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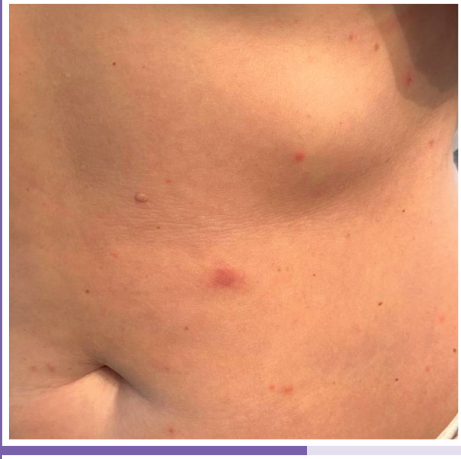

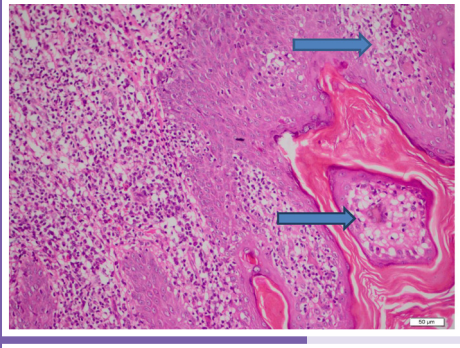

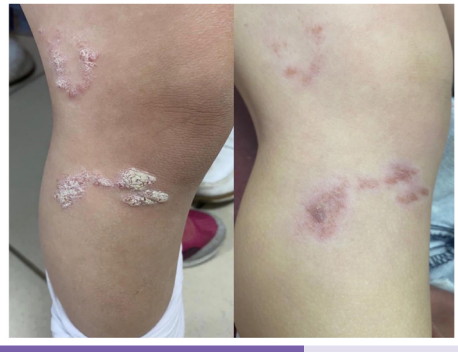

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Mareledwane NG. A randomized, open-label, comparative study of oral doxycycline 100 mg vs. 5% topical benzoyl peroxide in the treatment of mild to moderate acne vulgaris. Int J Dermatol 2006; 45: 1438-1439. PMID: 17184250

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REVIEW

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Clinical Approach to Erythroderma

Defne Özkoca, Tuğba Kevser Uzunçakmak

Istanbul University-Cerrahpasa, Cerrahpasa Faculty Medicine, Department of Dermatology and Venereology, Istanbul, Turkey

ABSTRACT

Erythroderma is a state in which greater than 90% of the total body surface area is erythematous and desquamated. It is a dermatological emergency which can be seen in every age group. The disease first presents with erythematous plaques that have a tendency to merge. Pruritus is frequently present. The rash spreads to the entire body within two to six days and widespread desquamation ensues. Etiological factors of erythroderma can be grouped into four categories which are pre-existing dermatological diseases, drug reactions, malignancy related and idiopathic. The most important part of erythroderma management is the supportive measures. Fluid and electrolyte balance should be maintained. Local wound care should be done with antiseptic wet dressings and emollients. Mid-potency topical corticosteroid creams should be used. The disease prognosis is dependent upon the etiology.

Keywords: Diagnosis, Erythroderma, Etiology, Treatment

Introduction

Erythroderma is a state in which greater than 90% of the total body surface area is erythematous and desquamated. It is a dermatological emergency which can be seen in every age group. The most common ages to present with erythroderma are 45 years and older. Erythroderma can be observed in children due to atopic dermatitis and hereditary diseases as well. It is two to four times more common in males compared to females. The incidence can vary according to the geographic region [1,2].

Clinical Presentation

The disease first presents with erythematous plaques that have a tendency to merge. Pruritus is frequently present. The rash spreads to the entire body within two to six days and widespread desquamation ensues. The skin is bright red, endurated, desquamating and warm. Wide desquamated plaques are seen in the chronic form of the disease whereas small plaques are present in acute forms. Heat and fluid loss due to erythroderma may lead to hypothermia and heart failure in severe cases. Chronic cases may lead to alopecia, longitudinal ridging of the nail plate and onychochysis. Lymphadenopathies, hepatomegaly and splenomegaly may also be observed [2,3].

Etiology

Etiological factors of erythroderma can be grouped into four categories which are pre-existing dermatological diseases, drug reactions, malignancy related and idiopathic [2]. A study from Singapore, regarding the etiological factors of erythroderma has concluded the following in 225 patients. Pre-existing dermatological diseases are the most common cause of erythroderma (68.9%) with eczema and psoriasis being the leading dermatoses. Idiopathic erythroderma is the second most common category (14.2%). Drug related erythroderma is the third most common group (10.7%). Malignancies are the least common cause of erythroderma (4%) with 2.2% consisting of cutaneous malignancies [4]. A study from Turkey revealed that the most common etiological factor for erythroderma

Address for Correspondence: Defne Özkoca MD, Istanbul University-Cerrahpasa, Cerrahpasa Faculty Medicine, Department of Dermatology and Venereology, Istanbul, Turkey
Phone: +90 536 656 10 00 E-mail: defneozkoca@yahoo.com ORCID ID: orcid.org/0000-0002-4211-2276
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was psoriasis vulgaris (59.6%) followed by drug eruption (17%), mycosisi fungoides (12.8%), atopic dermatitis (4.3%), bullous pemphigoid (2.1%), pytriasis rubra pilaris (2.1%) and polymorphic light eruption (2.1%) [5].

The common dermatoses that may present with or lead to erythroderma are psoriasis, airborne contact dermatitis, seborrheic dermatitis, atopic dermatitis, staphylococcal scalded skin syndrome, phytophotodermatitis, photosensitive dermatitis, pityriasis rubra pilaris, Pemphigus foliaceus, stasis dermatitis and ichthyosiform erythroderma. Less common pre-existing dermatological causes of erythroderma are candidiasis, dermatophytosis, mastocytosis, lichen planus, Reiter's syndrome, toxic epidermal necrolysis, diffuse/erythrodermic mastocytosis, sarcoidosis, pemphigoid, lupus erythematosus and crusted (Norwegian) scabies [2].

Common drugs to cause erythroderma are acetaminophen, minocycline, actinomycin-D, nitrofurantoin, allopurinol, omeprazole, arsenic, para-amino salicylic acid, barbiturates, penicillin, captopril, phenothiazine, chloroquine diphosphate, phenytoin, chlorpromazine, quinidine, cemetidine, rifampicin, dapsone, streptomycin, gold, sulfadiazine, hydantoin sodium, sulfonyl urea, interferon, tetracycline, isoniazid/isonicotinic hydrazide, thalidomide, isotretinoin, tolbutamide, lithium, vancomycin and mercurials [2].

