV (61.4%), and inguinal lymph nodes (14.3%) were the most prevalent location, clinical type, pathological level, and involved lymph nodes, respectively.

Conclusion: Acral lentiginous melanoma and extremities involvement are prevalent in our region. Most patients go to doctors at an advanced level due to delays in referral, lack of follow-up by patients, lack of recognition at the initial care level, and lack of access to specialty centers. We recommend general instructions through media and holding special workshops for physicians for better familiarity with melanoma.

Keywords: cancer, melanoma, epidemiology, Kermanshah

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INTRODUCTION

Skin cancers are among the most prevalent cancers in humans, and one million cases of non-melanoma cancers are recognized in USA annually. In the Islamic Republic of Iran, skin cancer is the

most prevalent cancer, with a male-to-female ratio of 1.6, observed in the seventh and eighth decades of life ¹. The prevalence of different types of skin cancer has increased in recent decades, and since most of these cancers originate from prolonged exposure to sunlight, atmosphere changes and

especially change in ozone thickness along with changes in personal and social habits can justify this increase ^{1,2}.

Skin cancer is a major health problem. In most countries, different types of skin cancer are prevalent and are increasing rapidly. Despite decreased cancer in recent years, 3 to 5% is added to the amount of cancer annually with the possibility of prevention and treatment ³. In Iran, limited studies have been done, and the reported prevalence of different types of skin cancer is between 10 to 15 cases in every 10,000 persons annually ⁴. Disability, cosmetic problems, and high costs of this disease, especially its long-term form, cause this cancer to be a general health problem in most communities ⁵.

Basal cell carcinoma is the most prevalent malignant tumor in whites, and squamous cell carcinoma is the second most prevalent tumor of the skin, accounting for about 20% of cancers ⁶ and representing one of the deadliest cancers that originate from epidermis melanocytes ^{6,7}.

Squamous and basal cell carcinomas are the most prevalent types of cancer throughout the world and in Iran ^{8,9}. Malignant melanoma includes 4% of all cancer cases, but it is the cause of death in about 79% of types of cancer ¹⁰.

Malignant melanoma prevalence increased in the last decades in many parts of the world. The prevalence of this malignancy has tripled in the last 40 years, which has been more than any other malignancy ^{11,12}. Melanoma prevalence is lower in Middle-Eastern countries like Iran in comparison to Europe and USA ^{7,13}.

When melanoma turns malignant, it becomes resistant to treatment and apoptosis and causes metastasis in deep parts of the skin and internal organs such as the spleen, liver, and lymph nodes ¹⁴. In clinical terms, malignant melanoma is usually without symptoms. Although itching may be one of the initial signs of the disease, a change in the size or color of a pigmented lesion is the most important clinical manifestation ¹⁵. The most critical histologic finding is radial and vertical growth. Radial growth is the initial trend to grow in a horizontal direction within the epidermis and surface dermal layers, which lack metastasis ability. In vertical growth, melanoma grows into deep dermal layers and causes metastasis ¹⁶. Growth of an old mole, itching or pain in an old mole, formation of a new pigmented lesion, irregularity in

the edges of a pigmented lesion, and color change are among the most important signs of melanoma in clinical examinations ¹⁵⁻¹⁷.

Risk factors involved in the formation of cancer and especially malignant melanoma are sunlight, light skin, big congenital moles, immunosuppression, genetic polymorphisms, alcohol use, numerous freckles, genetic factors, and familial melanoma history ^{18,19}.

Although limited studies have been conducted on some epidemiologic characteristics and indices of malignant melanoma in Iran ^{7,13,20,21}, they are quite dated, and new information is needed for policy-making. Therefore, the current study was done to examine the epidemiology of malignant melanoma in the Kermanshah province of Iran during 2010–2017 to guide health policy-makers.

MATERIALS AND METHODS

Data resources

The study population of this descriptive study included melanoma patients from 14 cities of Kermanshah province: Eslamabad-e Gharb, Ravansar, Paveh, Javanrood, Sarpol-e-Zahab, Sahneh, Hersin, Dalahoo, Salas-e-Babajani, Gilan-e Gharb, Qasr-e Shirin, Kangavar, Sonqor, and Kermanshah City. The patients were visited at the Imam Reza Hospital and Haj Daei Dermal Specialty Center from April 2010 to February 2017. These patients were diagnosed with melanoma based on American Joint Committee on Cancer, and their information was registered in the Kermanshah University of Medical Sciences registry system. This study was approved by the Ethics Committee of the Kermanshah University of Medicine Sciences.

Population and scope of Kermanshah

Kermanshah, with an area of 25,009 km², is one of the biggest provinces in Iran. Kermanshah makes up 5.1% of Iran and is among the western provinces, sharing the border with Iraq. This province is limited in the north by Kurdistan, south by Lorestan and Ilam, east by Hamadan, and west by Iraq. Kermanshah City is the capital of Kermanshah province. The population of this province was 1,977,000 in 2015, with 71.1% of people living in urban areas (Figure 1).



Figure 1. Map of Iran showing Kermanshah (cities are shown in the inset)

Statistical analysis

Data were analyzed by using SPSS 20. The results were shown based on Kermanshah's geography in ArcGIS (Arc MAP, Version 10.7) software in order to provide more comprehensive results. All of the maps used in the paper were extracted from the software and were not obtained from other sources and articles.

RESULTS

This study included 70 patients, 46 men (65.7%) and 24 women (34.3%), aged 60.49 ± 16.08 . Melanoma prevalence in Kermanshah province was about 4.4 in every 1,000,000 persons annually.

Based on the results in Table 1 and the demographic and epidemiologic status of malignant melanoma patients, most cancer cases were in 2015 (18 cases, 25.7%), while the fewest were in 2016 (4 cases, 5.7%). Notably, 46 patients (65.7%) had skin type III, 18 patients (25.7%) had skin type II, and 6 patients (8.6%) had skin type IV. Moreover, 43 (61.4%) had indoor jobs and 47 (67.1%) lived in the city.

Twenty-five patients (35.7%) had trauma history, eighteen patients (25.7%) smoked, eight

patients (11.4%) had familial melanoma history, three patients (4.3%) had atypical moles, and two patients (2.8%) had freckles. Sixty-eight patients (97.1%) did not have an immune system dysfunction history or immunosuppressing drug use history, and the most prevalent anatomic site of lesions in patients was the extremities (36 cases, 51.4%), where 23 cases (32.8%) were observed in the lower extremities, and 13 cases (18.5%) were observed in the upper extremities (Table 1).

Two patients (2.85%) had familial melanoma history. Twelve patients (17.1%) had a history of other types of skin cancer, including basal cell carcinoma in 3 (4.3%), squamous cell carcinoma in 8 (11.4%), and both in 1 patient (1.4%). In addition, examining the pathologic files of the patients revealed that the physician recognized melanoma at the first, second, and third visit for 46 (65.7%) patients, 19 (27.1%) patients and 3 (4.3%) patients, respectively. Melanoma recognition was not stated only for 2 (2.8%) patients (Table 1).

The clinical examination of patients showed that among the clinical forms of acral lentiginous melanoma, superficial spreading, malignant lentigo, nodular, malignant melanoma without initial origin, and malignant melanoma on an atypical mole were observed in 35 (50.1%), 16

Table 1. Examining the demographic and epidemiologic status of malignant melanoma patients

Variable	Frequency (%)
Age	60.49 ± 16.08
Sex	
Male	46 (65.7%)
Female	24 (34.3%)
Skin type	
Type II	18 (25.7%)
Type III	46 (65.7%)
Type IV	6 (8.6%)
Occupational Status	
Indoor	43 (61.4%)
Outdoor	27 (38.6%)
Location	
Urban	47 (67.1%)
Rural	23 (32.9%)
Risk factor	
Trauma	25 (35.7%)
Smoking	18 (25.7%)
History of melanoma	8 (11.4%)
Atypical mole	3 (4.3%)
Weak immune system	2 (2.8%)
Freckles	2 (2.8%)
Anatomical location of the infection	
Extremities	36 (51.4%)
Head and neck	28 (40%)
Trunk	6 (8.6%)
Family history of melanoma	2 (2.8%)
Types of skin cancers	
Basal cell carcinoma	8 (11.4%)
Squamous cell carcinoma	3 (4.3%)
Basal cell and squamous cell carcinoma	1 (1.4%)
Diagnostic accuracy	
As the first diagnosis	46 (65.7%)
As a second diagnosis	19 (27.1%)
As a third diagnosis	3 (4.3%)
Lack of diagnosis	2 (2.8%)

(22.8%), 10 (14.3%), 7 (10%), 2 (2.8%), respectively (Table 2). Involvement of inguinal lymph nodes was observed in 10 patients (14.3%), neck nodes in 3 patients (4.3%), and axillary nodes in 2 patients (2.8%). Pathologic examination of lesions revealed that Clark level II, III, IV, and V were observed in 2 (2.9%), 16 (22.8%), 43 (61.4%), and 9 (12.8%) patients, respectively (Table 2).

Based on results obtained from ArcGIS software and survey conducted from 2010 to 2016, Figures 2 to 8 show that Kermanshah City had the highest frequency and percent in all mentioned years: 2010 (60%), 2011 (78.5%), 2012 (77.5%), 2013 (85.7%), 2014 (90.95), 2015 (82.3%), and 2016 (50%). Moreover, most cases after Kermanshah City were in Paveh

Table 2. Examining the clinical status of malignant melanoma patients

Variable	Frequency (%)
Clinical type of acral lentiginous melanoma	
Surface extension	35 (50.1%)
Malignant lentigo	16 (22.8%)
Nodular	10 (14.3%)
Malignant melanoma without primary origin	7 (10%)
Malignant melanoma on an atypical mole	2 (2.8%)
Pathologic status according to Clark criteria	
Level II	2 (2.9%)
Level III	16 (22.8%)
Level IV	43 (61.4%)
Level V	9 (12.8%)
Involvement of lymph nodes	
Inguinal	10 (14.3%)
Cervical	3 (4.3%)
Axillary	2 (2.8%)
Death rate over a year	18 (25.7%)

(92.5%) and Eslamabad-e Gharb (12.5%) in 2016, and Kangavar (13.3%) in 2010 (Figures 2–8).

DISCUSSION

Results showed that most of our patients were males (1:9 ratio). In Hanjani *et al.*⁷, Ferdowsi¹³, and Naraqi²⁰ studies, the male-to-female ratio was 2, 1, and 1/2, respectively. The high prevalence of melanoma in men is related to more contact with environmental risk factors like sunlight and other potential factors like trauma.

In most studies^{6,7,12,13,19-21}, older adults develop melanoma, which is consistent with our study. It seems that the cumulative effects of environmental risk factors¹² and decreased function of immunity (immune senescence) have an important role in the formation of melanoma in older adults²².

Although melanoma is usually observed in white people²³, most of our patients were of skin type III. This can be because melanoma is a malignancy related to environmental and genetic factors²⁴. Moreover, most people in our region are of skin type III⁹.

Most of our patients lived in urban areas and had indoor jobs. In addition, acral melanoma was the prevalent form of clinical melanoma in our patients. These results reveal the possibility of risk factors other than sunlight in the pathogenesis of melanoma²⁵.

Trauma was the most prevalent risk factor registered in our patients. Moreover, the extremities

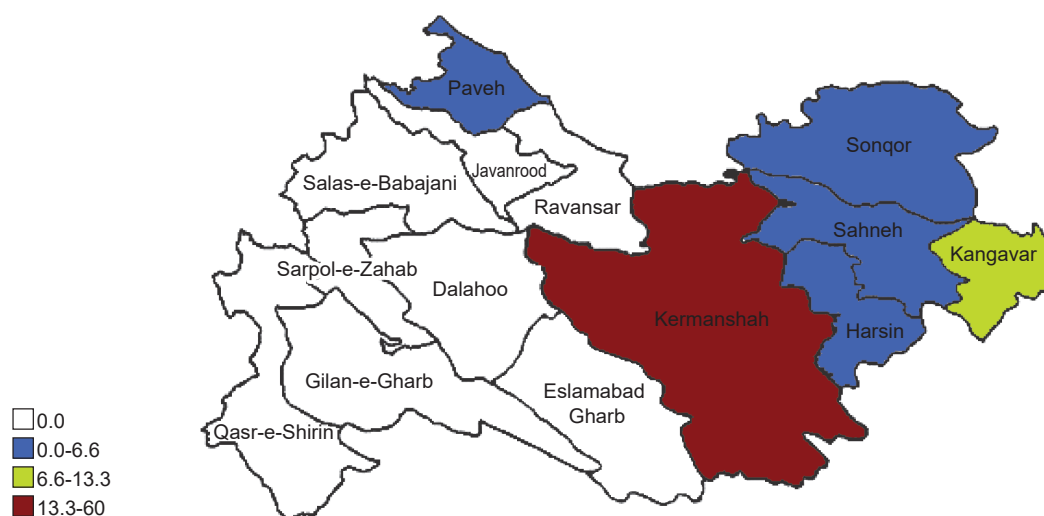


Figure 2. Percent of malignant melanoma cases in cities of Kermanshah province in 2010 based on ArcGIS map

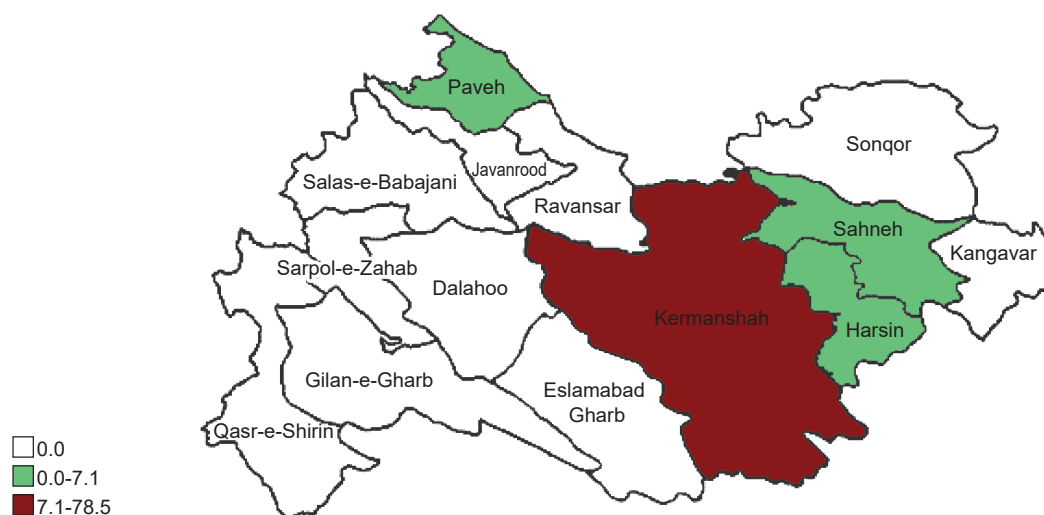


Figure 3. Percent of malignant melanoma cases in cities of Kermanshah province in 2011 based on ArcGIS map

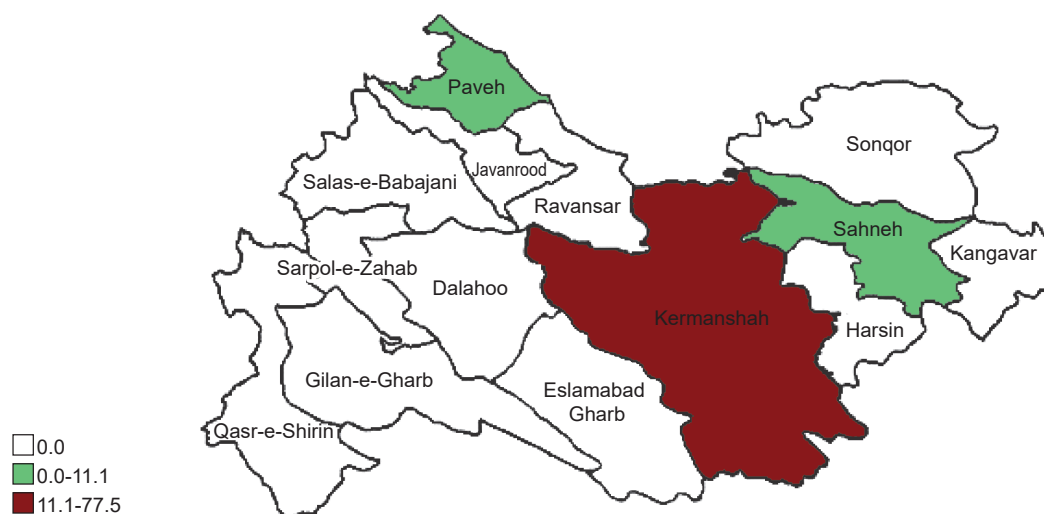


Figure 4. Percent of malignant melanoma cases in cities of Kermanshah province in 2012 based on ArcGIS map



Figure 5. Percent of malignant melanoma cases in cities of Kermanshah province in 2013 based on ArcGIS map



Figure 6. Percent of malignant melanoma cases in cities of Kermanshah province in 2014 based on ArcGIS map