The etiological factors can be grouped according to age as well. The causes of erythroderma in neonates and infants are grouped as congenital and non-congenital. The congenital causes are nonsyndromic congenital ichthyosis, syndromic congenital ichthyosis, Omenn syndrome, graft-versus-host disease, congenital cutaneous candidosis, psoriasis, diffuse cutaneous mastocytosis and staphylococcal scalded skin syndrome. The non-congenital causes are psoriasis, eczemas (atopic dermatitis, seborrheic dermatitis, staphylococcal scalded skin syndrome), drugs (vancomycin and ceftriaxone), metabolic disorders (holocarboxylase synthetase and biotinidase deficiency, essential fatty acid deficiency). The causes of erythroderma in the school ages are infections (staphylococcal scalded skin syndrome, crusted scabies), drugs (antiepileptics, amoxicillin, sulfonamides, antitubercular drugs), atopic dermatitis and psoriasis. The causes of erythroderma in adults are preexisting dermatoses (psoriasis, contact dermatitis, airborne contact dermatitis, chronic actinic dermatitis atopic dermatitis), drugs (antiepileptics, antimicrobials, analgesics), cutaneous T-cell lymphomas (Sézary syndrome, mycosis fungoides), internal malignancies, Multisystem disorders (dermatomyositis, subacute cutaneous lupus erythematosus) and idiopathic [1].

Diagnosis

Following the diagnosis of erythroderma, each patient should be assesed with the following [3,6]:

- Weight
- Body temperature
- Heart rate
- Respiratory rate
- Complete blood count
- Sedimentation rate/C-reactive protein
- Liver and kidney function tests
- Urinalysis
- Chest X-ray
- Electrocardiography
- Biopsy
- Viral serology

More specific test are total immunoglobulin E level if atopic dermatitis is considered; patch test if allergy is considered; skin scrapings if scabies or dermatophyte infections are considered; lymph node biopsy, peripheric staining and bone marrow aspiration if lymphoma is considered; and malignancy screening for elderly patients [3,6].

Management

The most important part of erythroderma management is the supportive measures. Fluid and electrolyte balance should be maintained. Hydration is of utmost importance. The patient should be kept at a warm and humid environment in order to prevent hypothermia. Protein rich nutritients are recommended. Local wound care should be done with antiseptic wet dressings and emollients. Mid-potencty topical corticosteroid creams should be used in treatment instead of high-potency creams because systemic side effects should be observed due to increased surface area of vulnerable skin. Seditising antihistaminic drugs are recommended for pruritic symptoms. Systemic antibiotherapy should be initiated if infection is suspected. Leg elevation and anti-diureticdrugs are recommended for peripheral edema [3,7].

The underlying diseases causing erythroderma should also be treated. Cyclosporine, retinoids, metothrexate, infliximab or phototherapy are recommended for the underlying psoriasis; systemic steroid and antimicrobials for atopic dermatitis; systemic steroid, retinoid and metothrexate for pytriasis rubra pilaris; intravenous immunoglobulin for toxic epidermal necrolysis; extracorporeal photophoresis, phototherapy, alkalizing chemotherapy or radiotherapy for lymphomas; and ivermectin and topical antiscabicidal drugs for scabies. Systemic steroid treatment can be initiated in idiopathic cases after the exclusion of psoriasis or staphylococcal scalded skin syndrome. The culprit drugs should be stopped in drug-induced cases as well [3,7].

In a study comparing the therapeutic options for idiopathic erythroderma, the authors concluded that the most effective treatment modality was cyclosporin (50-100 mg/day) [6].

Prognosis

The disease prognosis is dependant upon the etiology. Rapid treatment response is observed in drug-induced cases, lymphoma, leukemia, contact allergy and staphylococcal scalded skin syndrome. The response is slower if there is an underlying dermatosis such as psoriasis or atopic dermatitis. The disease may be mortal in elderly patients due to infectioni dehydration, electrolyte imbalances, heat intolerances and high-output heart failure. Postlesional hyperpigmentation or hypopigmentation may be observed in dark skinned individuals. Nail dystrophies, nevi evolvement, keloids, alopecia, generalized vitiligo and pyogenic granuloma have been reported in patients surviving erythroderma [3,7].

Ethics

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Authorship Contributions

Surgical and Medical Practices: D.Ö., T.K.U., Concept: D.Ö., T.K.U., Design: D.Ö., T.K.U., Literature Search: D.Ö., T.K.U., Writing: D.Ö., T.K.U.

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ORIGINAL ARTICLE

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Metabolic Syndrome in Patients with Plantar Corns and Calluses: A Case-Control Study

Müge Göre Karaali[1], Şevki Özdemir[2]

[1]Irmet International Hospital, Clinic of Dermatology, Tekirdag, Turkey
[2]Erzincan Binali Yildirim University, Mengucek Gazi Training and Research Hospital, Clinic of Dermatology, Erzincan, Turkey

ABSTRACT

Background: Corns and calluses are localized plaques of hyperkeratotic tissue over sites that are subjected to continual trauma. In this study, we aimed to investigate the presence of metabolic syndrome (MS) in patients suffering from plantar callosities.

Materials and Methods: Between February-December 2021, 32 patients with plantar callosities and 36 healthy subjects frequency-matched for age and sex were included in the study, which was designed as a prospective controlled study. Demographic, clinical and biochemical characteristics of the patients and the controls were recorded.

Results: Thirty-two patients with a mean age of 40.56±13.87 years and sex-age-matched 36 healthy controls with a mean age of 41.25±13.15 years were enrolled in the study. MS was present in 59.4% of the patient group. Hypertension (HT) was present in 28.1% of the patient group. Presence of MS and HT were significantly higher in the patient group than the control group ($p<0.05$). Waist circumference, triglyceride, fasting insulin and Homeostatic model assessment of insulin resistance levels were significantly higher in the patient group than in the control group ($p<0.05$). HDL cholesterol levels were significantly lower in the patient group that in the control group ($p<0.05$). It was determined that MS was more common in male patients and patients with unilateral lesion ($p<0.05$). The number of callosities in patients with MS was lower than in patients without MS ($p<0.05$).

Conclusion: Evaluation of MS may be recommended in patients diagnosed with corns and calluses. Studies about molecular mechanism of callus formation and common mechanisms with MS are needed to elucidate the pathogenesis of callus formation.

Keywords: Corn, Callus, Metabolic syndrome, Insulin Resistance, HOMA-IR

Introduction

Callosities are localized plaques of hyperkeratotic tissue over sites that are subjected to continual trauma [1]. These lesions, which are quite painful, significantly affect the quality of life of individuals by affecting person's gait and choice of footgear or activities [2]. It is commonly observed in palms and soles and one of the most frequent problem, especially in older people. Inadequate shoes, foot deformities and high levels of activity may induce callus formation by mechanical stress. The formation of callosities is suggested to be a protective response to trauma for protecting the underlying tissues [3].