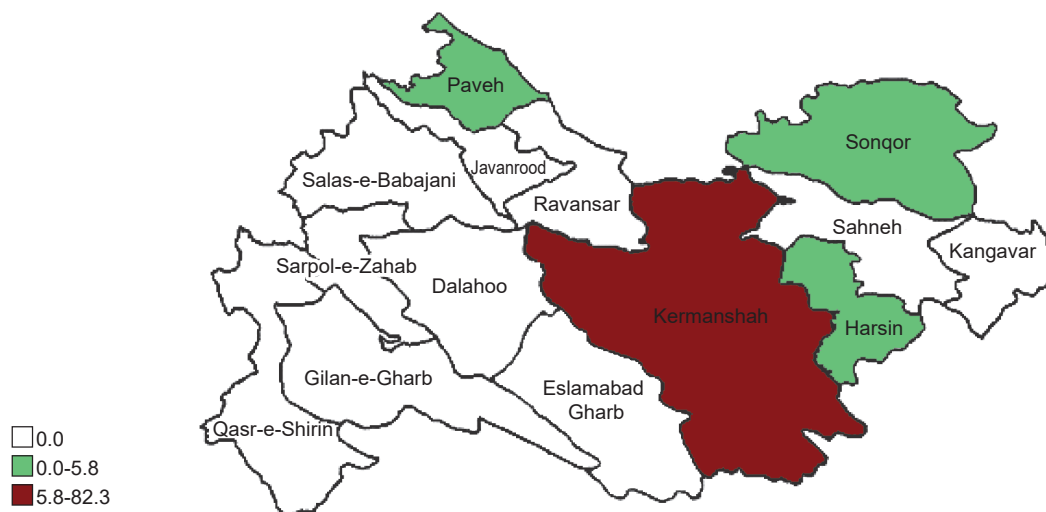


Figure 7. Percent of malignant melanoma cases in cities of Kermanshah province in 2015 based on ArcGIS map

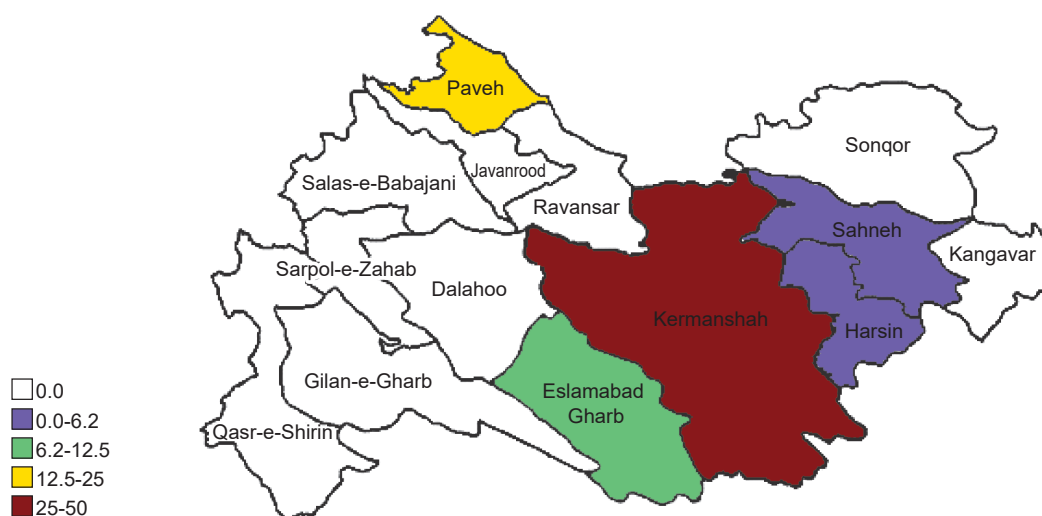


Figure 8. Percent of malignant melanoma cases in cities of Kermanshah province in 2016 based on ArcGIS map

(especially the lower extremities) were the prevalent places of lesions. Strong evidence from East Asia reveals trauma is accompanied by acral lentiginous melanoma, especially in the lower extremities ²⁶⁻²⁸.

Although environmental factors such as sunlight, genetics, internal factors, and other unknown factors play a role in the co-occurrence of melanoma and other skin cancers like squamous and basal cell carcinoma ^{29,30}, co-occurrence of basal cell carcinoma was more prevalent in the current study (two times), which can be due to similar pattern of contact with sunlight in basal cell carcinoma and melanoma patients ³¹.

Familial melanoma history was observed in a few patients (2.8%). Familial melanoma prevalence is about 3–15%; therefore, melanoma is a heterogeneous disease, and this disease is inherited in a multifactorial polygenic form despite its presence in second and third-generation relatives ³².

Although dermatologists use the manual dermatoscope as a standard for selecting atypical dermal lesions for biopsy and although computer software cannot be a reliable alternative to the experience of a physician [33], the recognition accuracy of dermatologists who done biopsy was 97.1%, with most cases being recognized on the first visit (65.7%). Thus, dermatologists in our region have good recognition accuracy despite the low prevalence of melanoma.

The prevalence of acral lentiginous melanoma is estimated at 2–3% of all melanoma cases in

American whites ³⁴. However, this clinical form is the most prevalent melanoma form in Africa, East Asia, and Hispanics ^{26-28,35}. Hanjani *et al.* ⁷, in a study in south Iran, cited acral lentiginous melanoma as the prevalent clinical form ^{7,13,20,21}. In line with our results, it appears that melanoma patients in Africa, East Asia, Latin America, and our region have similar clinical patterns. Therefore, older adults with pigmented lesions in the acral area should be assessed for melanoma, especially through a histopathology study.

Tumor thickness is one of the important prognostic factors for this disease. Early recognition can result in recognizing the disease with a low Clark level, which improves disease prognosis ³⁶. Safaei Naraqi *et al.* ²⁰, in a study on 47 melanoma patients, showed that 40.4% of patients were at Clark level III. Moreover, 61.4% of patients showed Clark level IV. Since acral lentiginous melanoma has a longer radial growth period, a high Clark level reveals the disease's long-term history and poor prognosis ^{35,36}.

In Eftekhari *et al.*'s review of melanoma cancer registration data from Razi Hospital (Tehran), the most frequent location for melanoma was the lower extremity (38.9%). The most frequent subtype for melanoma based on histopathology was acral lentiginous melanoma (38.3%). There was a statistically significant difference between histological subtypes of melanoma and Breslow thickness ³⁷.

In a study conducted in south Iran ⁷, most

melanoma patients came to the doctor at an advanced level of disease, mostly with problems in inguinal lymph nodes since acral lentiginous melanoma has a poor prognosis.

The clinical form of acral lentiginous melanoma and the involvement of extremities are prevalent in our region, as in Africa, East Asia, and Latin America. Most patients come to doctors at advanced levels of disease due to delayed referrals, lack of follow-up by the patient, lack of recognition at the initial care level, or lack of access to specialty centers. We recommend instructing society through public media and holding specialty workshops to familiarize physicians with melanoma. It is recommended to conduct cohort studies in several centers with more patients and register more information about patients in cancer registry centers.

CONCLUSION

The clinical form of acral lentiginous melanoma and the involvement of extremities are prevalent in our region. Most patients go to doctors at an advanced level due to delayed referrals, lack of follow-up by patients, lack of recognition at the initial care level, and lack of access to specialty centers. We recommend educating the public through media and holding special workshops for physicians for better familiarity with melanoma.

Abbreviation

GIS: Geographic Information System

Conflict of interest: None declared.

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Relationship between citation metrics and the characteristics of article titles in dermatology journals

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Background: Evidence shows that article titles might affect citation metrics. This study aimed to evaluate the association between selected citation metrics and the title characteristics in dermatology journals.

Methods: We enrolled 305 reviews and original articles published during 2016 from four dermatology journals consisting of the "Journal of the American Academy of Dermatology," "Journal of the European Academy of Dermatology and Venereology," "Indian Journal of Dermatology, Venereology and Leprology," and "International Journal of Dermatology" using a stratified and simple random sampling method. The list of articles was extracted from Scopus; then, the title characteristics were reviewed. Moreover, we extracted the citation metrics, including the citation count, Field-Weighted Citation Impact (FWCI), and citation benchmarking percentile of the articles until the end of October 2021 using Scopus. For statistical analysis, we used Stata software version 14.2.

Results: Overall, 239 (78.36%) original and 66 (21.64%) review articles were included. The citation count and FWCI significantly and positively correlated with the number of words, characters, and punctuation marks in the titles. By adjusting the covariates, linear logistic regression showed that the title length and the presence of acronyms in the title were the most effective factors in increasing the citation count and FWCI of the articles.

Conclusion: Using longer titles and including acronyms in the titles may help augment the citation of articles in dermatology journals.

Keywords: scientometrics, dermatology journals, title, citation

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INTRODUCTION

The article title is the first thing that any researcher will read. Therefore, it must be contemplated well to make an article stand out from millions of published articles. Researchers often try to obtain principal information about an article from a quick glance at the title. In addition, the article title is the first tool used to compare

and screen articles among a pool of scientific documents ¹⁻³. Furthermore, the title of an article is an instrument used by databases, indexing systems, libraries, journals, etc., to categorize them into related fields ⁴. Therefore, selecting a suitable and attractive article title could be the simplest way to increase article visibility.

The citation of articles is one of the most important indicators that researchers and policymakers

consider in any field of research, representing one of the most straightforward tools to judge the quality of an article. Moreover, citing a journal's articles affects that journal's impact factor. For researchers, citations lead to receiving grants, awards, and promotions from academic institutions during certain competitions and festivals^{5,6}. Universities and research centers also push researchers to publish high-quality articles with a high chance of receiving citations. Therefore, many universities prioritize studying factors effective in increasing the citation rate⁷.

Various indices have been considered for evaluating the visibility and importance of articles and article citations. These metrics allow article readers to evaluate the impact of citations and the degree of community participation around an article⁸. In this regard, the citation count indicates how many times a publication has been cited. Moreover, the Field-Weighted Citation Impact (FWCI) shows how well this document is visited and cited compared with similar documents. In this criterion, a value greater than 1 means citing the document more than expected⁹⁻¹¹. Furthermore, the citation benchmarking percentile demonstrates how citations received by the document compare with the average for similar documents^{12,13}. Finally, the Topic Prominence Percentile (TPP) is another index for evaluating an article's momentum according to its topic. This parameter is calculated by SciVal^{11,14}.

Researchers have so far discovered a number of factors that affect citation counts. The four main factors (domains) that affect the number of citations to an article are the article's authors, journal, study field, and characteristics¹⁵. Citation counts are affected by the first and last authors' rank, name of the first author's university mentioned in affiliations, country of residence of the first author, quality or ranking of the university where the authors work, number of organizational affiliations mentioned in articles, and number of citations of the first and last authors of the articles^{7,16,17}.

The citation count may also be affected by the characteristics of the article title. For instance, evidence revealed that longer titles often received more citations, and this association was more prominent in journals with higher impact factors¹⁸. However, others showed that the shorter the length, the greater the citations¹⁹. Moreover, according

to the literature, the title type and the inclusion of the year of study, study design, acronyms, punctuation marks, etc., could predict the citation rate^{1,7,20}, though findings have been inconsistent.

To the best of our knowledge, the relationship between the title characteristics of dermatology journal articles and their citation indices is yet to be examined. Therefore, this study aimed to address this gap in the literature.

PARTICIPANTS AND METHODS

Study design and sample size

This cross-sectional study was conducted on articles published in 2016 in four general English-language dermatology journals:

1. Journal of the American Academy of Dermatology (from USA) with 477 articles
2. Journal of the European Academy of Dermatology and Venereology (from Europe) with 246 articles
3. Indian Journal of Dermatology, Venereology and Leprology (from Asia) with 59 articles
4. International Journal of Dermatology (An independent journal from the International Association of Dermatology) with 328 articles

The Scopus search results were limited to "Articles" and "Reviews" in terms of the document type. Following a similar article²⁰, the minimum sample size of 304 was estimated by considering a first-type error (alpha) of 0.05, a power of 0.8, and a correlation coefficient between citation counts and title length of -0.16.

Data collection

Stratified and random cluster sampling was used to select articles from each journal. In this regard, we extracted the "articles" and "reviews" of 2016 from each journal separately in a the .CVS file format. After reviewing the titles in the list, if the documents were incorrectly categorized as "articles" and "reviews," they were excluded from the study. Then, four random numbering lists made by SPSS software version 25 separately for each journal were used to enroll articles into the study.

The authors read the titles one by one to define the title type: descriptive, informative, or question. Then, the title was evaluated for the number of

words, characters with and without spaces, simple or compound status, mentioning of study details (design, year, and place), and punctuation marks. Microsoft Word version 2016 was used to assess the number of words and characters. We recorded all data in a researcher-made data collection form.

Data related to citation indices until the end of October 2021 were extracted from the Scopus database. The measures included the citation count, self-citation count, FWCI, citation benchmarking percentile, and TPP. To control the biases made by self-citation, the number of self-citations was subtracted from the actual number of citations in the additional analysis. The FWCI and citation benchmarking percentile were evaluated in both continuous numerical and categorical data. In this regard, the FWCI was divided into two categories consisting of < 1 and ≥ 1 , according to its well-known cut-off point, and the citation benchmarking percentile was divided into two categories based on < 75 and ≥ 75 as a cut-off point to define the top-quartile articles as highly cited ones. P-values equal to and less than 0.05 were considered significant.

Statistical analysis

We used Stata software version 14.2 (StataCorp LLC, 4905 Lakeway Drive, College Station TX77845, USA) for statistical analyses. We used the frequency and percentage to describe categorical data and the mean, standard deviation, and median to present quantitative data. In addition, we used the independent t-test, analysis of variance (ANOVA), chi-squared test, and Pearson correlation to find the association between the variables. The mean difference (MD), standardized mean difference (SMD), and odds ratio (OR) with a 95% confidence interval (CI) were used to estimate the effect size of variables affecting citation metrics. Furthermore, based on the search in similar studies, we considered the potentially influential variables as predictors and ran a linear regression model using the enter method. We entered factors such as compound title type and mentioning of the study design, study place, and acronyms in the title into the regression model, accompanied by some characteristics of articles that probably affect this model, including the article type (reviews vs. original research), level of accessibility (open access vs. non-open access), and topic prominence percentile (defined as an

indicator that reveals the current momentum and encouragement of a topic according to Scopus).

Ethical considerations

The protocol of this study was approved by the

Table 1. Characteristics of the articles and article titles enrolled in the study

Variable	Frequency (%) N= 305
Journal name	
Journal of the American Academy of Dermatology	119 (32.02)
International Journal of Dermatology	92 (30.16)
Journal of the European Academy of Dermatology and Venereology	75 (24.59)
Indian Journal of Dermatology, Venereology and Leprology	19 (6.23)
Open access article	
Yes	69 (22.62)
No	236 (77.38)
Article type	
Original	239 (78.36)
Review	66 (21.64)
Title type	
Descriptive	241 (79.02)
Informative	49 (16.07)
Question	15 (4.92)
Compound title	
Yes	169 (55.41)
No	136 (44.59)
Presence of year (s) of study	
Yes	3 (0.98)
No	302 (99.02)
Presence of place of study	
Yes	48 (15.74)
No	257 (84.26)
Presence of study design	
Yes	100 (32.79)
No	205 (67.21)
Presence of acronyms	
Yes	85 (27.87)
No	220 (72.13)
Presence of at least one punctuation mark	
Yes	239 (78.36)
No	66 (21.64)
Type of punctuation mark	
Colon (:)	156 (51.15)
Hyphen (-)	113 (37.05)
Parenthesis ()	64 (20.98)
Comma (,)	45 (14.75)
Question mark (?)	15 (4.92)
Slash (/)	5 (1.64)
Quotation mark (' ')	3 (1.98)
Semicolon (;)	1 (33)

Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Ethics Code: IR.SUMS.REC.1400.087).

RESULTS

Characteristics of the articles and their titles

Overall, we enrolled 305 articles, including 239 (78.36%) original articles and 66 (21.64%) review articles from four selected dermatology journals. In this regard, 236 (77.38%) articles were subscription-based, and 69 (22.62%) were open-access articles. Moreover, 241 (79.02%) titles were of the descriptive type, followed by informative and question types with frequencies of 49 (16.07%) and 15 (4.92%), respectively. Only 100 (32.79%) and 48 (15.74%) articles mentioned the type and place of the study in the title, respectively. Additionally, the colon was the most punctuation mark the authors used in the titles. In addition, 169 (55.41%) titles were of compound type. The median title word count

was 14 (IQR: 10, 18). Tables 1 and 2 present the characteristics of the articles studied and their titles.

Relationship between citation metrics and title characteristics

Table 3 demonstrates that the article title word and character counts (with and without spaces) had weak to moderate positive correlations with the total citation count, citation count excluding self-citations, FWCI, and citation benchmarking percentile.

Table 4 shows that the mean differences of both total citation counts and citation counts after excluding the authors' self-citations were statistically significant in titles including at least an acronym in comparison with those without an acronym (MD = 9.85, 95% CI: 2.95 to 16.75, $P = 0.027$ and MD = 8.45, 95% CI: 0.71 to 16.19, $P = 0.033$, respectively). The presence of the study design in the title was associated with higher citation counts before (MD = 6.49, 95%CI: 0.20 to 13.07, $P = 0.057$)

Table 2. Measures of central tendency and dispersion of the length of the titles, number of punctuation marks in titles, and citation metrics of the selected articles published in dermatology journals

Variables	Mean $\pm$ SD	Median (IQR)	Min	Max
Title words count	14.22 $\pm$ 5.35	14 (10, 18)	1	29
Title characters count (with spaces)	106.45 $\pm$ 37.76	103 (80, 133)	14	228
Title characters count (without spaces)	93.21 $\pm$ 32.76	91 (70, 116)	13	201
Total citation count	21.46 $\pm$ 27.76	14 (7, 27)	0	263
Number of punctuation marks in the title	1.619 $\pm$ 1.45	1 (1, 2)	0	7
Self-citation excluded citation count	18.91 $\pm$ 24.85	11 (5, 23)	0	232
Field-Weighted Citation Impact (FWCI)	2.04 $\pm$ 3.10	1.31 (0.58, 2.44)	0	34.19
Benchmarking percentile	71.75 $\pm$ 21.62	78 (57, 90)	0	99

SD = standard deviation; IQR = interquartile range; min = minimum; max = maximum

Table 3. Correlation of title length and number of punctuation marks with citation metrics

Variable	Total citation count	Citation count after self-citation exclusion	Field-Weighted Citation Impact (FWCI)	Citation benchmarking percentile
Title words count				
Pearson r	0.14	0.12	0.23	0.11
P-value	0.017*	0.032*	< 0.001*	0.054
Title characters count (with spaces)				
Pearson r	0.12	.10	0.20	0.10
P-value	0.043*	0.075	< 0.001*	0.073
Title characters count (without spaces)				
Pearson r	0.11	0.10	0.20	0.10
P-value	0.047*	0.082*	< 0.001*	0.084
Number of punctuation marks in the title				
Pearson r	0.19	0.19	0.21	0.07
P-value	0.001*	0.001*	< 0.001*	0.240

* $P \leq 0.05$

Table 4. Association between some categorized characteristics of the title of articles in dermatology journals and the citation count

Characteristic	N	Total citation count			Citation count after excluding self-citations				
		Mean ± SD	MD (95% CI)	P-value	SMD (95% CI)	Mean ± SD	MD (95% CI)	P-value	SMD (95% CI)
Title type									
Descriptive	241	22.42 ± 29.96	Base		Base	19.80 ± 26.74	Base		Base
Informative	49	18.45 ± 18.32	-3.97 (-14.69 to 6.74)	0.480	-0.22 ^b (-0.53 to 0.09)	16.18 ± 17.05	-3.62 (-13.20 to 5.96)	0.446	-0.21 ^b (-0.52 to 0.10)
Question	15	15.87 ± 10.72	-6.56 (-24.75 to 11.63)		-0.61 ^b (-1.17 to -0.03)	13.46 ± 8.76	-6.33 (-22.61 to 9.94)		-0.72 ^b (-1.30 to -0.13)
Compound title									
No	136	19.65 ± 27.64	3.28 (-3.07 to 9.57)	0.306	-0.12 ^a (-0.34 to -0.11)	17.15 ± 24.90	3.17 (-2.46 to 8.80)	0.269	-0.13 ^a (-0.10 to 0.35)
Yes	169	22.92 ± 27.85				20.32 ± 24.78			
Presence of the place of study in title									
No	257	22.47 ± 28.84	-6.38 (-14.96 to 2.19)	0.068	-0.31 ^b (-0.62 to 0.004)	19.76 ± 25.86	-5.43 (-11.51 to 0.65)	0.079	-0.30 ^d (-0.61 to 0.01)
Yes	48	16.08 ± 20.48				14.33 ± 18.01			
Presence of the study design in title									
No	205	19.35 ± 27.65	6.49 (-0.20 to 13.07)	0.057	0.23 ^a (-0.01 to 0.47)	16.96 ± 24.85	5.94 (0.01 to 11.88)	0.049*	0.24 ^a (0.00 to 0.48)
Yes	100	25.79 ± 27.61				22.91 ± 24.48			
Presence of acronyms in title									
No	220	18.72 ± 22.01	9.85 (2.95 to 16.75)	0.027*	0.45 ^b (-.70 to -0.19)	16.55 ± 19.97	8.45 (0.71 to 16.19)	0.033*	0.42 ^b (0.17 to 0.68)
Yes	85	28.56 ± 38.15				25.01 ± 33.80			
Presence of punctuation marks in title									
No	66	19.09 ± 20.25	3.02 (4.57 to 10.63)	0.337	0.15 ^b (-0.13 to 0.42)	16.22 ± 18.73	3.43 (-2.24 to 9.09)	0.234	0.18 ^b (-0.09 to 0.45)
Yes	239	22.12 ± 29.50				19.65 ± 26.27			

SD = standard deviation; MD = mean difference; * $P \leq 0.05$; a. Cohen's d; b. Glass's delta

and after (MD = 5.94, 95% CI: 0.01 to 11.88, $P = 0.049$) excluding self-citations. Furthermore, the mean total citation count and citation count after excluding self-citations were significantly lower in articles that included the study location in the title (MD = -6.38, 95%CI: -14.96 to 2.19, $P = 0.068$, and MD = -5.43, 95%CI: -11.51 to 0.65, $P = 0.079$, respectively). Table 5 indicates that the behaviors of the FWCI and citation benchmarking percentile were similar to those of self-citation-excluded citation counts when an acronym was added or the study design was clarified in the title of the articles.

On the other hand, Table 6 reveals that 76 (76%) titles included the study design, and 65 (76.47%) titles contained at least one acronym. Articles with a title including the study design or at least one acronym were categorized in the FWCI > 1 group about 2.84 and 2.76 times more, respectively, in comparison with those titles that lacked these features ($P < 0.001$, OR = 2.84, 95%CI: 1.67 to 4.85 and $P < 0.001$, OR = 2.76, 95%CI: 1.56 to 4.86, respectively). Likewise, the majority of articles with titles that included the study design or at least one acronym were categorized into the first quartile of the citation benchmarking percentile index ($P = 0.005$, OR = 2.03, 95%CI: 1.24 to 3.32 and $P = 0.003$, OR = 2.19, 95%CI: 1.30 to 3.70, respectively). Although there was no association between the presence of at least one punctuation mark in the article title with citation metrics, there was a positive correlation between the number of punctuation marks used in article titles with citation counts and FWCI indices, as shown in Table 3.

Linear regression model to determine factors affecting the citation metrics

After adjusting the covariates, the total citation count and FWCI had statistically significant positive correlations with the title word count and the presence of acronyms in the titles. Furthermore, the review type of articles, open-access type of articles, and TPP could significantly affect the citation rate and FWCI. Moreover, according to this model, it seems that articles with descriptive titles received considerably more citations. Table 7 presents more details about linear logistic regression of the factors related to the article title that might affect the citation metrics of articles in dermatology journals.

DISCUSSION

This study showed that inserting at least one acronym and clarifying the study design in the title of dermatology articles are associated with receiving more citations, thus raising the FWCI and citation benchmarking percentile indices. Also, increasing the title length amplified the chance of receiving citations; however, these correlations were weak to moderate. On the contrary, clarifying the study location in the titles was a negative factor in receiving citations.

Falahati Qadimi Fumani *et al.* showed that article citation counts did not correlate with the title length²¹. Some documents claimed that articles with shorter titles, on average, often received more citations. They argued that shorter titles might be simpler to read, making them more citable^{20,22,23}. On the contrary, the study of Habibzadeh *et al.* demonstrated that the longer the title, the higher the citation count in general medicine and multidisciplinary scientific journals, and this relationship was statistically significant¹⁸. Similarly, Jacques *et al.*'s study revealed that the articles with higher word count often received significantly more citations²⁴. Our results also revealed that articles with longer titles often received more citations in dermatology journals, which could increase the FWCI and citation benchmarking percentiles. This correlation may be due to some factors; for example, longer titles might be more informative and include keywords or repetitive words, which make the article more findable, searchable, and attractive to read and cite.

Although our study revealed that articles with compound titles and those with at least one punctuation mark were cited more than simple (one-part) titles, these differences were insignificant. However, we found that if there were punctuation marks in the title, and the number of punctuation marks increased, the number of citations would increase. Further, we found that the colon and then the hyphen were the most punctuation marks that the authors used in the titles. Otherwise, Jacques *et al.*'s study demonstrated a positive correlation between the articles' citation count and the presence of a colon in the title, as well as choosing a compound title instead of a simple type²⁴. Likewise, Shekhani *et al.* reported a strong relationship between the presence of punctuation

Table 5. Association between some categorized characteristics of the title of articles in dermatology journals and their Field-Weighted Citation Impact (FWCI) and citation benchmarking percentile

Characteristics	N	Field-Weighted Citation Impact (FWCI)				Citation benchmarking percentile			
		Mean ± SD	MD (95% CI)	P-value	Effect size (95% CI)	Mean ± SD	MD (95% CI)	P-value	Effect size (95% CI)
Title type									
Descriptive	241	2.15 ± 3.40	Base		Base	71.98 ± 21.68	Base		Base
Informative	49	1.70 ± 1.61	-0.45 (-1.65 to 0.75)	0.47	-0.28 ^b (-0.59 to 0.03)	70.80 ± 22.67	-1.19 (-9.55 to 7.17)	0.933	-0.054 ^a (-0.36 to 0.25)
Question	15	1.40 ± 1.01	-0.76 (-1.29 to -2.78)		-0.74 ^b (-1.32 to -0.14)	71.06 ± 18.24	-0.92 (-15.11 to 13.28)		-0.04 ^a (-0.56 to 0.48)
Compound title									
No	136	1.90 ± 3.15	0.25 (-0.45 to 0.96)	0.483	0.08 (-0.15 to 0.31)	71.76 ± 21.63	-0.02 (-4.92 to 4.89)	0.994	0.001 ^a (-0.23 to 0.23)
Yes	169	2.15 ± 3.07				71.74 ± 21.67			
Presence of the place of study in title									
No	257	2.10 ± 3.21	-0.37 (-1.17 to 0.43)	0.364	-0.15 ^b (-0.46 to 0.16)	72.27 ± 21.84	-3.31 (-9.10 to 3.38)	0.331	-0.15 ^a (-0.46 to 0.16)
Yes	48	1.73 ± 2.43				68.96 ± 20.39			
Presence of the study design in title									
No	205	1.80 ± 3.09	0.72 (-0.09 to 1.47)	0.056	0.23 ^a (-0.01 to 0.47)	69.65 ± 21.54	6.40 (1.25 to 11.55)	0.015*	0.30 ^a (0.06 to 0.54)
Yes	100	2.53 ± 3.09				76.05 ± 71.84			
Presence of acronyms in title									
No	220	1.69 ± 2.20	1.25 (0.22 to 2.28)	0.018*	0.57 ^b (0.31 to 0.82)	69.53 ± 21.36	7.97 (2.60 to 13.33)	0.004*	0.37 ^a (0.12 to 0.63)
Yes	85	2.94 ± 4.60				77.49 ± 21.32			
Presence of punctuation marks in title									
No	66	1.68 ± 1.33	0.47 (-0.08 to 1.01)	0.092	0.35 ^b (-0.07 to 0.63)	73.03 ± 19.15	-1.63 (-7.56 to 4.29)	0.587	-0.076 ^a (-0.35 to 0.20)
Yes	239	2.14 ± 3.43				71.39 ± 22.27			

SD = standard deviation; MD = mean difference; * $P \leq 0.05$; a. Cohen's d; b. Glass's delta

Table 6. Association between some categorized characteristics of the title of articles in dermatology journals and their Field-Weighted Citation Impact (FWCI) and citation benchmarking percentile using the indices' cut-off points

Characteristics	Field-Weighted Citation Impact (FWCI)				Citation benchmarking Percentile			
	FWCI < 1 (N = 121) No. (%)	FWCI ≥ 1 (N = 184) No. (%)	P-value	Odds Ratio (95% CI)	Benchmarking < 75 (N = 142) No. (%)	Benchmarking ≥ 75 (N = 163) No. (%)	P-value	Odds Ratio (95% CI)
Title type								
Descriptive	93 (38.59)	80.43 (61.41)		Base	109 (45.23)	132 (54.77)		Base
Informative	21 (42.86)	28 (57.14)	0.729	0.84 (0.45 to 1.56)	24 (48.98)	25 (51.02)	0.503	0.86 (0.47 to 1.59)
Question	7 (46.67)	4.35 (53.33)		0.72 (0.25 to 2.05)	9 (60.00)	6 (40.00)		0.55 (0.19 to 1.59)
Compound title								
No	55 (40.44)	81 (59.56)		1.06 (0.66 to 1.68)	63 (46.32)	73 (53.68)	0.941	0.98 (0.63 to 1.55)
Yes	66 (39.05)	103 (60.95)	0.805		79 (46.75)	90 (53.25)		
Presence of the place of study in title								
No	99 (38.52)	158 (61.48)		0.74 (0.40 to 1.38)	117 (45.53)	140 (54.47)	0.403	0.77 (0.41 to 1.43)
Yes	22 (45.83)	26 (54.17)	0.342		25 (52.08)	23 (47.92)		
Presence of the study design in title								
No	97 (47.32)	108 (52.68)	< 0.001*	2.84 (1.67 to 4.85)	107 (52.20)	98 (47.80)	0.005*	2.03 (1.24 to 3.32)
Yes	24 (24.00)	76 (76.00)			35 (35.00)	65 (65.00)		
Presence of acronyms in title								
No	101 (45.91)	119 (54.09)	< 0.001*	2.76 (1.56 to 4.86)	114 (51.82)	106 (48.18)	0.003*	2.19 (1.30 to 3.70)
Yes	20 (23.53)	65 (76.47)			28 (32.94)	57 (67.06)		
Presence of punctuation marks in title								
No	24 (36.36)	42 (63.64)	0.535	0.84 (0.48 to 1.47)	30 (45.45)	36 (54.55)	0.839	0.94 (0.55 to 1.63)
Yes	97 (40.59)	142 (59.41)			112 (46.86)	127 (53.14)		

* P ≤ 0.05; CI = confidence interval

Table 7. Association between the title characteristics of the articles and citation metrics after controlling the probable covariates by linear regression

Variables	Total citation count			Citation count without self-citations			Field-Weighted Citation Impact (FWCI)			Citation benchmarking percentile		
	Beta (SE) ^a	SBC ^b	P-value	Beta (SE)	SBC	P-value	Beta (SE)	SBC	P-value	Beta (SE)	SBC	P-value
Title word count	0.68 (0.31)	0.13	0.031*	0.55 (0.28)	0.12	0.055	0.11 (0.04)	0.19	0.002*	0.25 (0.25)	0.06	0.306
Compound title	0.86 (3.53)	0.02	0.804	1.03 (3.18)	0.02	0.746	-0.04 (0.39)	-0.01	0.917	-2.97 (2.77)	-0.07	0.285
Presence of the place of study in the title	-6.61 (4.30)	-0.09	0.125	-5.54 (3.89)	-0.08	0.154	-0.66 (0.48)	-0.08	0.172	-4.16 (3.38)	-0.07	0.219
Presence of the study design in the title	1.37 (3.77)	0.02	0.717	1.59 (3.40)	0.03	0.641	0.15 (0.42)	0.02	0.726	6.03 (2.96)	0.13	0.043*
Descriptive title type ^c	6.67 (3.80)	0.10	0.080	6.10 (3.43)	0.10	0.076	0.63 (0.43)	0.08	0.139	1.11 (2.99)	0.11	0.710
Presence of acronyms in the title	8.56 (3.59)	0.14	0.018*	7.50 (3.23)	0.14	0.021*	0.85 (0.40)	0.12	0.034*	5.13 (2.81)	0.02	0.710
Open-access modality ^d	7.47 (3.67)	0.11	0.042*	5.85 (3.30)	0.10	0.078	0.96 (0.41)	0.13	0.020*	-0.49 (2.88)	-0.01	0.865
Article type ^e	13.63 (3.86)	0.20	0.001*	12.01 (3.50)	0.20	0.001*	0.37 (0.43)	0.05	0.400	0.98 (3.05)	0.02	0.748
Topic Prominence Percentile (TPP)	0.23 (0.09)	0.14	0.011*	0.18 (0.08)	0.12	0.025*	0.03 (0.01)	0.16	0.005*	0.31 (0.07)	0.25	< 0.001*
Adjusted R ²	0.10			0.09			0.10			0.09		

a. Standard error; b. Standardized beta coefficients; c. Descriptive title vs. informative and question title types; d. Open-access articles vs. non-open access; e. Review articles vs. original articles,

* P ≤ 0.05

marks in the titles of articles and the citations received by radiology articles²⁵. In this regard, Piva *et al.* showed that the articles with titles that included a question mark, colon, and hyphen were cited less than other articles²⁰. Otherwise, Jamali *et al.*'s study revealed that the articles with a colon in the title received fewer citations and downloads¹. Furthermore, some studies demonstrated that the application of a colon in the article titles was different in various disciplines, but there was no correlation between the presence of a colon in the title of academic articles and their future citation count^{26,27}. Finally, Falahati Qadimi Fumani *et al.* revealed that the number of punctuation marks in the article title could not predict the citation rate, though at least one punctuation mark was usually present, with the colon and hyphen being most frequently used²¹.

The literature indicates that the type of article title can affect the citation rate, but there is inconsistency in this regard. Generally, article titles are divided into three categories in terms of type: informative, descriptive, and interrogative. Informative titles, also called declarative titles, are those in which the main result of the article is mentioned in the title of the article. Descriptive titles, also called neutral titles, describe what is going on in this study but does not reveal the study's main result. Question titles, also called interrogative titles, are those in which a question is posed that arouses the reader's curiosity. Another classification is simple (one-part) and compound (two-part) titles, where the latter commences with a question phrase and continues with a noun phrase or begins with a short noun phrase followed by a question or another phrase (e.g., states the main finding)^{1,28}.

The study of Piva *et al.* on articles published by the Public Library of Science (PLOS) and Biomed Central (BMC) journals revealed that articles with titles that clarified some parts of the study results were cited more in comparison with the other types of titles²⁰. Moreover, Jamali HR *et al.* found that although the articles with question titles were downloaded more in comparison with other types of titles, they received lower citation counts¹. Our findings demonstrated that articles with interrogative and informative titles, in order, received lower citation counts in comparison with articles with descriptive titles. In addition, dermatology articles with informative and

interrogative titles were categorized 16% and 28% less in the FWCI > 1 group and 14% and 45% less, respectively, in the group of articles with a citation benchmarking percentile > 75%, in comparison with the articles with descriptive titles. Although these differences were not statistically significant, the value of the odds ratios indicated that this factor might have a small to moderate effect on the citability of dermatology articles. Accordingly, it might be probable that ambiguous titles are more attractive for authors to read the text of the article more carefully, so the chance for citation would increase.

Hafeez *et al.* showed that clarification of the study design in the title of the articles in psychiatry journals was associated with increased citations²⁹. On the other hand, Piva *et al.* demonstrated that the articles whose study design was clarified in their title were cited less than those that clarified the study results²⁰. In our study, there was a considerable positive association between the presence of the study design in dermatology article titles with a moderate effect size. The discrepancy between the results of different studies in this issue can be due to the diversity of studies in different fields of science.