Callosities may be seen clinically as corns and calluses [2]. A corn is a circumscribed lesion with permanent hyperkeratosis and a central conical core of keratin which causes pain and inflammation. This central core distinguishes the corn from the callus [4]. Corns are devided into two subtypes: The hard corn (heloma durum) and the soft corn (heloma mole). The hard corns, which is described

Address for Correspondence: Müge Göre Karaali MD, Irmet International Hospital, Clinic of Dermatology, Tekirdag, Turkey
Phone: +90 530 309 33 28 E-mail: mugegore@hotmail.com ORCID ID: orcid.org/0000-0003-0645-0662
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as dry corns, are frequently localized on the dorsolateral aspect of the fingers. The soft corns are frequently localized interdigitally, especially in the fourth interdigital space of the foots and characterized with macerated plaques. However a callus is a broad based, diffuse hyperkeratotic plaque frequently located on the plantar surface of metatarsophalangeal joints [2].

Histopathologically, the increase in keratinization and lower rate of desquamation have been shown to cause to the thickness of stratum corneum [3]. The thickness of stratum corneum and stratum granulosum, a decrease in keratinocyte density, abnormal rete ridge patterns are the most prevalent histopathological changes in calluses [3,5].

The exact cause of callus formation in the molecular aspect has not been proven. Kim et al. [6] reported that hyperproliferation and incomplete cornification and differentiation of keratinocytes, and increased expression of adhesion molecules may be the reason of callus formation.

We observe in dermatology outpatient clinics, that patients with callus are more overweight than other patients. Various growth factors and inflammatory mediators are suggested to be stimulated in tissues exposed to mechanic stress, and it may induce callus formation [1]. Weight actually increases the pressure on the feet and may promote callus formation. We also know that inflammation is higher in overweight and especially in patients with metabolic syndrome (MS).

We aimed to investigate MS in patients suffering from plantar callosities. To the best of our knowledge, there is no study in the literature evaluating this relationship.

Materials and Methods

The study was approved by Erzincan Binali Yildirim University Scientific Research and Publication Ethics Board (decision number: 02/08, date: 26.01.2021). A prospective controlled study was carried out between February-December 2021. Patients over 18 years diagnosed with plantar callosities in dermatology outpatient clinic; and age- and sex-matched healthy people as controls were included in the study. Written informed consent was obtained from all the patients and the controls.

Patients <18 years and patients with other chronic and/or any systemic inflammatory diseases were excluded for patient and control groups.

The age, sex, habits of smoking, the duration of the disease, lesion localization, number of lesions, type of callosities (corn/callus), body mass index (BMI kg/m^2), waist circumference in cm were recorded. Blood pressure was measured manually in both arms after 10 minutes of rest. Fasting blood glucose (FBG), triglycerides (TG), total cholesterol, low-density lipoproteins (LDL-cholesterol), high-density lipoproteins (HDL-cholesterol), fasting insulin were measured after 12-hours fasting.

The diagnosis of MS was evaluated according to the criterien established by Society of Endocrinology and Metabolism of Turkey, NCEP ATP III and World Health Organization [7,8,9].

Statistical Analysis

The Statistical Package for Social Sciences 22.0 was used for statistical analysis. Ratios of categorical variables between patient and control groups were tested by chi-square test. The distribution of variables was evaluated by the Kolmogorov-Smirnov test. For normally distributed data, t-test was used for independent groups and Mann-Whitney U was used for data not normally distributed. A p value of <0.05 was considered statistically significant.

Results

Thirty-two patients [female (n=23), male (n=9)] with a mean age of 40.56±13.87 years and sex-age-matched 36 healthy controls [female (n=27), male (n=9)] with a mean age of 41.25±13.15 years were included in the study. Of the patient 59.4% (n=19) had callus, 9.4% (n=3) isolated corn, 31.2% (n=10) mixed type callosities. Callosities were located on unilateral foot in 59.4% (n=19), on bilateral foots in 40.6% (n=13) of the patients. MS was present in 59.4% of the patient group. Hypertension (HT) was present in 28.1% of the patient group. Presence of MS and HT were significantly higher in the patient group than the control group (p<0.05). Smoking was statistically significantly higher in the patient group compared with the control group (p<0.05). The demographic and clinical properties of patients were shown in Table 1.

When metabolic control variables were compared between the patient and the control group, waist circumference, triglyceride, fasting insulin and homeostatic model assessment of insulin resistance (HOMA-IR) levels were significantly higher in the patient group than in the control group (p<0.05). HDL cholesterol levels were significantly lower in the patient group that in the control group (p<0.05). There was no significant difference regarding BMI, LDL cholesterol, FBG between the patient and control group. MS parameters of the patients and controls were shown in Table 2.

The relationship between demographic and clinical characteristics of the patients and the presence of MS in the patient group were evaluated and shown in Table 3. It was determined that MS was more common in male patients and patients with unilateral lesion (p<0.05). The number of callosities in patients with MS was lower than in patients without MS (p<0.05). There was no significant difference between the presence of MS and habit of smoking, age, and the lesion type (p>0.05).

Table 1. Descriptive and disease-related characteristics of the patients and controls

	Patient (n=32)		Control (n=36)		Total (n=68)		x^2/p
	n	%	n	%	n	%	
	Mean ± SD		Mean ± SD		Mean ± SD		t/p
Age (year)	40.56±13.87		41.25±13.15		40.92±13.40		-0.210/0.835
Sex							
Female	23	71.9	27	75.0	50	73.5	0.085/0.771
Male	9	28.1	9	25.0	18	26.5	
Duration of the disease (year)	31.16±36.19						
Type of lesion							
Callus	19	59.4					
Corn	3	9.4					
Mix type	10	31.2					
Number of lesions	2.19±1.53						
Lesion localization							
Unilateral	19	59.4					
Bilateral	13	40.6					
Smoking							5.333/0.021*
Present	11	34.4	4	11.1	15	22.1	
Absent	21	65.6	32	88.9	53	77.9	
Hypertension							6.364/0.012*
Present	9	28.1	2	5.6	11	16.2	
Absent	23	71.9	34	94.4	57	83.8	
Metabolic syndrome							9.768/0.002*
Present	19	59.4	8	22.2	27	39.7	
Absent	13	40.6	28	77.8	41	60.3	

*p<0.05, x^2: Chi-square test, t: T-test, SD: Standard deviation

Table 2. Comparison of metabolic control variables of the patient and the control group