Abramo *et al.*'s study revealed that titles mentioning the name of a country systematically received fewer citations³⁰. Similarly, Jacques *et al.*' showed that articles with titles mentioning the country of origin received significantly fewer citations²⁴. On the other hand, Alimoradi *et al.*'s study demonstrated no association between featuring the country name in the title and the citation count³¹. Our study showed that those articles that clarified the geographic area in their title were cited, on average, at least six times less. It seems that mentioning a specific location in the title suggests to other researchers that these results are specific to that geographic area and do not possess sufficient generalizability to other contexts, eventuating in fewer citations.

Articles with titles that include acronyms appear to be cited more by others, especially in medical journals^{24,32}. The prevalence of using acronyms in the title has increased by about 3.5 folds from 1995 to 2019, and up to 19% of scientific article titles include at least one acronym³³. In line with the literature, we found that articles with acronyms in their title received about ten more citations,

on average, in comparison with other articles. Additionally, the articles that included acronyms were categorized more as highly cited ones in the viewpoint of the FWCI and citation benchmarking percentile (by 2.76 and 2.19 folds, respectively) in comparison with those that lacked acronyms. In this context, Sagi *et al.* indicated that acronyms were linguistic tools that psychologically create linguistic simplicity, rendering a text more attractive³⁴. It seems that adding acronyms to titles makes them easier and faster to read; then, readers select them to read the full text and later cite the data and information of the article.

Linear regression analysis of our study's data revealed a weak positive correlation of both citation rate and FWCI indices with the title word count and the presence of acronyms in article titles. In addition, it demonstrated that open-access articles, review articles, and TPP played significant roles in the acceleration of the citation rate and FWCI. Accordingly, previous studies have reported different results on the effect of the characteristics of the article on the rate of citations and visibility³⁵⁻³⁷. One challenge is that the literature possesses few points of comparison in terms of the effects of FWCI and citation benchmarking percentile on citation metrics.

To our knowledge, this is the first study to evaluate the impact of the title characteristics of dermatology articles on the citation metrics. Selecting journals affiliated with four important organizations in the world from different continents, considering the authors' self-citation counts in the statistical analysis, and investigating the FWCI and citation benchmarking percentile in addition to the citation count were the most important strengths of our study. However, there were some limitations. First, the journals surveyed in this study were the more general dermatology journals, so it is recommended to design future studies by considering more dermatology journals and greater sample size to increase the generalizability. Next, this study was conducted according to information extracted only from the Scopus database. It is recommended that future studies be conducted using other databases which estimate the scientometric information of articles differently, such as Clarivate Analysis (Web of Sciences) and Google Scholar, and the degree of compatibility of the results from different databases

should be examined. Finally, due to conflicting results from various studies, a systematic review and meta-analysis should be performed to conclude on the association between citation metrics and the characteristics of article titles.

CONCLUSION

Our study indicates that longer titles, using acronyms and some punctuation marks, mentioning the study design, and not clarifying the place of study in the title were the most effective factors that might improve the citation metrics of dermatology articles. Moreover, according to the linear regression model, the title word count and the presence of acronyms in titles, along with open-access modality, review article type, and top level of TTP, could help dermatology journals to improve their ranking. Further studies are suggested to determine more factors that could affect the citation metrics of articles in dermatology journals.

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Efficacy and safety of 1064 nm long-pulsed neodymium-doped yttrium garnet (Nd:YAG) laser for treating acne vulgaris: a prospective clinical trial

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Background: Acne vulgaris is a common chronic inflammation of pilosebaceous units with a multifactorial pathogenesis. Traditional treatment may have limited success with potential side effects. The long-pulsed neodymium-doped yttrium garnet (Nd:YAG) laser may be a desirable alternative.

Methods: A prospective clinical trial was conducted on 61 acne patients at the Department of Dermatology, Basrah Teaching Hospital, from April 2019 to April 2020. Three treatments with long-pulsed Nd:YAG were performed across two-weeks intervals (fluence 50 J/cm², spot size 5 mm, pulse duration 15 ms, and frequency 1.5 Hz). Patients were assessed at baseline and 2, 4, 6, and 12 weeks later by counting the acne lesions and scoring the response according to the percentage of lesions' reduction.

Results: Sixty-one patients completed the study (49 females and 12 males); the mean age was 18.7 ± 1.67 years. A significant reduction of acne lesions at the end of therapy was observed compared to the baseline. The mean number of total lesions was reduced from 84.2 ± 25.8 to 16 ± 23.3 ($P < 0.05$). Overall, 49 (80.3%) patients achieved an excellent response, 3 (4.9%) good, 1 (1.6%) moderate, and 8 patients (13.1%) showed a poor response. The treatment was well tolerated with insignificant adverse effects.

Conclusion: Long-pulsed Nd:YAG laser is an effective and safe modality for treating acne vulgaris and may be considered an alternative option for cases of recurrence after conventional treatment. However, more sessions are needed for severe cases.

Keywords: long-pulsed Nd:YAG, laser, acne, treatment

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INTRODUCTION

Acne vulgaris is a common chronic inflammatory skin disease of the pilosebaceous unit. It is considered one of the most prevalent global diseases and is a common cause of dermatological consultation ¹. Most acne cases begin in the prepubertal period when androgens begin affecting the pilosebaceous unit. Both ovarian and testicular androgen have a major role in acne pathogenesis ² in addition

to plugging of the pilosebaceous units and *Cutibacterium* (formerly known as *Propionibacterium*) *acne* overgrowth ^{3,4}, resulting in characteristic acne lesions ⁵ that include comedones, papules, pustules, and, less commonly, nodules, cysts, and scarring ⁶. Several modalities of treatment have been used for acne vulgaris; however, conventional therapy such as topical and systemic therapy is characterized by poor compliance and efficacy, lack of long-lasting remission, high cost, recurrence, and several

side effects⁷. Therefore, a new effective and safe treatment modality is needed.

Acne treatment with light-based devices and lasers shows a different degree of efficacy. The long-pulsed 1064 nm neodymium-doped yttrium garnet (Nd:YAG) laser introduces selective heat into the dermis⁸. It has been successfully used in the treatment of a variety of conditions such as varicose veins, rhytids, photo epilation, and removal of pigmented lesions⁹⁻¹¹, and more recently for collagen remodeling¹². Its target chromophores are melanin, hemoglobin, and water. The laser deeply penetrates the lower dermal layer, reaching the pilosebaceous unit and creating diffuse heating of the dermis and selective photothermolysis of the overactive sebaceous glands. This minimizes the sebum activity and *C. acne* population, thereby reducing the inflammatory acne lesions without damaging the epidermis¹³. In the literature, a few studies have been published that address the efficacy of the 1064 nm long-pulsed Nd:YAG in the treatment of acne scars with encouraging results^{14,15}. However, its effects on active acne lesions are not well investigated, and the evidence-based research on its use is limited and primarily based on case reports or case series studies. Therefore, this study aimed to assess the efficacy and safety of the 1064 nm long-pulsed Nd:YAG laser in treating acne vulgaris in a cohort of young adult patients.

PARTICIPANTS AND METHODS

Participants and study design

A prospective clinical trial was conducted on 66 young patients with acne at the Department of Dermatology, Basra Teaching Hospital, Basrah, Iraq, from April 2019 to April 2020. According to the Lehman grading system, patients were clinically diagnosed and scored as mild, moderate, and severe¹⁶. A detailed history was taken from each patient focusing on the following points: age, sex, duration of the illness, family history, menstrual history for females, and previous treatments, if any. Physical examination was performed, including the site, number, and types of lesions.

Inclusion criteria were patients aged more than 17 years diagnosed with acne of various severity who either recurred after repeated courses of conventional treatments and looking for alternative

therapy or those who did not receive any treatment in advance and asked for laser therapy for their acne. Exclusion criteria were nodulocystic acne, coexisting skin diseases, history of photosensitivity, pregnant and lactating women, prior therapy with isotretinoin within the last six months, and use of systemic antibiotics or topical acne preparations within one month. Patients were not allowed to use topical, systemic, or other light-based acne treatments during the study.

Eligible patients were treated with the 1064 nm long-pulsed Nd:YAG laser (Quanta system, new Q- Plus *1, made in Italy). Device settings were as follows: fluence 50 J/cm², spot size 5 mm, pulse duration 15 ms, and frequency 1.5 Hz. The device is equipped with an active contact cooling system. On a fortnightly interval, three treatments were performed over the entire face without topical anesthesia in a one-pass stamping technique, side by side without overlapping. Topical emollient and sunscreen cream were applied immediately after the session. Upon completion of three sessions, there was a follow-up eight weeks later.

Clinical assessment

The trial's primary endpoint was the percentage of patients who achieved at least 80% or more reduction in the total number of acne lesions. The patients were assessed at the baseline visit and during each subsequent treatment session using the following parameters:

1. Numerical counting of the acne lesions, performed by an independent, qualified dermatologist using the photographs snapped by Galaxy Note 5 phone camera (16 Megapixels) for every patient at baseline and at the follow-up visits.
2. Compared to the baseline value, we calculated the percentage of the total reduction of acne lesions.
3. We graded the response according to the percentage of the total reduction of acne lesions using the following scale¹⁷: $\geq 80\%$ reduction (excellent response), 60–79% reduction (good response), 40–59% reduction (moderate response); $< 40\%$ reduction (poor response).
4. We monitored for any side effects at each visit.
5. At the end of the study, patients' satisfaction

and their attitude toward the treatment were assessed using a three-point scale: 0 = unsatisfied, 1 = partially satisfied, 2 = fully satisfied.

Ethical considerations

Before beginning the laser sessions, personal consent was taken from each patient after fully explaining the nature and method of laser treatment, the duration of follow-up, and anticipated complications. The trial was approved by the Ethical Committee of Basrah College of Medicine (Approval No: 03040853-2020).

Statistical methods

Data analysis was performed using IBM SPSS version 25. Means $\pm$ standard deviation (SD) was used for descriptive data; frequencies with the percentage used to describe the quantitative data. The one-way ANOVA (analysis of variance) test was used to analyze any significant differences between the results of treatment sessions. *P*-values below 0.05 were considered significant.

RESULTS

Out of the 66 patients enrolled, 61 completed the study (49 females and 12 males). The mean age was 18.7 ± 1.67 (range:16–22) years. Other demographic characteristics are shown in Table 1.

The mean $\pm$ SD of the total lesions for all patients was significantly reduced from 84.2 ± 39.6 at the baseline to 16 ± 23.3 at the end of the trial (*P* < 0.05) (Table 2; Figure 1).

The mean $\pm$ SD of comedones was significantly

Table 1. Demographic characteristics of patients with acne vulgaris (n = 61)

Variable	Frequency (%)
Sex	
Female	49 (80.3%)
Male	12 (19.7%)
Marital status	
Married	3 (4.9%)
Single	58 (95.1%)
Positive family history	27 (44.2%)
Fitzpatrick skin phototype	
Type II	12 (19.6%)
Type III	39 (63.9%)
Type IV	10 (16.3%)
Treatment-naïve	9 (14.8%)
Previous treatment	52 (85.2%)
Severity	
Mild	2 (3.3%)
Moderate	47 (77%)
Severe	12 (19.7%)

reduced from 6.7 ± 5.7 to 1.54 ± 2.2 at the end of the trial (*P* < 0.05), and the inflammatory lesions also showed a remarkable and significant reduction; papular and pustular lesions were reduced from 56 ± 23 and 19.2 ± 12.1 to 10.9 ± 16 and 2.94 ± 4.5 , respectively (*P* < 0.05).

Table 3 shows a significant reduction in the percentage of acne lesions after the first session, with a gradual escalation in subsequent sessions (56% cumulative reduction of comedones, 82% clearance of papules, and 84% of pustules at the end of the trial).

Table 4 indicates that 49 patients (80.3%) achieved an excellent response, with an $\geq 80\%$ reduction of total acne lesions (Figure 2) and good or partial response was seen in 3 patients (4.9%) (Figure 3). In contrast, 8 patients (13.1%) were classified as poor responders (Figure 4); 87.5% of them were severe

Table 2. Number of acne lesions (mean $\pm$ SD) at baseline as well as after each session and during the follow-up period

Lesion	Baseline	1st session	2nd session	3rd session	Follow-up
Total	84.2 ± 39.6 CI (74.1–94.4)	53.2 ± 25.8 CI (46.6–59.8)	37 ± 23.3 CI (31.05–43)	22.4 ± 22.1 CI (16.7–28)	16 ± 23.3 CI (10.–21.9)
Comedones	6.7 ± 5.7 CI (5.3–8.2)	4.8 ± 4.6 CI (3.6–6)	3.4 ± 3.5 CI (2.5–4.3)	2.1 ± 2.5 CI (1.5–2.8)	1.5 ± 2.2 CI (0.9–2.1)
			<i>P</i> < 0.05		
Papules	56 ± 23 CI (49.8–62.1)	36.63 ± 18.1 CI (32–41.2)	25.4 ± 16.9 CI (21.1–29.8)	15.5 ± 16.0 CI (11.4–19.6)	10.9 ± 16.1 CI (6.7–15.1)
			<i>P</i> < 0.05		
Pustules	19.2 ± 12.1 CI (16–22.3)	11.9 ± 7.8 CI (9.8–13.9)	8 ± 5.8 CI (6.4–9.5)	4.7 ± 4.7 CI (3.4–1.7)	2.9 ± 4.5 CI (5.9–4.1)
			<i>P</i> < 0.05		

Abbreviations: SD: standard deviation, CI: confidence interval

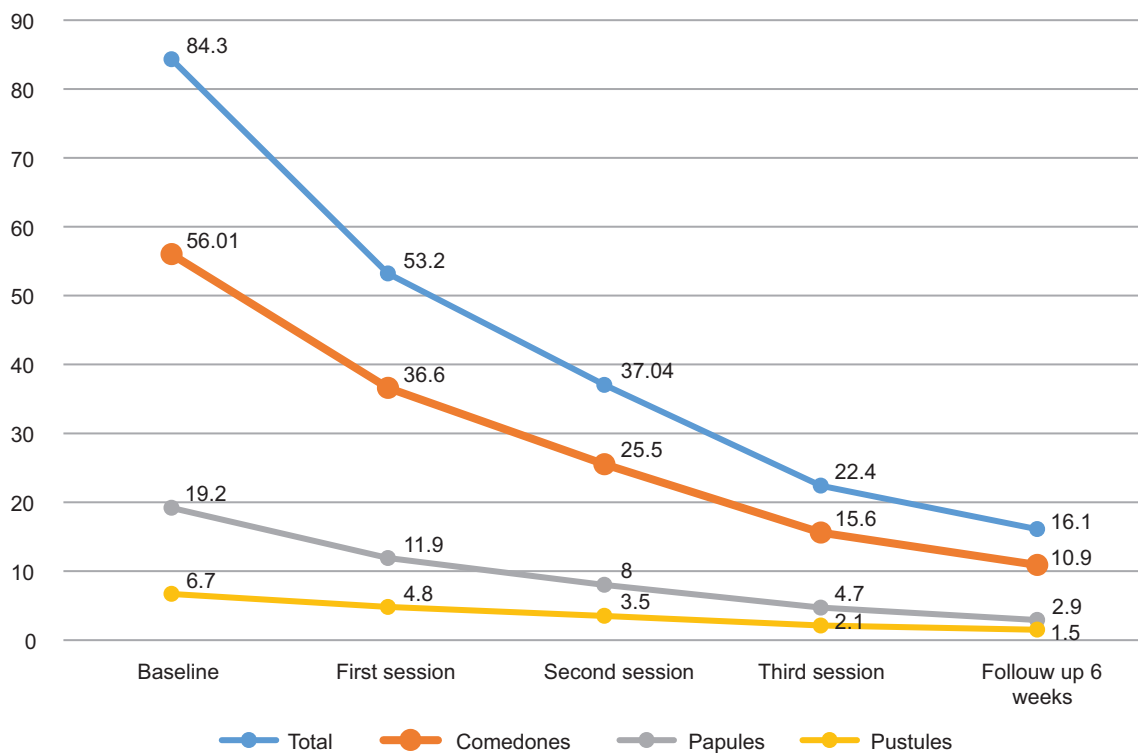


Figure 1. Line chart of the mean acne lesions at the baseline as well as after each session and during the follow-up (six weeks) period

Table 3. Percentage of reduction of total acne lesions during each session and the follow-up period compared to the baseline value

Type of lesion	Percentage of reduction				P-value
	1st session	2nd session	3rd session	After 6 weeks	
Total	35.4%	55.3%	72.9%	80.5%	< 0.005
Comedones	26%	42%	56%	56%	
Papules	36%	55%	73%	82%	
Pustules	39%	58%	74%	84%	

Table 4. Scoring the patients' responses according to percentage of total reduction in acne lesions by the end of the trial

Percentage of the total reduction in acne lesions	No (%)
≥ 80% (excellent response)	49 (80.3)
60–79% (good response)	3 (4.9)
40–59% (moderate response)	1 (1.6)
< 40% (poor response)	8 (13.1)

types with III and IV Fitzpatrick skin phototypes.

Twenty-five patients (41%) developed mild erythema that faded within a few hours after treatment, and 28 patients (45.9%) experienced mild transient pain at the moment of treatment. No pigmentary changes, burns, or blistering was seen after the therapy.

Forty-nine (81%) patients were fully satisfied with the improvement achieved, while 2 (3%) were partially satisfied and 10 (16%) were unsatisfied.

DISCUSSION

Acne vulgaris is a common skin disease among adolescents. In Iraq, the prevalence rate of acne vulgaris is 73% in men and 62% in women; it is associated with long-term sequelae like scarring, post-inflammatory hyperpigmentation, and adverse psychological effects¹⁸. Laser- and light-based therapies are currently considered an alternative modality for acne vulgaris treatment, especially for those with a contraindication to classic anti-acne treatment. Moreover, these new modalities can bypass issues in traditional acne treatment, such as teratogenicity and antibiotic resistance¹⁹. In acne vulgaris, the light-based therapies with blue and red light, in addition to intense pulsed light, target the porphyrins produced by *C. acne* with a resultant toxic effect on these bacteria. However,



Figure 2. A 19-year-old male patient with moderate acne at baseline (a, c), showed an excellent response (b, d) following three sessions of laser treatment

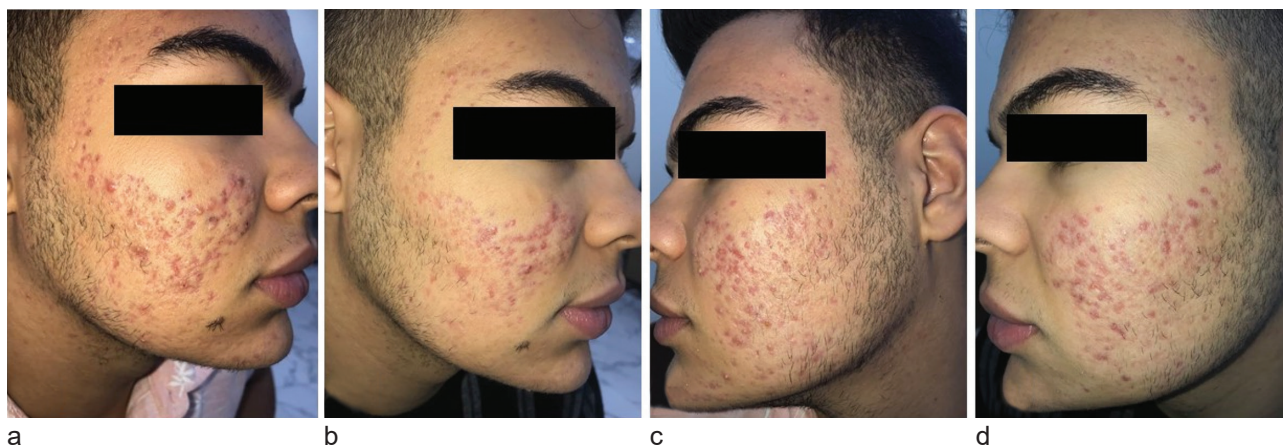


Figure 3. An 18-year-old male patient with moderate acne at baseline (a, c), showed a partial response (b, d) following three sessions of laser treatment

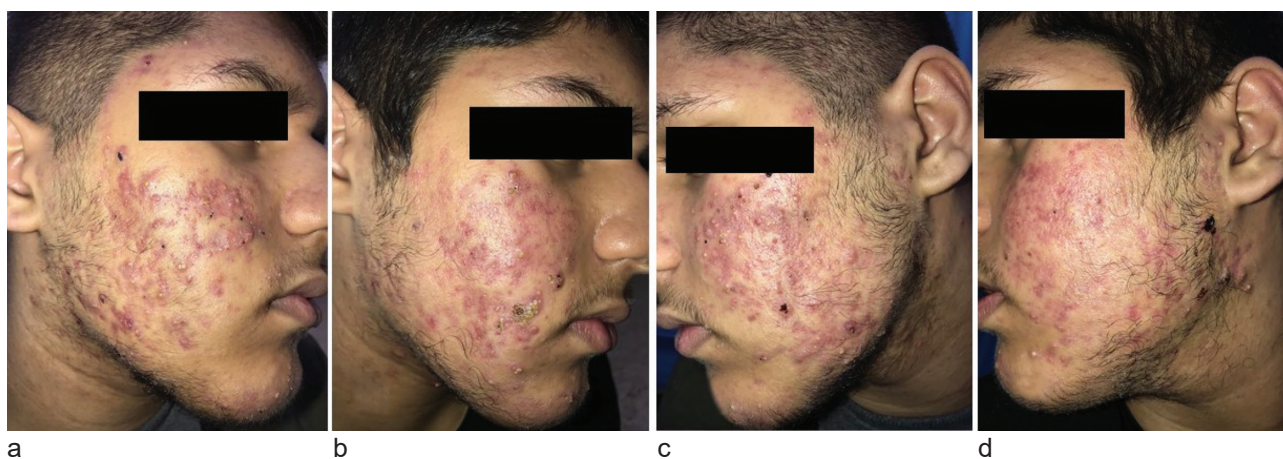


Figure 4. A 20-year-old male patient with severe acne at baseline in (a, c) showed a poor response (b, d) following three sessions of laser treatments

because these modalities do not target the sebaceous glands, the recurrence rate is high²⁰. Lasers with a wavelength near the infra-red spectrum

produce selective photothermolysis that damages the sebaceous glands and subsequently decreases sebum production and *C. acne* density²¹. Several

laser modalities with this spectrum, such as 1320 nm Nd:YAG ²², 1450 nm diode lasers ²³, and 1540 nm erbium lasers ²⁴, are used for acne vulgaris treatment. In addition to their effect on improving inflammatory acne lesions, these lasers have been shown to improve acne scars ²⁵.

Although the 1064 nm long-pulsed Nd:YAG laser's proposed mechanism of action in treating acne lesions is not completely understood, it may be related to the aforementioned selective photothermolysis of the sebaceous glands and a decrease in the *C. acne* population, in addition to the effect on inflammation by reducing TLR 2, IL8, and TNF-alpha levels ²⁶.

In this study, we demonstrated that the 1064 nm long-pulsed Nd:YAG laser is an effective therapeutic modality for acne patients, with successful clearance of more than 80% of total acne lesions in 80.3% of cases after three treatment sessions. Even more importantly, perhaps, the response was sustained and continued throughout the six-week follow-up period with no sign of relapse.

At first, Robin successfully treated four cases with mild and moderate acne with remarkable improvement after one session of 1064 nm long-pulsed Nd:YAG laser with no significant side effects apart from mild erythema. He also found an additional effect of the laser in the improvement of acne scars ²⁷, while Ruta *et al.* used the long-pulsed Nd:YAG laser to treat 19 patients with mild to moderate acne vulgaris across five weekly sessions. They reported a 75% reduction in acne lesions in a patient with the mild to moderate type ¹⁵. Mohamed *et al.* reported comparable improvements using either intense pulsed light (IPL) or long-pulsed Nd:YAG in treating mild to severe acne in a face-split design study. They reported a 67.1% and 70.2% reduction in inflammatory lesions for the IPL and 1064 nm long-pulsed Nd:YAG laser, respectively ²⁷. In this study, we have the advantage of a larger number of patients compared to other studies and the need for a small number of treatment sessions to achieve significant clinical and durable improvement of acne lesions. The difference between the results of various studies may be related to different demographic features of the candidate patients, laser device settings, total number of laser sessions, and the time interval between each session.

Although 80.3% of patients achieved an excellent

response, 8 (13.1%) patients were considered poor responders—they showed less than 40% reduction of their acne lesions despite rigorously adhering to scheduled sessions. Moreover, their demographic criteria were comparable to that of the responders. Despite the interpersonal variation in response to the laser treatment, severe acne is likely less responsive than mild or moderate acne, and additional laser sessions may be required. Accordingly, we were unable to perform additional sessions for these patients because of the citywide lockdown during the COVID-19 pandemic. The pandemic also affected the number and period of follow-up of our patients.

There are certain limitations to this study. It was an uncontrolled, non-comparative, single-arm clinical trial, which may impede the precision of our conclusions. The possibility of confounders such as sex, age, occupation, and environmental factors were not accounted for while analyzing our data. Finally, our findings are based on evidence from a single-center study.

CONCLUSION

In conclusion, the 1064 nm long-pulsed Nd:YAG laser is a safe and effective alternative treatment modality for mild to moderate acne vulgaris and offers a sustained and durable effect; however, severe acne was less responsive. Further evidence on the safety and efficacy of the 1064 nm long-pulsed Nd:YAG in treating acne vulgaris needs to be confirmed in controlled clinical trials, especially for severe acne, while accounting for the impact of confounding factors.

Conflict of Interest: None declared.

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A cutaneous-only variant of rheumatoid vasculitis with symmetric flexural pyoderma gangrenosum-like lesions

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Rheumatoid vasculitis, an uncommon extraarticular manifestation of rheumatoid arthritis, usually develops in long-standing cases affecting small-to-medium-sized vessels. It is a poor prognostic marker when multiple systems are affected, skin and neurologic involvement being most frequent. Rheumatoid vasculitis is seen more commonly in seropositive and nodular rheumatoid arthritis patients who are male or smoke. Herein, we present the peculiar case of a 48-year-old female with rapid onset, progressive, multiple ulcers predominantly over the flexures. Differential diagnoses of pyoderma gangrenosum, pyoderma vegetans, pemphigus vegetans, and vasculitis were considered, and the patient was evaluated. On investigation, her rheumatoid factor titer was strongly positive; a skin biopsy revealed leukocytoclastic vasculitis. On clinical, serological, and histopathological correlation, a diagnosis of rheumatoid vasculitis was made, responding well to high-dose prednisolone. On follow-up at six months, her skin lesions had healed well with moderate scarring; however, she developed severe joint pain, warranting the initiation of disease-modifying antirheumatic drugs. To the best of our knowledge, this is a previously unreported clinical and morphological presentation of rheumatoid vasculitis.

Keywords: rheumatoid vasculitis, rheumatoid arthritis, cutaneous-only vasculitis, secondary vasculitis.

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INTRODUCTION

Rheumatoid vasculitis is a relatively uncommon disease manifestation in patients with rheumatoid arthritis ¹. The morphological pattern can include palpable purpura, nodulo-ulcerative lesions, livedo reticularis, erythema elevatum diutinum, and hemorrhagic bullae. Bannatyne first described vascular involvement in rheumatoid arthritis in 1898 ². Rheumatoid vasculitis may occur in association with pyoderma gangrenosum, though it can also present alone with ulcerated lesions ^{3,4}. Herein, we present a peculiar case of a 48-year-old female with multiple, rapid-onset, progressive ulcers predominantly over the flexures.

CASE PRESENTATION

A 48-year-old lady came to our emergency room with a one-week history of multiple, rapid-onset, progressive, somewhat painful, ulcerated lesions, predominantly over the flexures. She had a history of documented low-grade fever associated with these lesions. Mild arthralgia and morning stiffness in the shoulder, wrist, and small joints of the hands were noted on and off for the last three months. The symptoms were mild and sporadic, so the patient did not seek any specific treatment. She was also a known hypertensive and diabetic.

The systemic examination revealed no abnormalities. On mucocutaneous examination,

multiple, well-defined, circular-to-elongated ulcers with few smaller satellite lesions were present over the right axilla, bilateral inframammary folds, and bilateral groins (Figure 1 a-c). The margins were punched out, and the floor of the ulcers had adherent yellowish to brown-black crusts (Figure 1 a-c). Similar isolated lesions were seen over the abdomen and thighs. No regional lymphadenopathy was noted, and the mucosae were unremarkable.

Routine & relevant investigations, including a complete blood count (CBC), renal function test (RFT), liver function test (LFT), urine microscopy, chest X-ray (CXR) & electrocardiogram (ECG), were within normal limits. A screening anti-nuclear antibody (ANA) [ELISA] and an anti-neutrophilic cytoplasmic antibody (ANCA) profile were sent and returned negative. However, her rheumatoid arthritis (RA) factor (46.9 IU/ml) was strongly positive, and the erythrocyte sedimentation rate (ESR) was extremely elevated at 120 mm/hr. The pathergy test was negative. A skin biopsy, keeping

differential diagnoses of pyoderma gangrenosum, pyoderma vegetans, pemphigus vegetans, and vasculitis, was done after informed consent.

The biopsy revealed epidermal necrosis and ulceration; the dermis had a dense neutrophilic infiltrate in and around the vessel wall. Endothelial cell swelling, leukocytoclasia, and extravasation of red blood cells (RBCs) were present, and fibrinoid necrosis was seen (Figure 2 a-b).

On clinicopathological correlation, a provisional diagnosis of rheumatoid vasculitis was made. She was started on high-dose prednisolone (1 mg/kg/day), showing marked improvement. The steroid dose was gradually tapered over two months, and the lesions healed well with post-inflammatory hyperpigmentation and mild scarring (Figure 3).

On follow-up at six months, she developed severe joint pain restricting her movements, and a rheumatological consult was requested. She subsequently fulfilled the EULAR (European League Against Rheumatism) criteria for rheumatoid



Figure 1. Multiple ulcers with punched-out margins; floor covered with yellowish necrotic slough and brown-black crusts in the (a) right axilla, (b) right infra-mammary fold, and (c) right groin

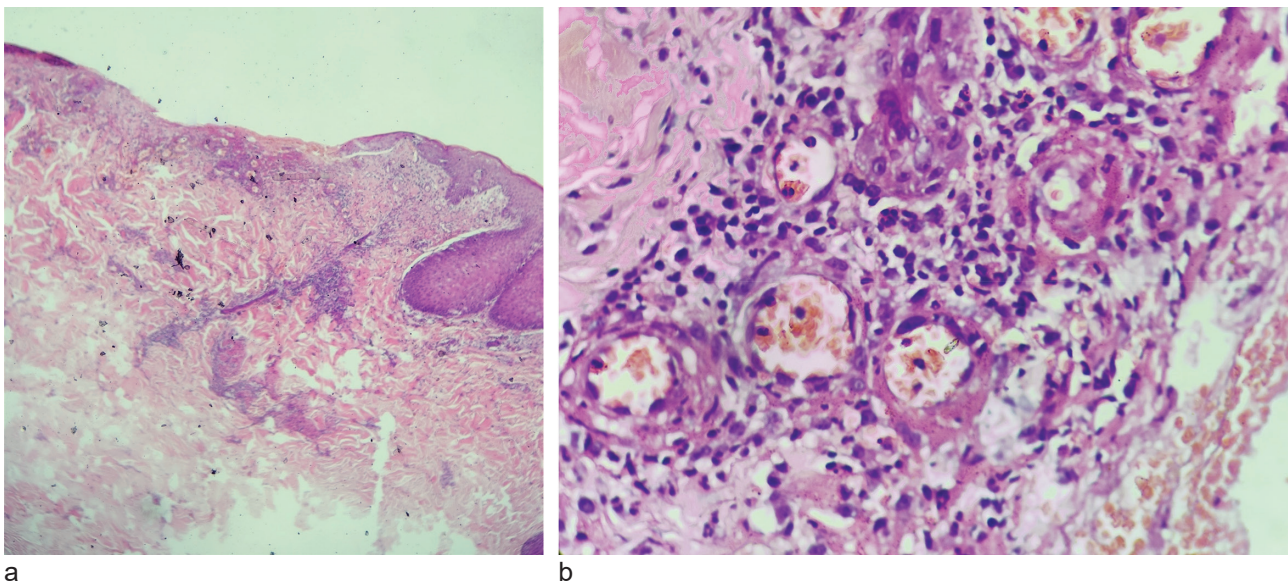


Figure 2. Skin biopsy (hematoxylin & eosin stain) showing epidermal ulceration and necrosis. The dermis shows infiltration of the vessel wall by neutrophils with fibrinoid necrosis, leukocytoclasia, endothelial cell swelling, and extravasation of erythrocytes; (a) 100x; (b) 400x

arthritis (score = 8) and was started on a disease-modifying anti-rheumatoid drug (DMARD). Hence, a final diagnosis of rheumatoid vasculitis was

made, where the vasculitic lesions preceded the development of frank rheumatoid arthritis.

DISCUSSION

Rheumatoid vasculitis is seen in approximately 1–5% of patients with rheumatoid arthritis⁵⁻⁷. Due to the morphology and rapid onset, our first impression was an atypical pyoderma gangrenosum, even though the lesions were only slightly painful, with minimal tenderness on palpation. However, biopsy findings did not corroborate this. Since pyoderma gangrenosum is a diagnosis of exclusion, we considered other possibilities. Wegener's granulomatosis, a small vessel vasculitis, has been reported to present with such pyoderma gangrenosum-like lesions in the flexures⁸. However, the ANCA profile was negative, and no granulomas were seen.

Thus, on clinical, serological, and histopathological grounds, we reached a diagnosis of cutaneous-only rheumatoid vasculitis. To the best of our knowledge, such symmetric flexural pyoderma gangrenosum-like lesions have not been previously reported in rheumatoid vasculitis.

Rheumatoid vasculitis usually presents after a mean rheumatoid arthritis disease duration of 13 years, with anecdotal reports of vasculitis preceding or occurring early in rheumatoid arthritis (Table 1). Rheumatoid vasculitis preceding or occurring in



Figure 3. Healed lesions with post-inflammatory hyperpigmentation and scarring over the right inframammary region at the six-month follow-up

Table 1. Rheumatoid vasculitis (RV) presentations preceding or in early stages of rheumatoid arthritis (RA)

No.	Author, year	Age (yrs.) /sex	Features of RV	Associated arthritic features	Temporal relation of RV with RA
1.	Parker <i>et al.</i> , 2007 ⁹	63/M	1. Mononeuritis multiplex 2. Acute abdomen: abdominal pain, nausea, and vomiting due to small bowel perforation	Symmetrical inflammatory polyarthritis of small joints	RV 7 months after RA diagnosis
2.	Sandhu <i>et al.</i> , 2013 ¹⁰	74/M	Acute abdomen: periumbilical & right upper quadrant pain; recurrent emesis due to cholecystitis	Symmetrical inflammatory polyarthritis of small joints	RV 1 week after RA diagnosis
3.	Tourin <i>et al.</i> , 2013 ¹¹	61/M	Acute pulmonitis: pleuritic chest pain & dry cough	Symmetric inflammatory polyarthritis of small joints	RV 2 months prior to RA diagnosis
4.	Lee <i>et al.</i> , 2017 ¹²	72/F	Hepatic artery vasculitis: elevated liver enzymes only, asymptomatic	Symmetric inflammatory polyarthritis of small joints	RV 2 months after RA diagnosis
5.	Sacks <i>et al.</i> , 2017 ¹³	38/M	Mononeuritis multiplex	Symmetrical inflammatory polyarthritis of small joints	RV 6 years prior to RA diagnosis
6.	Anwar <i>et al.</i> , 2019 ¹⁴	44/M	1. Nodulo-ulcerative cutaneous vasculitis 2. Pericarditis	Symmetrical inflammatory polyarthritis of small joints	Concurrent diagnosis of both.
	Our case	48/F	Cutaneous-only variant with multiple, symmetric, flexural pyoderma gangrenosum-like lesions	Symmetrical inflammatory polyarthritis of small joints	RV 6 months prior to RA diagnosis

early rheumatoid arthritis has been seen as an acute pulmonary syndrome due to vasculitis and even as an acute abdomen in the form of cholecystitis, hepatic artery involvement, and acute bowel perforation⁹⁻¹². Since rheumatoid vasculitis is usually a systemic vasculitis, an unusual feature in our case was the cutaneous-only pattern.