	Patient group (n=32)	Control group (n=36)	
	Mean ± SD	Mean ± SD	
Body mass index (kg/m^2)	28.54±5.15	27.08±4.79	t=1.207 p=0.232
Waist circumference (cm)	90.65±13.75	80.69±10.03	z=-3.179 p=0.001*
Triglycerides (mg/dL)	154.00±63.04	123.50±73.06	z=-2.458 p=0.014*
Low-density lipoproteins (mg/dL)	125.03±31.96	115.50±36.67	z=-1.555 p=0.120
High-density lipoproteins (mg/dL)	45.34±9.82	52.61±10.80	t=-2.889 p=0.005*
Fasting blood glucose (mg/dL)	104.71±29.66	98.27±26.94	z=-1.469 p=0.142
Insulin (IU/mL)	17.01±11.52	13.04±18.74	z=-2.838 p=0.005*
HOMA-IR	4.58±3.60	4.18±10.09	z=-3.023 p=0.003*

*p<0.05, t: T-test in independent groups, z: Mann-Whitney U test, SD: Standard deviation, HOMA-IR: Homeostatic model assessment of insulin resistance

Table 3. Comparison of disease-related characteristics of individuals in the patient group with the presence of metabolic syndrome (n=32)

	Metabolic syndrome Present (n=19)	Metabolic syndrome Absent (n=13)	
	n (%)	n (%)	
Sex			x^2=8.658 p=0.004*†
Female	10 (43.5)	13 (56.5)	
Male	9 (100)	0 (0)	
Smoking			x^2=3.680 p: 0.072†
Present	4 (36.4)	7 (63.6)	
Absent	15 (71.4)	6 (28.6)	
Lesion localization			x^2=7.428 p=0.006*
Unilateral	15 (78.9)	4 (21.1)	
Bilateral	4 (30.8)	9 (69.2)	
Type of lesion			x^2=2.412 p=0.299
Callus	10 (52.6)	9 (47.4)	
Corn	3 (100)	0 (0)	
Mix type	6 (60.0)	4 (40.0)	
	Mean ± SD	**Mean ± SD**	
Age (year)	43.94±14.19	35.61±12.26	z=-1.576 p=0.115
Duration of disease (year)	2.29±3.09	3.04±2.95	z=-1.200 p=0.230
Number of lesions	1.42±0.60	3.30±1.79	z=-3.908 p=0.000*

*p<0.05, x^2: Chi-square test, †Fisher Exact test, z: Mann-Whitney U test

Discussion

MS is characterized with abdominal obesity, high levels of TG and FBG, low levels of HDL-cholesterol and presence of HT [10]. MS, which is stated to be seen with equal frequency in men and women, affects 30-40% of all people, the prevalence of MS is increasing especially because of sedentary lifestyle [11]. Cardiovascular diseases are the most common cause of death all over the world, and one of the most important causes of cardiovascular diseases is the presence of MS. Therefore, early diagnosis and prevention of MS are important.

Psoriasis vulgaris, hidradenitis suppurativa, acne vulgaris, acanthosis nigricans, androgenetic alopecia, atopic dermatitis, and rosacea are the disorders which are showed to be associated with MS in dermatology [12,13,14,15]. Although the exact cause of association between MS and cutaneous disorders is unknown, burden of inflammation is suggested to be the common mechanism of MS and dermatological diseases.

Callosity is a very frequent disease in dermatology practice, and we observe in dermatology outpatient clinics, that patients with callosities are more overweight than other patients. To the best of our knowledge, there have been no study in the literature examining the relationship between MS and callus formation. Repetitive trauma is the main reason for callus formation and weight may increase the pressure on the feet and may promote callus formation. We know that inflammation is higher in overweight and especially in patients with MS. The molecular mechanisms of callosities should be clarified, but inflammation may be an effective factor in callus formation.

In our study, the presence of MS in the patients with callosities was statistically significantly higher compared to the control group. Waist circumference, triglyceride, fasting insulin and HOMA-IR levels were significantly higher, however HDL cholesterol levels were significantly lower in the patient group than in the control group. Booth and McInnes [1] mentioned that mechanic stress in tissues stimulate various growth factors and cytokines, and it promotes callus formation. In patients with MS systemic inflammation is triggered especially by adipokines, and various growth factors are also promoted in insulin resistance, which is an important component of MS. The association of callus formation with MS can be explained by induced inflammation. However, Kim et al. [6] reported that hyperproliferation and incomplete cornification and differentiation

of keratinocytes, and increased expression of adhesion molecules may be the reason of callus formation. Stimulation of inflammation at the cellular level may also impair differentiation of keratinocytes.

In our study cigarette consumption was statistically significantly higher in the patient group compared with the control group. With chronic mechanic trauma, a repair mechanism begins in the skin, since the skin wants to protect the underlying tissues. Vascular structures also play a role in the supply of substances needed in this repair mechanism. Oxygen supply to the tissues is impaired with cigarette consumption, as well as vascular damage is seen in chronic cigarette consumption and increases the negative effects of MS. Impaired cellular differentiation and wound healing may promote callus formation. Clarifying the pathogenesis of callus at the molecular level may provide a clearer explanation of this relationship.

In our study, it was seen that we should be more careful in terms of MS in male patients with corns and calluses, patients with lesions on unilateral foot, and patients with fewer lesions.

Study Limitations

The main limitation of the study is small sample size.

Conclusion

According to our results, patients with corns and calluses may be evaluated in terms of MS. MS is the main cause for inducing cardiovascular diseases, which are the most frequent reasons for death. Therefore, early diagnosis and prevention of MS are crucial. The exact etiopathogenesis of the association of MS and cutaneous disorders has not been clarified, but it is important to elucidate the common mechanisms of MS and associated skin diseases, especially for the advancement of new therapeutic agents. Chronic inflammation and vascular damage may be the reason of callus formation. Although corns and calluses are common, there are limited studies on this subject. Studies about molecular mechanism of callus formation are needed to elucidate the pathogenesis of callus.

Ethics

Ethics Committee Approval: The study was approved by Erzincan Binali Yildirim University Scientific Research and Publication Ethics Board (decision number: 02/08, date: 26.01.2021).

Informed Consent: Written informed consent was obtained from all the patients and the controls.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G.K, Ş.Ö., Concept: M.G.K, Ş.Ö., Design: M.G.K, Ş.Ö., Data Collection or Processing: M.G.K, Ş.Ö., Analysis or Interpretation: M.G.K, Ş.Ö., Literature Search: M.G.K., Writing: M.G.K.

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ORIGINAL ARTICLE

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A Retrospective Analysis from Turkey: The Effect of the COVID-19 Outbreak Quarantine on Dermatology Outpatient Clinics

Funda Kemeriz[1], Emine Müge Acar[1], Burcu Tuğrul[2], Gülhan Aksoy Saraç[3]

[1]Yuksek İhtisas University Faculty of Medicine, Department of Dermatology, Ankara, Turkey
[2]Ankara City Hospital, Clinic of Dermatology, Ankara, Turkey
[3]Ufuk University Faculty of Medicine, Department of Dermatology, Ankara, Turkey

ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) pandemic has affected daily life in many aspects with lockdowns, restrictions and social isolation. It also has a significant impact on dermatologic practice. In this study, it is aimed to evaluate the applications of dermatology patients to the outpatient clinics during the quarantine period in the first 2 months of the COVID-19 epidemic in one center from Turkey. We also aimed to investigate the incidence of patients infected with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) examined at dermatology visits, and the frequency of patients were getting worse while their treatments were interrupted due to the outbreak.

Materials and Methods: This retrospective study included 416 participants. According to the anamnesis, dermatological examination, laboratory, and SARS-CoV-2 tests written in the files, 416 patients' files were reviewed. The age, sex, occupation, diagnosis of the patients, disease duration of the patients, their medical history were evaluated.

Results: According to the study results of 416 patients, female dominance (57.7%) was observed. The lesions in 157 of 416 patients (37.7%) were localized on the face. The most common diagnosis of the patients were acne vulgaris (n=113, 27.16%). Three of 416 patients (0.72%) were co-diagnosed with COVID-19 during hospital visits. Acute urticaria was observed after COVID-19 infection in 1 patient. Stress (31.25%) was the most triggering factor for the dermatological diseases reported by the patients.

Conclusion: According to the results of the study, pandemic process negatively affected on the dermatological patients in many ways, including treatment interruptions, restriction of outpatient clinic applications.

Keywords: Dermatology outpatients, Pandemic, SARS-CoV-2, Treatment

Introduction

The outbreak of a newly identified coronavirus in Wuhan province of China, in December 2019 was reported as the beginning of a novel pandemic named the coronavirus disease-2019 (COVID-19). COVID-19 is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. SARS-CoV-2 viruses are enveloped, positive single-stranded large RNA viruses, that can lead to severe extensive viral pneumonia, significant morbidity and mortality in infected patients. According to the World Health Organisation, SARS-CoV-2 is transmitted through respiratory droplets of infected people in either direct (close contact with an infected person) or indirect (fomites surrounding the infected persons or tools used during examination such as dermatoscope) way. Hidden transmission from asymptomatic carriers was also reported [2,3].

In Turkey, the first case was reported on March 11, 2020. Some outbreak rules of isolation, which prevented the gathering of people were implemented by the Turkish government as other countries, including curfew for citizens over the age of 65 and those with

Address for Correspondence: Funda Kemeriz MD, Yuksek Ihtisas University Faculty of Medicine, Department of Dermatology, Ankara, Turkey
Phone: +90 312 326 66 54 E-mail: dr.fkmrz@hotmail.com ORCID ID: orcid.org/0000-0003-3504-9886
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chronic diseases. Schools and cafes were closed. Matches in sports leagues and flights with suspicious countries were cancelled. The services of outpatient and inpatient clinics and surgery operations in hospitals were partially restricted. Outpatient clinics started service only by appointment.

Dermatological diseases rarely require urgent treatment, however, immunosuppressive agents are frequently used in dermatological diseases and if the drugs are discontinued, the diseases may exacerbate in patients through remission period. Additionally, dermatology practices have a risk for SARS-CoV-2 transmission during the close physical examination as reported before [4,5].

In this retrospective study, it was aimed to determine the characteristics of patients who applied to dermatology outpatient clinics during the early pandemic period. It is also aimed to investigate the incidence of the patients infected with SARS-CoV-2 who visited to dermatology clinics.

Materials and Methods

Study Design

The Institutional Review Board approval was obtained from the local committee of Clinical and Laboratory Research Ethics in Aksaray University (decision number: 2020/06-15, date: 22.06.2020) in "Aksaray University Research and Training Hospital", Dermatology Department for this study. This research was carried out compatible with the Declaration of Helsinki principles. This retrospective and single-centered research included patients admitting to dermatology outpatient clinics of Aksaray University Research and Training Hospital from the beginning of April 2020 to the end of May 2020.

Anamnesis, dermatological examination, laboratory results, and SARS-CoV-2 tests written in the files 416 patients' files were reviewed and analyzed from hospital database. The age, sex, occupation, diagnosis of the patients, disease duration of the patients, their medical history were evaluated. Locations of the lesions and possible triggers for the disease were noted.

Statistical Analysis

SPSS 23.0 version Package program was used to analyze the data. The data distribution normality was assessed by the Shapiro-Wilk test. Continuous variables and were represented by numbers and percentages as "mean ± standard deviation" and categorical variables by numbers and percentages. Categorical variables were analyzed with the test of chi-square and the analysis of the difference between continuous non-normally distributed variables were done by the "Mann-Whitney U test." $P<0.05$ was accepted as statistically significant.

Results

A total of 416 patients' records were reviewed and analyzed from the beginning of April 2020 to the end of May 2020. The mean age of the patients was 32.31±17.45 (range, 2-86 years old). Two hundred and forty of 416 patients (57.7%) were female, and 176 of 416 patients (42.3%) were male. According to the occupation, 252 of 416 patients (60.6%) were those who could stay isolated at home (housewives, students), 130 of 416 patients (31.2%) were those who had to work in offices (13.7% civil servant, 17.5% worker). There were 29 (6.97 %) patients over the age of 65 who had a partial curfew. Thirty-four of 416 patients (8.17%) were children.

The five most common diagnosis of the patients were acne vulgaris (n=113, 27.16%), acute or chronic dermatitis (n=96, 23.07%), cutaneous fungal infections (n=30, 7.21%), hair disorders (n=29, 6.96%), and psoriasis (n=16, 3.84%). Disease distributions of the patients were presented in detail in Table 1. Thirty-eight of 416 patients (9.13%) needed urgent treatment. These were presented in detail in Table 2. Acute urticaria was observed after COVID-19 infection in 1 patient.

The lesions in 157 of 416 patients (37.7%) were localized on the face. Thirty-nine of 416 patients (9.4%) had symptoms on the scalp. Other localizations of the lesions were presented in detail in Table 3.

Two hundred and twelve of 416 patients (50.96%) were admitted to the clinic for the first time, the remaining (n=204, 49.04%) were follow-up patients. Fifty-one (12.3%) patients with acne vulgaris were on isotretinoin treatment. One-hundred and ninety-seven of 416 patients (47.4%) had dermatological symptoms for more than 6 months, 132 of 416 patients (31.7%) had the symptoms for 1 to 6 months, and 87 of 416 patients (20.9%) had them for less than 1 month.

Systemic therapies of 8 psoriasis vulgaris patients who were followed up in our dermatology outpatient clinic were interrupted due to the pandemic. Systemic treatment and regular follow-up were interrupted in 6 of 113 acne vulgaris patients (5.31%). One wart patient who was treated with cryotherapy stopped regular visits to our clinic due to the pandemic, and the lesion progressed. Systemic treatment and regular follow-up were interrupted in 6 patients using systemic isotretinoin, 2 patients on narrowband ultraviolet B, 3 patients on methotrexate, 2 patients on acitretin, 1 patient on adalimumab therapy. Decreased treatment efficacy was seen in 74 patients (17.8%), no change in treatment efficacy was seen in 96 patients (23.1%).