CONCLUSION

We reported an unprecedented presentation of cutaneous-only rheumatoid vasculitis preceding overt rheumatoid arthritis. Histopathology plays a crucial role in diagnosis; since rheumatological diseases evolve with time, following up on such patients may improve our diagnostic ability and therapeutic interventions.

Conflict of interest: None declared.

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Toxic epidermal necrolysis-like bullous pemphigoid: a rare case report

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Bullous pemphigoid is the most common type of subepidermal autoimmune bullous disease. It usually affects older people; isolated cases among people younger than 65 have been reported with various presentations, usually more severe and active than those seen in the elderly. Toxic epidermal necrolysis (TEN) is a potentially life-threatening dermatologic disorder characterized by widespread necrosis and bullous detachment of the epidermis and mucous membranes resulting in exfoliation and possible sepsis. Various morphological variants of bullous pemphigoid have been reported, with reports of the TEN-like variant of bullous pemphigoid being scarce. In this study, we report a case of bullous pemphigoid with TEN-like presentation in a middle-aged female.

Keywords: bullous pemphigoid, toxic epidermal necrolysis, middle-aged female

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INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune subepidermal bullous dermatosis that generally affects people older than 70¹. Lesions start as itchy urticarial lesions mostly along the abdomen followed by the extremities, eventually erupting to form tense blisters with sero-hemorrhagic content². Confluent bullae with large areas of denuded epidermis can mimic the epidermal sloughing classically seen in toxic epidermal necrolysis (TEN)³. Little has been documented about TEN-like bullous pemphigoid. This case highlights the vigilance required by healthcare workers in recognizing the change in the disease course with prompt management to prevent undue complications.

CASE PRESENTATION

A 34-year-old uneducated female farmer presented to the skin emergency department with multiple fluid-filled lesions over the entire body since seven days earlier and oral intolerance to food since five days earlier. She was alright seven days back before she developed red-colored, intensely itchy lesions over the dorsum of the hand, which progressed to involve the trunk, both extremities, and face, followed by the appearance of tense blisters and the development of oral lesions. On general examination, the patient had pallor with left pedal edema. On dermatological examination, there were multiple tense bullae on an erythematous urticarial base with widespread erosions over the trunk, both limbs, and face

(Figure 1). We admitted the patient with differential diagnoses of bullous pemphigoid and erythema multiforme. Routine laboratory investigations were normal except for anemia. Histopathology showed subepidermal blister formation consistent with bullous pemphigoid. We started her on injectable dexamethasone 6 mg with supportive therapy. Still, 10-12 new blisters emerged every day. Five days after admission, the patient developed generalized peeling of the skin over her entire body with

tenderness involving more than 50% of the body surface area. On examination, there was peeling of the skin with a positive pseudo-Nikolsky sign (Figure 2). In view of this, we clinically reviewed her differentials and took a skin biopsy, which was again suggestive of bullous pemphigoid, with no necrotic keratinocytes (Figure 3). Direct immunofluorescence was negative, and electron microscopy re-confirmed the diagnosis as bullous pemphigoid. The lesions had improved by day 17



Figure 1. Day 1 of admission; multiple tense bullae on an erythematous urticarial base with widespread erosions over the trunk, limbs, and face



Figure 2. Day 5 of admission; generalized peeling of the skin over the entire body, involving more than 50% of the body surface area

of admission, evidenced by healing and crusting (Figure 4).

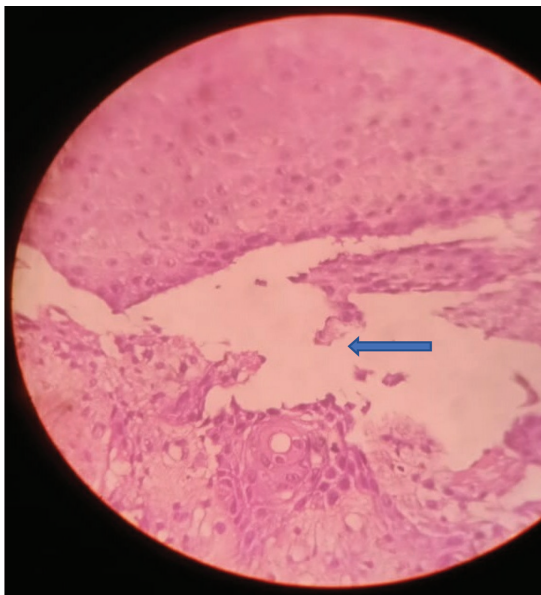


Figure 3. Histopathology section, with a blue arrow showing subepidermal splitting

DISCUSSION

Bullous pemphigoid is a blistering autoimmune disease caused by autoantibodies against the collagen XVII (BP180/BPAG2) and BP230 (BPAG1) components of the hemidesmosome⁴. Various morphological variants are described clinically. Common ones include classic, localized, nodular, and vegetating; erythrodermic-like, ecthyma-like⁵, and TEN-like⁶ are some of the rare ones.

Our patient had urticarial plaques with the development of multiple tense blisters at admission that rapidly evolved to tender confluent bullae and widespread epidermal detachment. Bullous pemphigoid features subepidermal blister formation with eosinophilic infiltrates, while in TEN, there is



Figure 4. Day 17 of admission; improved lesions, evidenced by healing and crusting

subepidermal bullae, loss of the entire epidermis, and the presence of necrotic keratinocytes. As the initial presentation was confirmed as bullous pemphigoid, the course of the disease altered rapidly to evolve into generalized peeling. Also, histopathology specimens at different times of the disease course correlated with eosinophil-rich sub-epidermal blisters seen in bullous pemphigoid. Negative immunofluorescence studies, as in

this case, occur in 4% of patients with bullous pemphigoid⁷. It was electron microscopy that further confirmed the diagnosis as bullous pemphigoid.

Bullous pemphigoid presents with urticarial papules or eczematous plaques, whereas TEN begins with tender, dusky, ill-defined erythematous patches. The classic bullous pemphigoid lesion is a 1–3 cm tense bulla on an erythematous base,

differentiating bullous pemphigoid from TEN. Mucosal involvement occurs almost always (90%) in TEN, but is only seen in roughly 20% of bullous pemphigoid patients ⁸.

CONCLUSION

Bullous pemphigoid usually presents as red itchy lesions with urticarial plaques followed by tense blisters. TEN-like BP is a rare presentation that was seen in our case.

Conflict of interest: None declared.

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Serum matrix metalloproteinases in patients with different types of cutis laxa: a case series

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Background: Cutis laxa (CL) is a connective tissue disease that is either inherited or acquired. It is characterized by redundant, pendulous, and inelastic skin. Loss of elasticity is a pathological feature of some degenerative and inflammatory diseases. Matrix metalloproteinases (MMPs) can cleave elastin fibers by damaging the microfibrils and the elastin core, resulting in the loss of elasticity.

Patients and Methods: In this study, we report eight patients with different types of cutis laxa along with the quantitative measurement of serum levels of MMP-2 and MMP-9.

Results: The cutis laxa patients showed various clinical and histopathological findings, indicating the heterogeneity of this rare skin connective tissue disease. The serum level of MMP-2 and MMP-9 were elevated in these patients.

Conclusion: Increased MMP-2 and MMP-9 might be associated with cutis laxa. However, our findings need to be validated in larger clinical settings.

Keywords: cutis laxa, matrix metalloproteinases, elastin, collagen

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INTRODUCTION

Cutis laxa is a rare cutaneous syndrome belonging to a group of heterogeneous disorders. The disease manifests as wrinkled and redundant skin. In addition, excessive skin folds represent the histological hallmark of cutis laxa ¹. The condition can be classified as acquired cutis laxa or inherited cutis laxa, but the clinical presentations overlap between the different types ¹.

Acquired cutis laxa comprises a monogenic defect that starts with inflammatory skin eruptions that

induce abnormal elastin metabolism, proneness to elastic degradation, and skin wrinkling ². Elastolysis may spread to internal organs, giving rise to emphysema and aortic root alteration ¹. Inherited cutis laxa syndrome can be classified as autosomal dominant, autosomal recessive, and X-linked recessive cutis laxa, resulting from monogenic defects that impair elastic fiber assembly ³. Moreover, several forms of cutis laxa remain unclassified.

Autosomal dominant cutis laxa is a genetically heterogeneous disorder regarded as a connective

tissue disorder characterized by wrinkled and sagging inelastic skin along with some internal organ involvement ^{4,5}. Autosomal recessive type 2 cutis laxa (ARCL2A and ARCL2B) is a more benign condition of genetically heterogeneous disorder associated with growth, developmental, and skeletal anomalies ⁶.

The diagnosis of cutis laxa is primarily based on clinical evaluation, which is supported by histopathological and molecular analysis ¹. Microscopic observation of cutis laxa skin biopsies generally reveals a reduction in elastic fibers with fragmentation ⁴. These findings can help differentiate cutis laxa from other skin connective tissue disorders, including Ehlers-Danlos syndrome, pseudoxanthoma elasticum, and Marfan syndrome. However, clinical and molecular heterogeneity associated with cutis laxa might result in some difficulties in the diagnosis.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that consist of several proteins, enabling the degradation of almost all components in the cutaneous extracellular matrix, especially structural collagen molecules and elastic fibers ⁷. Gelatinase B (MMP-9), among the subclasses of MMPs, is required for the degradation of collagen IV and degenerated collagen I ⁸. MMP-12 (macrophage metalloelastase) has been associated with the hydrolysis of elastic tissues in anetoderma and macrophage migration in cutaneous granulomas ⁹. Some studies indicate the alteration of collagenase activity in cutis laxa, suggesting a possible role in its pathogenesis ^{8,9}. In this study, we report eight patients with different types of cutis laxa along with the quantitative measurement of their serum MMP-2 and MMP-9 levels.

PATIENTS AND METHODS

This study recruited eight patients with cutis laxa at Loghman Hospital, Tehran, Iran. The Ethics Committee of our center approved the study (Code: 4-519-24.07.90). All the patients provided written informed consent, and the study was performed as per the principles outlined in the Declaration of Helsinki. Enrolled patients were completely examined, and photographs were taken using an SLR camera (Canon EOS-40D). Skin biopsies were taken and sent to the laboratory for histopathology examination under the light microscope, electronic

microscope, and direct immunofluorescence.

Genetic analysis was performed on some patients with inherited cutis laxa (patients 2, 4, and 5). According to the standard salting-out method, genomic DNA was isolated from the patients' tissues. Sanger sequencing of *ELN*, *FBLN4*, *FBLN5*, *LTBP4*, *ATP6V0A2*, *PYCR1*, *ALDH18A1*, *ATP7A*, and *COG7* were performed in these patients.

Furthermore, 8 ml of blood was taken from each patient and centrifuged. The serums were stored at -70 °C for less than one month. Subsequently, MMP-2 and MMP-9 were assayed with a commercial ELISA kit (Ray Biotech, Norcross, GA, USA). The normal range of serum MMP-2 was 70-93 ng/ml, while the normal range of serum MMP-9 was 84-103 pg/ml.

CASE DESCRIPTION

Inherited cases of cutis laxa

Patient 1

The patient was a 16-year-old girl with a two-year history of severe skin laxity on the upper limbs and the trunk, though the face was spared (Figure 1a). Mild mitral and tricuspid regurgitation were detected on echocardiography. A hiatal hernia was also demonstrated on a barium swallow. Osteoporosis was conspicuous. The patient was mildly mentally disabled, but neuromotor development was normal. No musculoskeletal or internal organ abnormality was found.

The histopathology examination revealed severe elastorrhexis (fragmentation of elastin) and a sharp decrease in elastin fibers in the dermis (Figure 2a). Electron microscopy revealed disorganized and thick collagen fibers and amorphous materials around degenerated elastic fibers (Figure 3a). The result of direct immunofluorescence was negative.

Patient 2

The patient was a one-month-old neonate girl with severe laxity of the skin and joints. On the physical examination, the skin was completely lax and had lost its elasticity. She had facial dysplasia with special features, including micro-retrognathia, a flat midface, frontal bossing, wide fontanels, a wide nasal bridge, and hypertelorism (Figure 1b). Her parents were cousins. She was the second child of the family. The patient's brother had died at six



Figure 1. Clinical photographs of the patients with inherited cutis laxa: (a) Skin laxity on upper limbs and the trunk in a 16-year-old girl (Patient 1); (b) Severe laxity of skin and joints in a one-month-old neonate girl with facial dysplasia (Patient 2); (c) Pedunculated and lax skin of the trunk (Patient 3); (d) Increased skin laxity with a pinched nose, triangular and pulled face, and pectus excavatum in a two-year-old girl (Patient 4); (e) Pinched nose, triangular face, drawing chin, lax skin, and prominent skin vessels in a seven-year-old girl (Patient 5)

months because of a similar disease.

The echocardiography assessment detected moderate tricuspid regurgitation and a patent foramen oval. Multiple diverticula (tortuosity) were also found in the intestinal wall, bladder, and urethra. The patient was hospitalized several times because of severe respiratory distress and tracheomalacia. Unfortunately, the patient died at six months, similar to her brother. The patient's frozen samples were sent for genetic analysis. According to genetic analysis, a homozygous likely pathogenic variant of latent transforming growth factor binding protein (LTBP4) was detected. The variants in LTBP4 are associated with autosomal recessive type cutis laxa, also known as Urban-Rifkin-Davis Syndrome.

Patient 3

The patient was a 27-year-old girl. The skin was lax and pedunculated over the extensor surfaces of the limbs, abdomen, and thighs (Figure 1c). The face was not involved. Coxa varus and mild intellectual disability were also observed. Histopathologic examination showed a severe decrease in elastin fibers along with a critical decrease in collagen fibers (Figure 2b). In addition, elastin fibers were damaged by electron microscopy examination (Figure 3b). Unfortunately, the patient refused any further evaluation.

Patient 4

The patient was a two-year-old girl, and her parents were relatives. The pregnancy was

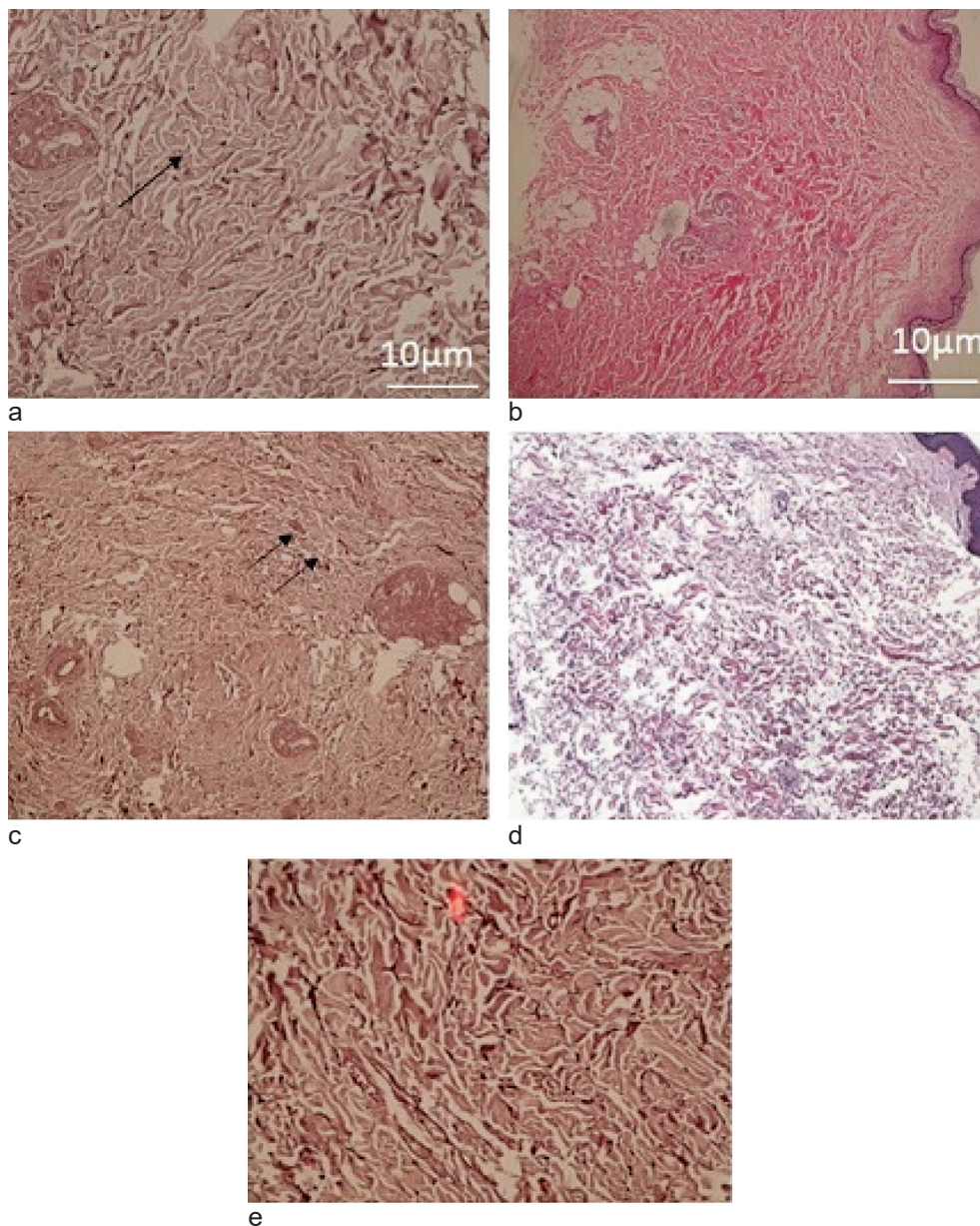


Figure 2. Histopathological H&E staining revealed: (a) Severe elastorrhexis with a sharp decrease in elastin fibers in the dermis (H&E ×40) (Patient 1); (b) A sharp decrease in elastin and collagen fibers in the dermis (H&E ×40) (Patient 3); (c) A severe decrease in elastin fibers along with a critical decrease in collagen fibers in the dermis (H&E ×40) (Patient 6); (d) Decreased to complete loss of elastin fibers with some bundles of collagen in the dermis (H&E ×40) (Patient 7); (e) Sparse to nearly absent elastin fibers in the dermis (H&E ×100) (Patient 8)

uncomplicated. Some motor and cognitive disorders were found after birth. Moreover, she had a pinched nose, triangular and pulled face, pectus excavatum, and hyperextensibility of joints, particularly at the wrists, ankles, and toes (Figure 1d). Lax skin, prominent vessels on the chest and abdomen due to the atrophy of the skin and subcutaneous fat, congenital hip dysplasia, knee subluxation, and osteoporosis were also noted. Wrinkles were most

prominent on the back of the hands, feet, and abdominal skin. The genetic analysis confirmed the diagnosis of cutis laxa with homozygous variations on the *PYCR1* gene.