Twenty-seven of 416 patients (6.49%) had symptoms of COVID-19, but 3 of 416 patients (0.72%) were diagnosed with COVID-19 during hospital visits.

Fifty of 416 patients (12.01%) gave a history of more than one triggering agent, 38.8% (n=161) of the patients did not give a history of a triggering agent. The triggering factors were presented in Table 4.

Table 1. The diseases of patients admitted to dermatology outpatient clinic

	n	%
Acne	113	27.16
Acute/Chronic dermatitis Contact Dermatitis Seborrheic Dermatitis	96 81 15	23.07
Fungal infections	30	7.21
Hair disorders Alopecia Areata Telogen Effluvium Androgenetic Alopecia	29 22 4 3	6.96
Psoriasis	16	3.84
Warts	16	3.84
Urticaria	15	3.60
Scabies	12	2.88
Bacterial skin infections	11	2.64
Herpes infections	9	2.16
Melasma	8	1.92
Aphteous stomatitis	8	1.92
Chronic prurigo generale	7	1.68
Vitiligo	7	1.68
Rosacea	6	1.44
Pityriasis Rosea	6	1.44
Benign neoplastic lesions	4	0.96
Pre-malign neoplastic lesions **Actinic keratosis**	2 2	0.48
Malign neoplastic lesions **Basal cell carcinoma** **Squamous cell carcinoma**	4 2 2	0.96
Uncus incarnatus	3	0.72
Drug eruptions	2	0.48
Other skin diseases **Callus** **Stria distensae** **Keratosis pilaris** **Neurofibromatosis** **Epidermal cyst** **Granulosis rubra nasi** **Skin burn** **Molluscum Contagiosum** **Pityriasis alba**	12 2 2 2 1 1 1 1 1 1	2.88

Table 2. Distribution of diseases needed urgent treatment

Skin diseases	n	%
Urticaria	15	3.6
Scabies	12	2.9
Herpes infections	9	2.1
Drug eruptions	2	0.5

Table 3. Distribution of the patients according to the localization of the lesions

	n	%
Face	157	37.7
Scalp	39	9.4
Upper extremity	71	17.1
Lower extremity	46	11
Trunk	17	4.1
Genital area	7	1.7
Oral mucousa	5	1.2
Total body	74	17.8
Total	416	100

Table 4. Distribution of triggering factors in patients

	n	%
Stress	130	31.25
Food	37	8.89
Sun exposure	30	7.21
Chemical/allergic exposure	19	4.56
Season change	12	2.88
Hormonal factors (pregnancy, menstruation)	10	2.40
Drug	9	2.16
Hyperhidrosis	9	2.16
Infection	6	1.44
Other factors (genetic, trauma, animal contact)	14	3.36

Discussion

COVID-19 pandemic has affected daily life in many aspects with lockdowns, restrictions and social isolation. The economy, education, health-care systems are the essentials of the population and any deprivations in these fields may result in irrevocable harm. It has a significant impact on dermatologic practice.

According to the current study results of 416 patients, female dominance (57.7%) was observed. As the suggestion in a study, this might give information about the difference in risk perception of the pandemic between the gender [6] and, female patients may have cared less about the risk posed by the pandemic compared to their skin problems than male patients. A total of 8.17% of the patients were children, and this patient group had a partial curfew. Twenty-nine of the patients (6.97%) were over the age of 65 which had a high risk for a severe infection of COVID-19, and this patient group had a partial curfew, too. The restrictions of these age groups may explain the small number of dermatology outpatient applications.

The most common triggering factor for dermatologic diseases was stress (31.25%). Stress and dermatological diseases may accompany to each other. Some studies reported the role of life stress events as

factors provoking the development of dermatologic diseases such as urticaria, vitiligo, atopic dermatitis [7,8,9]. The association between illness and psychological states has been studied recently. Anxiety, sleep loss, grief, and certain external stressors have been shown to affect immune function in some way. The support provided by social relationships can protect against immune dysregulation during acute and chronic stressors [10]. However, with COVID-19 pandemic, social isolation was imposed and personal relationships had to decline. Due to pandemic stress and loss of social support, dermatological diseases may have been increased. Additionally, post-traumatic stress disorder (PTSD) is a condition in which symptoms develop after exposure to one or more traumatic events and may be considered as a predisposan factor in the chronic, recurrent, or treatment-resistant stress-reactive dermatoses according to Gupta et al. [11]. So, dermatological diseases which occur after COVID-19 pandemic may be considered as a PTSD.

The most common reason for admitting to dermatology outpatient clinic was acne vulgaris and mostly localized on face. Acne vulgaris is a commonly seen, chronic, relapsing skin disease and that affects the quality of social life in patients mostly due to facial involvement. The disease is related to stress and psychiatric disorders, psychological instability in the causation and the course of the disease [12,13]. The pshycological stress on patients with acne vulgaris on face may lead patients to visit dermatology outpatient clinics although the situation is not urgent.

In a study, it was reported that dermatology practices were as vectors for COVID-19 transmission. They suggested that the majority of the outpatient visits were non-emergent [4]. In our study, similarly, only 9.13% of the patients who were admitted to dermatology outpatient clinic needed urgent treatment. 49.04% of the patients were follow-up patients. Additionally, according to the results of the study, 197 of 416 patients (47.4%) had dermatological symptoms for more than 6 months. We suppose that people in quarantine are more interested in their own and skin problems, and these problems may become more important than usual and may get ahead the fear of catching the virus in their perception.

In contrast with calls for staying at home, the importance of social distancing, these non-emergent patients carried on to visit the dermatology outpatient clinic. Most (60.6%) of the patients were those who could stay at home (housewives, students). Staying at home may increase the stress on patients, and it may make them think more about their skin problems as mentioned above.

Systemic treatment and regular follow-up were interrupted in 6 patients using isotretinoin, 2 patients on narrowband ultraviolet B, 3 patients on methotrexate, 2 patients on acitretin, 1 patient on adalimumab therapy. One patient with a wart treated with cryotherapy stopped regular visits. Hospital serving only by appointment, calls for staying at home and the importance of social distancing, uncertainties about the effects of drugs on the course of SARS-CoV-2 infection may cause interruptions in treatment of the patients. Decreased treatment efficacy was seen in 74 patients (17.8%). Increasing stress as a triggering factor may have an effect on decreased treatment response as it is found in the results of this study.

In a study, it was observed that 5 of 390 patients (1.28%) were diagnosed as COVID-19 while they were at hospital visits [5]. In our study, 6.49% of the patients had symptoms of COVID-19, but 3 of 416 patients (0.72%) were diagnosed as COVID-19 at hospital visits. As their suggestion, we think these patients may have been exposed after their hospital visit.

Study Limitations

The study had some limitations. First of all, the results of study was from only one center, and we evaluated the patients who admitted to the clinic at the first two months of the outbreak period, short-term patients. Additionally, we did not evaluate the chronic follow-up patients in detail. It would be better if dermato-oncology patients were analyzed in detail, they could not be assessed in detail since data in the files were missing due to flexible working procedure and dermatologists on covid duties.

Conclusion

In conclusion, this retrospective analysis is an evaluation of dermatology outpatients at the first two months of SARS-CoV-2 outbreak quarantine period from Turkey. According to the results of the study, pandemic process negatively affected on the dermatological patients in many ways, including treatment interruptions, restriction of outpatient clinic applications, the negative effects of the quarantine period for patients. To prevent stress related dermatologic conditions, people may have psychological support in traumatic situations. After all, new pandemics may appear in the future, thus, in the new pandemic world, dermatologists may turn more towards teledermatology so that diagnoses are not delayed and treatments are not disrupted.

Ethics

Ethics Committee Approval: The Institutional Review Board approval was obtained from the local committee of Clinical and Laboratory Research Ethics in Aksaray University (decision number: 2020/06-15, date: 22.06.2020) in "Aksaray University Research and Training Hospital", Dermatology Department for this study.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: F.K., Concept: F.K., E.M.A., B.T., G.A.S., Design: F.K., E.M.A., B.T., G.A.S., Data Collection or Processing: F.K., Analysis or Interpretation: F.K., E.M.A., B.T., G.A.S., Literature Search: F.K., E.M.A., B.T., G.A.S., Writing: F.K.

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ORIGINAL ARTICLE

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Comparison of the Diagnoses of Dermatology Patients in COVID-19 Period with Previous Year: What Has Changed?

Emine Müge Acar[1], Kemal Özyurt[2], Belkız Uyar[3], Ömer Faruk Elmas[4]

[1]Medicalpark Kecioren Hospital, Clinic of Dermatology, Ankara, Turkey
[2]Ahi Evran University Faculty of Medicine, Department of Dermatolgy and Venerology, Kirsehir, Turkey
[3]Duzce University Faculty of Medicine, Department of Dermatolgy and Venerology, Duzce, Turkey
[4]Medicana International Istanbul Hospital, Clinic of Dermatology, Istanbul, Turkey

ABSTRACT

Background: Coronavirus disease-19 (COVID-19) pandemics has caused changes in the profile of the dermatology patients due to restrictions and changing conditions.

Materials and Methods: Patients administered to dermatology outpatient clinic during years 2019 and 2020 were included to study. Demographic characteristics, admission dates and definitive diagnoses of the patients were obtained in the hospital automation system. Among the dermatological diagnoses, those that are likely to be affected by the pandemic were selected.

Results: In 2019, 16107 patients administered to dermatology clinic while 5,887 patients administered in 2020 ($p=0.00$). The percentage of the patients diagnosed with scabies, contact dermatitis, pityriasis rosea (PR), telogen effluvium, zona zoster, alopecia areata and lichen planus increased in 2020 comparing with 2019 ($p<0.05$). The percentage of acne and psoriasis patients significantly decreased ($p<0.05$). When compared according to genders no significant difference in terms of percentages of male and female patients in scabies and PR was detected ($p>0.05$). The ratio of male patients with contact dermatitis, telogen effluvium, alopecia areata and lichen planus significantly increased ($p<0.05$). The percentage of female patients with zona zoster and psoriasis vulgaris significantly increased compared to pre-pandemic period ($p<0.05$).

Conclusion: COVID-19 outbreak caused some changes in the distribution of some dermatological diseases. These changes give information about the effect of pandemic conditions on the administration of the patients to the hospital and the role of stress and COVID-19 as triggers of the diseases.

Keywords: Comparison, Dermatology, Diagnoses, COVID-19 period

Introduction

A worldwide pandemic caused by new coronavirus, severe acute respiratory syndrome coronavirus 2 began in late 2019 [1]. The first case in Turkey was identified in March 2020 [2]. It is critical to predict the course, duration, and effect of the ongoing pandemic all over the world to improve health perspectives and it may be worthy to share case features during the pandemic at intensive patient application polyclinics. Recently numerous reports pointed the change of dermatology admissions such as increase in the frequency of urticaria, psoriasis, allergic/irritant contact dermatitis, scabies, and zona zoster [3].

In our study we aimed to evaluate the change in the overall profile of dermatology outpatient admissions during the early pandemic focusing on selected diagnosis.

Address for Correspondence: Emine Müge Acar MD, Medicalpark Kecioren Hospital, Clinic of Dermatology, Ankara, Turkey
Phone: +90 312 666 08 00 E-mail: drmugeacar@gmail.com ORCID ID: orcid.org/0000-0001-9592-5599
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Materials and Methods

Current study was conducted in an Education and Research Hospital. Patients administered to dermatology outpatient clinic during years 2019 and 2020 were included to study. Ethical approval for this retrospective study was gained from Kirsehir Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee (decision number: 2021-02/24, date: 26.01.2021). Demographic characteristics, admission dates and definitive diagnoses of the patients were obtained in the hospital automation system. Among the dermatological diagnoses, those that are likely to be affected by the pandemic were selected. Data of patients with final diagnosis as scabies, contact dermatitis, alopecia areata, telogen effluvium, lichen planus, pityriasis rosea (PR), urticaria, psoriasis and acne vulgaris were reviewed. The frequency of those dermatological diagnosis in the last year before pandemic, 2019 and ongoing pandemic during 2020 were analyzed and compared.

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) software version 21.0. (SPSS Inc., Chicago, IL, USA). Pearson's Chi square test was used for the comparison of the percentage values between groups.

Results

In 2019, 16107 patients administered to dermatology clinic while 5887 patients administered in 2020. The percentage of the patients diagnosed with scabies was 4.7% in 2019 and 6% in 2020 respectively (p=0.000). As for contact dermatitis these percentages were 24.9% and 27.8%, (p=0.000) for PR 1.7 and 2% (p=0.037) for telogen effluvium 0.5% and 0.8% (p=0.048), for zona zoster 0.020% and 0.025% (p=0.000), for alopecia areata 4.9 and 5.2% (p=0.03), for lichen planus 0.2% and 0.3% (p=0.045). The frequency of psoriasis 4.4% in 2019 and 3.7% in 2020 (p=0.000), acne (58%) in 2019 and (54.1%) in 2020 (p=0.01). The frequency of urticaria was 0.054% in 2019 and 0.059% in 2020 respectively (p=0.686), (Table 1). No significant difference in terms of percentages of male and female patients in scabies and PR was detected (p>0.05). The ratio of male patients with contact dermatitis, telogen effluvium, alopecia areata and lichen planus significantly increased (p<0.05). The percentage of female patients with zona zoster and psoriasis vulgaris significantly increased compared to pre-pandemic period (p<0.05), (Table 2).