Patient 5

The patient was a seven-year-old girl, the second child of the family born to related parents. The patient had a family history of a similar disease, but the

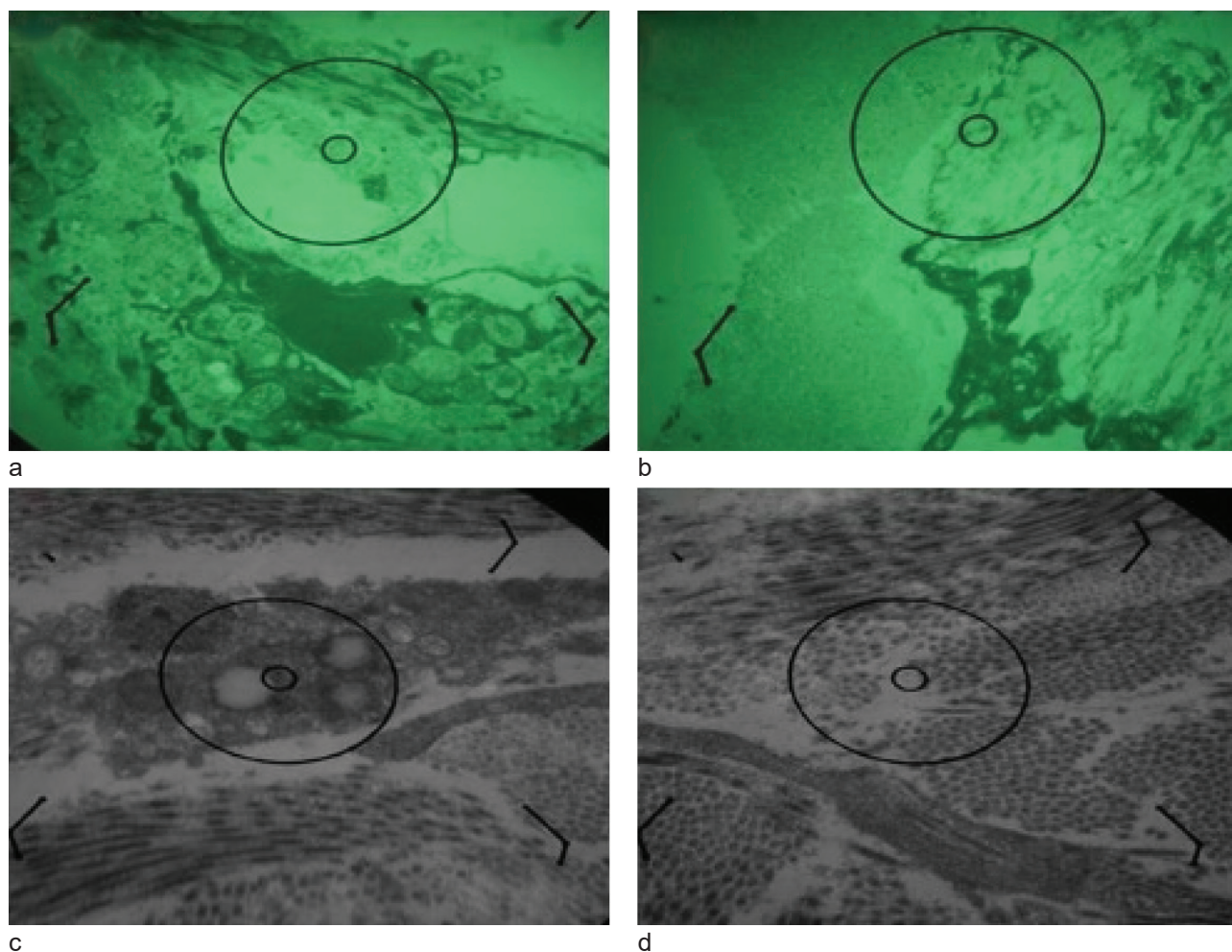


Figure 3. Electron microscopic analysis of the skin: (a) Disorganized and thick collagen fibers and amorphous materials around degenerated elastic fibers (Patient 1); (b) Globules of elastin fiber in the dermis with adjacent bundles of microfibrils (arrows) indicating elastin fibers damage (Patient 3); (c) Disorganized and thick collagen fibers and amorphous materials around degenerated elastic fibers (Patient 6); (d) Damaged elastic fibers with amorphous materials in destructed areas (Patient 8)

family's first child was normal. Although she initially developed normally, mental retardation was seen later on after birth. Additionally, a pinched nose, triangular face, drawing chin, lax skin (especially on the trunk and limbs), and prominent skin vessels were observed (Figure 1e). Moreover, mild myopia and astigmatism, congenital hip dysplasia, osteoporosis, bone growth retardation, pes planus, pectus excavatum, and sunken eyes were detected. Cutis laxa was confirmed by genetic analysis, which revealed *PYCR1* gene homozygous variations.

Acquired cases of cutis laxa

Patient 6

The first patient was a 40-year-old woman with severe recalcitrant urticaria following the

administration of penicillin. Progressive skin laxity occurred in the patient six months after the appearance of urticaria. The disease was insidiously progressive, and the 40-year-old patient looked older than her actual age (Figure 4a). Moreover, membranoproliferative glomerulonephritis (MPGN) and umbilical hernia appeared about one year later. The renal involvement was recalcitrant. In bone densitometry, severe osteoporosis was detected.

Histopathology examination, including orcein staining, showed decreased to complete loss of elastin fibers in the dermis, fragmented epidermis, and epidermal atrophy. The histopathological analysis also displayed collagen bundles in the dermis (Figure 2c). In electron microscopy, scattered, disorganized, and thick collagen fibers were seen in the dermis. Moreover, areas of amorphous



Figure 4. Clinical photographs of the patients with acquired cutis laxa: (a) Progressive skin laxity in a 40-year-old female adult (Patient 6); (b) Considerable skin laxity on the eyelids a few months after the blepharoplasty (Patient 7); (c) Considerable skin laxity on the scar of a previous skin surge (Patient 8)

materials around degenerated elastic fibers were noticeable (Figure 3c).

Patient 7

The patient was a 26-year-old man with a history of blepharoplasty due to a severe drooping eyelid a few months before. He was referred to us after blepharoplasty surgery, so we could not access his preoperative photos. A few months after blepharoplasty, the patient demonstrated considerable skin laxity on the eyelids, trunk, and extremities (Figure 4b). The patient had no history of drug use or prior urticarial reaction. Histopathological evaluation revealed sparse to nearly absent elastin fibers in the dermis (Figure 2d). These findings could be compatible with the diagnosis of cutis laxa, which manifested first as a localized form by blepharochalasis. The patient refused to cooperate with further evaluations due to his severe depression.

Patient 8

A 23-year-old girl was referred to us with a

history of multiple surgeries for repairing her lax pedunculated skin. She showed considerable skin laxity on the extensor surfaces of the joints, with numerous scars from previous skin surgeries (Figure 4c). The face was not involved. The patient had no history of any musculoskeletal disorder. Neuromotor and cognitive development were also normal. On skin histopathology examination, a sharp decrease in elastin and collagen fibers was revealed in the dermis (Figure 2e). In addition, elastin fibers were damaged according to electron microscopy examination (Figure 3d). Unfortunately, the patient refused further evaluations.

Serum MMP-2 and MMP-9 measurement

In this case series, serum MMP-2 and MMP-9 levels were assessed in all eight patients. The results showed that the MMP-2 and MMP-9 serum levels were significantly higher than the normal ranges of 70-93 ng/ml and 84-103 pg/ml, respectively (Table 1).

Table 1. The patients' serum MMP-9 and MMP-2 levels

	P1	P2	P3	P4	P5	P6	P7	P8
MMP-9 (pg/ml)	310,400	184,200	3,750	36,950	127,400	67,000	70,000	250
MMP-2 (ng/ml)	16,426	1,350	5,734	3,986	4,410	1,988	3,694	7,242

P = patient; MMP = matrix metalloproteinase

DISCUSSION

Cutis laxa is characterized by abnormal elastic fibers resulting in loose, redundant, hypoelastic skin. The skin can easily be pulled away from the underlying tissue and slowly returns to its original position. These findings are often most noticeable on the neck, hands, and groin, but can also be seen on the face, creating a premature aging appearance. Cutis laxa is not characterized by easy bruising or abnormal scarring in comparison with some other skin connective tissue diseases. Cutis laxa may be related to autoimmune disease and can also be inherited or acquired. Inherited forms include autosomal dominant cutis laxa, autosomal recessive cutis laxa, Urban-Rifkin-Davis syndrome, macrocephaly-alopecia-cutis laxa-scoliosis syndrome, and arterial tortuosity syndrome (ATS) or X-linked cutis laxa¹⁰. Herein, we have reported both inherited and acquired forms of cutis laxa with their various clinical and histopathological characteristics. However, there are significant overlaps among different types of cutis laxa, and definite clinical classification can be difficult. The acquired form is rare and has been associated with different conditions, such as heavy chain deposition disease¹¹.

Previous studies have demonstrated an imbalance between proteases such as trypsin, cathepsin, and matrix metalloproteinases (MMPs) and their inhibitors, which can result in abnormal elastin and collagen catabolic processes. MMPs are involved in tissue remodeling, cell migration, angiogenesis, and tumor cell metastasis^{10,12}. Moreover, MMPs are responsible for the breakdown of collagen in the skin of cutis laxa patients; an increased level of collagenase activity has been shown in fibroblasts derived from patients' skin¹⁰. The study by Hatamochi *et al.* indicated elevated expression levels of MMP-1, MMP-3, and MMP-9 in the fibroblasts of cutis laxa patients. They concluded that increased expression of MMPs may be associated with histopathological abnormality in cutis laxa patients¹³. In another study, levels of expression of MMP-3, MMP-7, and MMP-9 were significantly increased in the culture media of anetodermic skin compared to uninvolved skin. They suggested that these metalloproteinases could be involved in the degradation of elastic fibers in anetodermic skin¹⁴. Thus, MMP expression may

provide considerable insight into the pathogenesis of cutis laxa. In the current study, we investigated the serum levels of MMP2 and MMP9 in eight patients with cutis laxa. Most of our patients revealed loss of elastin fibers in their histopathological analysis. In addition, elevated MMP-2 and MMP-9 were observed in all eight cases, which agreed with previous studies^{10,15}.

In our study, patients 1 and 2 revealed the highest serum levels of MMP-9, and we found severe skin laxity in patient 1. Moreover, patient 2 died of systemic complications of cutis laxa. Moreover, the severe skin laxity in patient 1 displayed a positive correlation with the highest serum levels of both MMP-2 and MMP-9. Regarding the lowest serum levels of MMP-9 in patients 3 and 8 associated with the mildest type of cutis laxa, we suggest that the elevated level of MMP-9 may be correlated with the disease severity. Therefore, sharply elevated MMP-9 and MMP-2 may lead to severe cutis laxa and elastin degradation.

Our study had limitations, such as limited sample size and lack of any control group due to the rarity of this skin disease and our restricted facilities. However, this report could be a completely distinctive pilot study about eight patients with different types of cutis laxa as a rare skin condition, along with the measurement of their serum levels of MMPs. The results suggest the possible role of MMP-2 and MMP-9 in the pathogenesis of cutis laxa. Surely, future multi-center studies with a more structured and controlled design could be beneficial to elucidate any possible role of MMPs in the pathogenesis of cutis laxa.

Author contributions

AE: Conceptualization, study supervision, and study validation

FM: Study supervision, conceptualization, and study validation

MK: Data gathering and electron microscopic evaluation

AK: Data gathering and writing the manuscript

FS: Data interpretation and writing the manuscript

RR: Data interpretation, writing, reviewing, and revising the manuscript

All authors have read and approved the final manuscript.

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Consent for publication

The patients or patient guardians provided written informed consent to the publication of their case details.

Conflict of interest: None declared.

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Suction pearl: standardization of syringe suction cup sizes for the three-way cannula-cup device

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Dear Editor,

Suction devices are used to produce blisters for epidermal grafting over the vitiliginous patch and achieve a good cosmetic result, but the process takes 1 to 3 hrs¹⁻³. To hasten the suction process, heat and normal saline intralesional injection can be given over the site; the blister formation takes about 1 hour using a modified disposable syringe with a small disposable syringe cup and a three-way cannula^{4,5}. However, the cup suction device is small and more stable than the syringe device, and it is easier to create negative pressure in the suction cup. Considering the advantages of the small three-way cannula-cup device over longer suction devices, a set of small cups of various radii can be used to produce suction blisters.

There is a relation between the height (h), radius (r), and volume (v) of the suction cup and the blister. The syringe suction cup is a small cylinder, and its produced blister is a small hemispherical structure. If the suction cup is cut at the height/length of its radius, then the cup's height will equal its radius ($h = r$). This means that the volume of the cup (cylinder), given by $\pi r^2 h$, can be considered as πr^3 , and the volume of the blister (half of a sphere/hemisphere), given by $1/2 \times 4/3 \pi r^3$, can be considered as $2/3 \times \pi r^3$. So, the ratio of the volume of the cup to the volume of the blister is equal to $(\pi r^3) \div (2/3 \pi r^3)$, simplified to $3/2$ or 1.5. This shows that the volume of the suction cup, even at its radial height ($h = r$), is about 1.5 times the volume of the blister. Thus, even at its radius height, the cup has an adequate volume for producing an intact and complete blister.

Syringes of 5, 10, 20, and 50 ml capacity with radii of 6, 8, 10, and 15 mm, respectively, were selected. Then, the syringes were smoothly cut from their needle hub side at suction heights equal to their radii, and the volume of the cups

(πr^3) was calculated as 0.67, 1.6, 3.14, and 10.6 ml, respectively. After this, vaseline was applied to the rim of the cups on its needle hub and over the aseptic suction site to improve its air-sealed property. Following this, each of the four three-way cannula-cup devices was applied airtight over the lateral side of the thigh. A vacuum was created inside the cup by sucking out 1.7, 4.0, 7.6, and 26 ml of air, respectively, equal to about 2 to 2.25 times the volume of the cups, including the airspace in the needle hub of the cup and in the outlet of the three-way cannula, with an appropriate syringe size. In another practical way, the air can be sucked out with a syringe from the cup till a well-formed hemispherical shape of skin tissue is formed inside the cup. Following this, the air connection of the cannula was blocked, and the syringe was detached from the suction device. The suction process was continued for 1 hour, and the changes inside the cups were noted at intervals of 15 minutes. During the suction process, the patient was advised to immobilize the part as far as possible.

Upon observation, vesicles were produced at 15 to 20 minutes, started to coalesce at 30 to 40 minutes, and formed different shapes of blisters and vesicles at 50 to 60 minutes. The suction process was well tolerated. Complete bullae were produced in 5 ml and 10 ml cups without hemorrhage. In 20 ml and 50 ml cups, various sizes of hemorrhagic vesicles were produced, which coalesced to form large blisters by applying painless lateral pressure with the finger and thumb (Figure 1 a-f).

Therefore, a small three-way cannula-cup device of its radial height is an effective, fast, and stable suction device for producing suction blisters. Intralesional hemorrhage and incomplete blisters were observed with bigger cups, which is why their negative pressure should be titrated with a barometer, and the air suction volume should

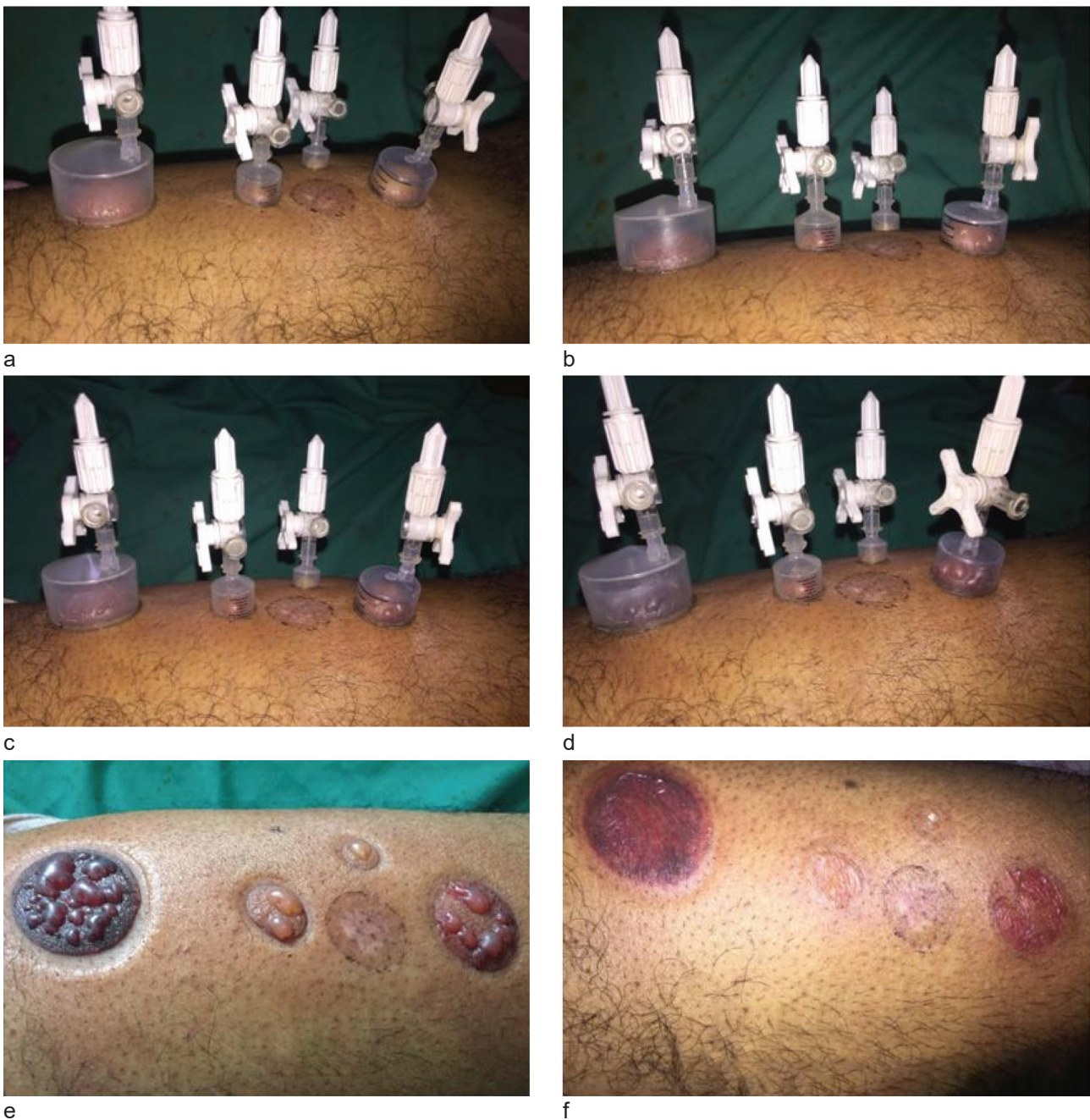


Figure 1. (a-f). Changes observed at 15-minute intervals during the suction process using the three-way cannula-suction cup device

not be more than two times the cup volume in larger cups to achieve a flawless blister. In case of a vesicle is not seen after 15 to 20 minutes, then a few ml of air can be sucked out to enhance the suction process but with care about hemorrhage or rupture of the blister. To remain on the safe side, it is best to suck out air about two times the cup volume. Heat can be applied over the site to enhance the suction process. Less mobile, plain

sites are better for a successful suction procedure.

Conflic of Interest: None declared.

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An asymptomatic scaly plaque over the glans penis in an elderly male

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CASE HISTORY

A 68-year-old man complained of a two-year history of an asymptomatic, slow-growing lesion over his glans penis. The physical examination revealed a single, well-defined, non-tender, dry, rough, hyperkeratotic, mica-like scaly plaque measuring 3.8 cm × 2.8 cm over the dorsal aspect of the glans penis (Figure 1). There were no other skin lesions or regional lymphadenopathy. The patient had undergone circumcision for phimosis ten years ago. There was no history suggestive of any previous sexually transmitted infections. Serological studies for HIV and syphilis were negative.

Microscopic description

A 4-mm punch biopsy was taken from the lesion. The histopathological examination revealed a hyperkeratotic epidermis with parakeratosis, acanthosis, papillomatosis, spongiosis, and neutrophilic exocytosis. Mild focal atypia was observed. The papillary dermis showed chronic inflammatory infiltrates composed predominantly of lymphocytes and plasma cells admixed with few eosinophils (Figure 2).

What is your diagnosis?

Pseudoepitheliomatous keratotic micaceous balanitis

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Figure 1. A solitary, yellow, mica-like scaly lesion over the glans penis

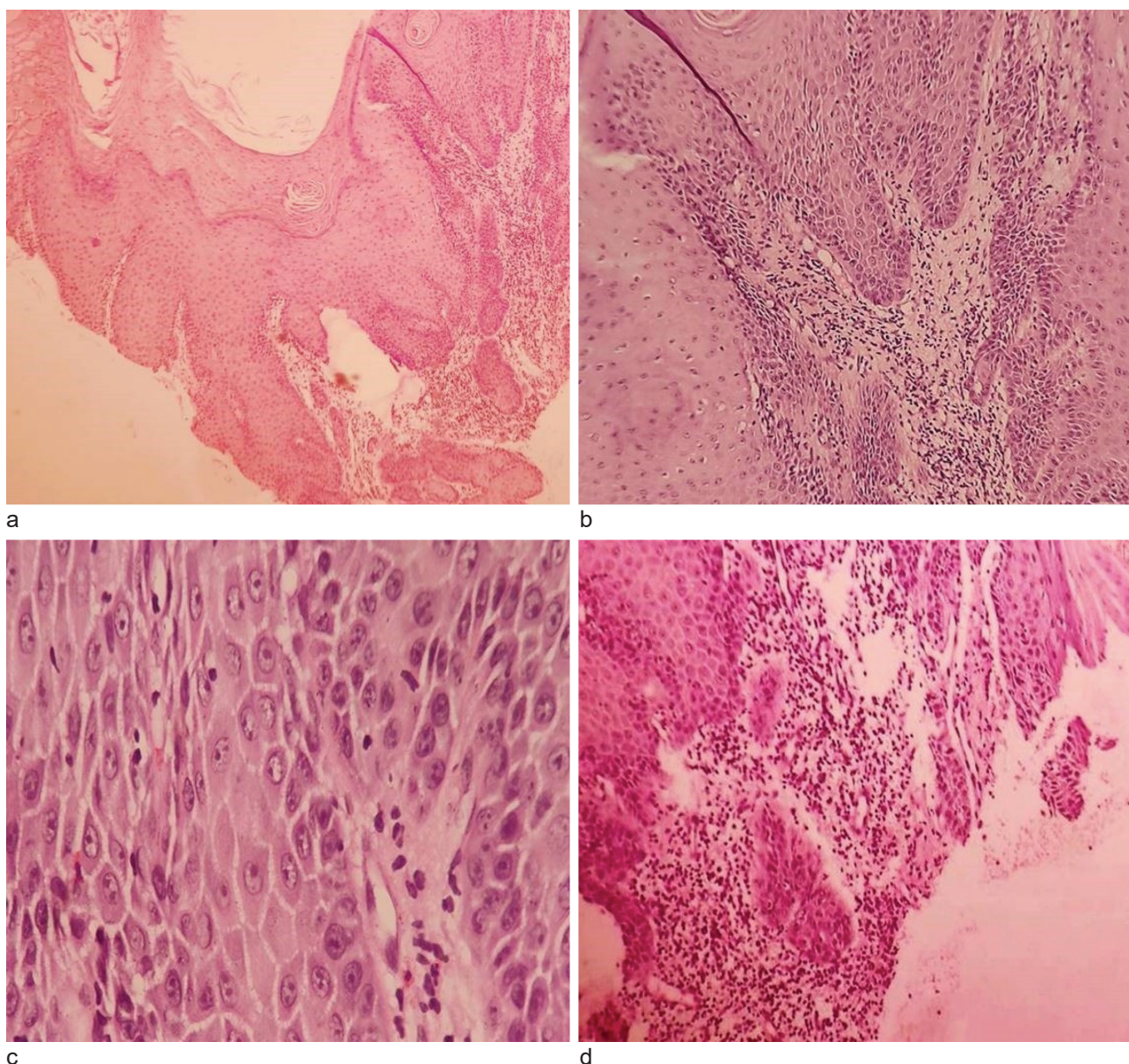


Figure 2. (a) Parakeratotic, hyperkeratotic, acanthotic epidermis showing features of papillomatosis (H&E $\times 4$). (b) Spongiosis with focal neutrophilic exocytosis (H&E $\times 40$). (c) Papillary dermis showing capillary-sized blood vessels and inflammatory infiltrates (H&E $\times 4$). (d) Fragment of tissue showing focal atypia (H&E $\times 10$)

DISCUSSION

Pseudoepitheliomatous keratotic micaceous balanitis (PKMB) was originally described in 1961 by LortatJacob and Civatte¹. It is an extremely rare penile disease, with few cases reported in the literature. The exact etiopathogenesis of this condition remains elusive, though it is considered a form of pyodermitis or a pseudoepitheliomatous response to an infection². It commonly affects men above 50 years, particularly those who have been

circumcised for their phimosis in their adult life³. Chronic irritation and inflammation secondary to long-standing phimosis may predispose to this condition⁴.

As a generally asymptomatic and chronic form of balanitis, PKMB gradually develops a silvery-white appearance. The distinct clinical findings are mica-like crusts and a keratotic horny mass over the glans penis. It may be occasionally associated with irritation, burning sensation, maceration, or fissuring^{2,5}. Rare clinical presentations include a

nail-like lesion over the glans or a penile horn². The peri-meatal involvement can lead to multiple urinary streams upon micturition, thereby giving a “watering-can penis” appearance⁵. Krunic *et al.* described four stages of the evolution of PKMB; i) initial plaque stage, ii) late tumor stage, iii) verrucous carcinoma, and iv) squamous cell carcinoma and invasion⁶.

The condition can also arise from a previously treated squamous cell carcinoma². The differential diagnoses of PKMB include giant condyloma, penile horn, penile psoriasis (early plaque stage), hypertrophic lichen sclerosis, keratoacanthoma, erythroplasia of Queyrat, Buschke-Lowenstein tumor, squamous cell carcinoma, and verrucous carcinoma^{2,7}. For an accurate diagnosis, a deep biopsy including the sub-epithelial tissues is required⁷.

The chronic clinical course of PKMB is associated with frequent recurrence². Treatment depends on the stage of the disease. During the early stages when there is no histological evidence of malignancy, topical 5-fluorouracil, imiquimod, and cryotherapy can be used. In the malignancy stage, local surgical excision or a partial penectomy is performed depending on the degree of involvement. Alternative therapeutic options include CO₂ laser, shave biopsy plus electrocoagulation, X-ray radiation, and photodynamic therapy^{1,4}. Post-treatment biopsies are warranted if topical chemotherapy is utilized³.

Our case is of interest since the occurrence

of PKMB is rare. Physicians should consider the diagnosis of PKMB in the differentials of a hyperkeratotic, scaly plaque over the glans penis in elderly circumcised patients.

Conflic of Interest: None declared.

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A 56-year-old with pustular lesions on extensor areas: what is your diagnosis?

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CLINICAL PRESENTATION

The patient was a 56-year-old woman with a history of hypertension and hyperlipidemia from one year ago. About two years ago, papule and pustular lesions emerged in the extensor area of both elbows; the lesions were accompanied by purulent discharge and brief itching, gradually turning into erythematous perforated indurated plaques and nodules within a month. These skin lesions then spread to the extensor surfaces of the knees, fingertips (painful lesions), scalp, and neck (Figures 1-3). The skin lesions appeared periodically and persisted for one month, with a two-three-month interval between each period. The patient complained of dyspnea on exertion but had no symptoms of cough, hemoptysis, weight loss, fever and chills, and night sweats. A PPD skin test was performed and returned positive; tuberculosis was also reported on a CT scan of the lungs. Furthermore, evidence in favor of tuberculosis was reported in a sample of the right axillary lymph nodes. After treatment, the lesions healed entirely, and only the elbow and knee scars remained.

What is your diagnosis?

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Figure 1. Pustular lesions first emerged in the extensor area of both elbows; the lesions were accompanied by purulent discharge and brief itching, gradually turning into erythematous perforated indurated plaques and nodules within a month



Figure 2. An erythematous, perforated, indurated plaque on the anterior aspect of the right leg

DIAGNOSIS

Cutaneous leukocytoclastic vasculitis associated with tuberculosis.

Microscopic examination

Leukocytoclastic vasculitis with dermal necrosis and ill-defined granulomas

Microscopic examination showed large subcorneal abscess, ulceration, nearly full-thickness dermal necrosis, fibrinoid necrosis of small vessels, leukocytoclasia, and fibrin thrombi partially surrounded by palisaded histiocytes. There were scattered ill-defined granulomas, lymphoplasmacytic cell infiltration, and few eosinophils in the deep dermis (Figures 4 & 5).

DISCUSSION

Vasculitis refers to blood vessel wall inflammation. Leukocytoclastic (neutrophil fragmentation) vasculitis is a small vessel vasculitis that can be idiopathic or secondary to infections, neoplasms, collagenosis, or the use of drugs¹; infections and drugs are the most common causes².

For the first time in 1967, Parish *et al.* showed that *Mycobacterium tuberculosis* could cause vasculitis³. Tubercle bacilli aggression, immune complex deposition in the vessel wall, delayed hypersensitivity response, or rifampicin-dependent antibodies are possible reasons for cutaneous vasculitis associated with tuberculosis⁴. Unlike



Figure 3. Lesions at various stages on the extensor surface of both knees

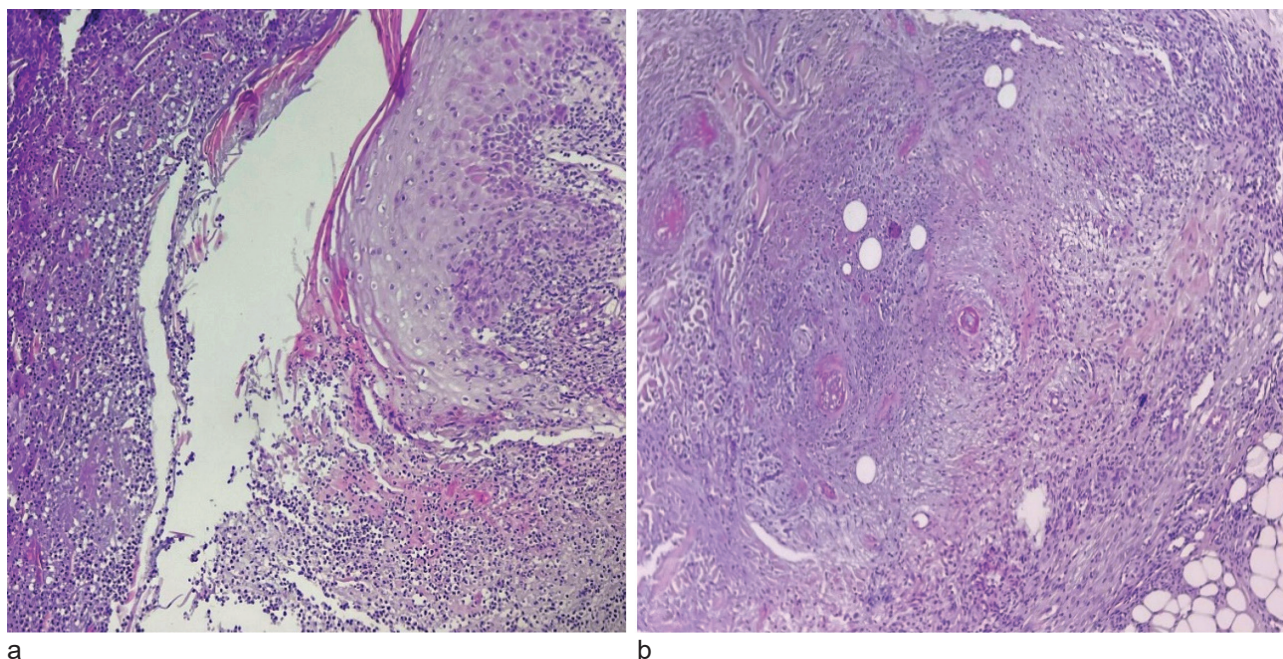


Figure 4. (a) Large subcorneal abscess, ulceration, and acanthosis. (b) Fibrinoid necrosis of small vessels wall, fibrin thrombi, dermal necrosis surrounded by histiocytes, ill-defined granulomas, and round cell infiltrate in the deep reticular dermis (H&E $\times 100$)

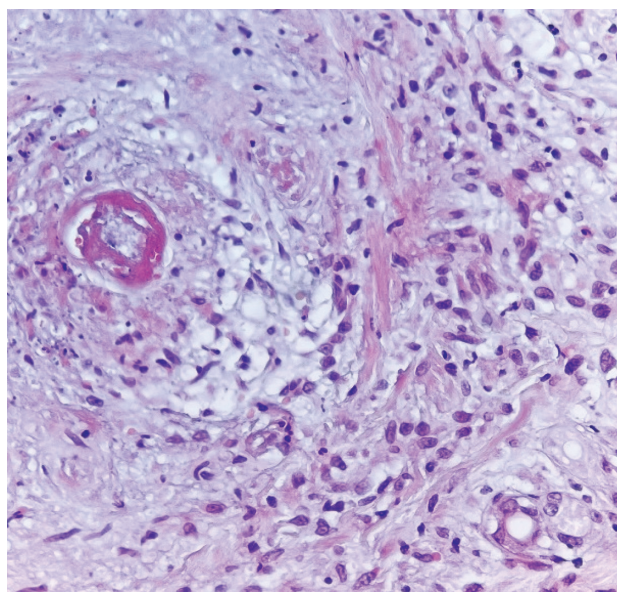


Figure 5. Leukocytoclastic vasculitis with fibrinoid necrosis surrounded by histiocytes (H&E $\times 400$)

cutaneous tuberculosis, the tubercle bacilli itself is not present in the vessel wall in leukocytoclastic vasculitis^{5,6}. Instead, the deposit of immune complexes in small vessels of the lower extremities is the primary mechanism of this type of vasculitis⁵. To treat these skin lesions, immunosuppression is not necessary, and treatment of tuberculosis is sufficient⁷.

Conflc of Interest: None declared.

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