Discussion

With the pandemic period the number of the patients administered to dermatology clinic decreased in number since limitations have been applied to all clinics to avoid the spread of the pandemic. However, as detected in our study, the percentages of some diseases showed some changes. The frequency of scabies which showed an increasing frequency in Turkey in the last three years was higher in pandemia period comparing with pre-pandemia period [4]. Our results were in line with the previous studies [3,5,6]. This increase may be attributed to staying in closed areas for a long time as a part of stay-at-home orders which caused more interactions between people. Increased hospitalization causing hygiene defects may be also another contributing factor. The frequency of contact dermatitis also became higher as reported in previous studies [3,5,6]. The patients' more frequent consumption of disinfectant spreys, cologne and detergents may play a role in this result. The patients most commonly presented with hand dermatitis since hands are more frequently washed and disinfected.

The decrease in the percentage of psoriasis patients in our study may be attributed to patients behaviours possibly avoiding to coming to

Table 1. The distribution of dermatological diseases in 2019 and 2020

	2019		2020		
	Total	Percentage (%)	Total	Percentage (%)	p value
Total number of patients	16,107		5,887		0.00
Diagnosis					
Scabies	757	4.7	353	6	0.00
Contact dermatitis	4,010	24.9	2,398	40.7	0.00
Pityriasis rosea (PR)	274	1.7	118	2	0.037
Telogen effluvium	290	1.8	130	2.2	0.048
Zona zoster	33	0.2	15	0.25	0.00
Alopecia areata	789	4.9	306	5.2	0.03
Acne vulgaris	9,117	58	2,299	39.0	0.01
Lichen planus	32	0.2	18	0.3	0.04
Urticaria	97	0.6	32	0.54	0.68
Psoriasis	708	4.4	218	3.7	0.00

Table 2. The distribution of dermatological diseases in both years according to gender

Diagnosis	2019				2020				p value
	Male	Female	Total	Percentage (%)	Male	Female	Total	Percentage (%)	
Scabies	509 (67.2%)	248 (32.7%)	757	4.7	231 (65.4%)	122 (35.6%)	353	6	0.071
Contact dermatitis	2,278 (56.8%)	1,732 (43.2%)	4,010	24.9	1,527 (63.7%)	871 (36.3%)	2,398	27.8	0.00
Pityriasis rosea	165 (60.2%)	109 (39.8%)	274	1.7	73 (61.9%)	45 (30.1%)	118	2	0.063
Telogen effluvium	170 (58.7%)	120 (41.3%)	290	1.8	90 (69.2%)	40 (30.8%)	130	2.2	0.00
Zona zoster	16 (48.4%)	17 (52.6%)	33	0.2	6 (40%)	9 (60%)	15	0.25	0.00
Alopecia areata	645 (81.7%)	144 (18.3%)	789	4.9	296 (96.7%)	110 (3.3%)	306	5.2	0.00
Acne vulgaris	5,216 (55.8%)	3,901 (42.7%)	9,117	58	1,232 (53.6%)	1,067 (46.4%)	2,299	54.1	0.078
Lichen planus	8 (25%)	24 (75%)	32	0.2	9 (50%)	9 (50%)	18	0.3	0.00
Urticaria	77 (79.4%)	20 (20.6%)	97	0.6	22 (68.7%)	10 (31.3%)	32	0.54	0.00
Psoriasis	379 (53.5%)	329 (46.5%)	708	4.4	90 (41.3%)	128 (58.7%)	218	3.7	0.00

hospital as the treatments of some patients were stopped in the first months of pandemics because of the unclear effects of antipsoriatic drugs such as methotrexate and cyclosporine on Coronavirus disease 2019 (COVID-19) prognosis. It was observed that the patients with psoriasis who had disturbing symptoms such as severe itch administered to hospital in this period. Concordant with previous studies, there was also an increase in the frequency of alopecia areata and telogen effluvium since stress has been reported to play a major role in the development of these diseases [5,6,7,8]. Also the effect of hydroxychloroquine, azithromycin, or other medications can also contribute to the emergence of telogen effluvium [9].

Lichen planus is a dermatological disease with a frequency of 0.38-6% of the outpatients. Stress has been noted to play a role in the onset and progression of the disease. In a study by Picardi and Abeni [10] stress was found to be related with lichen planus between 10% and 51% of the patients [10]. Mansur et al. [11] described stressful events in almost 90% of patients with cutaneous lichen planus. Turkmen et al. [3] reported a significant increase in the frequency of lichen planus patients while Kartal et al. [6] reported a decreased frequency during pandemia period [3,6]. In our study, the frequency of lichen planus increased comparing with 2019. This result may support the role of stress in the etiology of lichen planus.

PR is another disease that showed increased frequency in pandemic period. Similar to our study, Kutlu and Metin [5] and Kartal et al. [6] also found an increase in the frequency of PR [5,6]. Reactivation of Human Herpesvirus 6 and 7, other viral agents, vaccination, psychological stress, and drugs have also been implicated in the etiology of PR [12]. It has been suggested that PR can also be a manifestation of COVID-19 [13,14,15,16]. One of the factors causing activation of Herpesviruses is coronaviruses [15]. The reactivation of HHV-6 may have a role in increased PR frequency during pandemic period. Psychological stress may also be another cause leading to this result.

Zona zoster frequency also increased in our study similar to the previous studies. The close relationship between zona zoster and stress seems to have a role in this result. Reports revealing that zona zoster can be a manifestation or complication of COVID-19 also exist [17,18].

The frequency of acne patients decreased in pandemic period. This may be related to the fact that most acne patients are teenagers and restrictions were applied to this age group in certain periods of pandemics. Similarly Kutlu and Metin [5] reported a significant decrease in the frequency of acne patients in a month after the COVID-19 (April, 2020) pandemic attributing these changes to the restrictions to the age groups under 20 [5]. In our study the overall frequency of acne vulgaris also declined. In a study by Kartal et al. [6] it was reported that the overall frequency of acne patients did not change after pandemics and however an increase in acne

frequency was seen in the centers with lower COVID incidence [6]. Since our hospital was the only pandemics hospital in the city, it's also possible that acne patients did not prefer to come to hospital leading to a decrease in the acne frequency.

The frequency of urticaria did not show a change in our clinic. Kartal et al. [6] reported an increase in the frequency of urticaria during pandemic period. Since urticaria is closely related to stress and infection, an increase in urticaria frequency is expected. There are also reports indicating that acute urticaria can be also a presentation of COVID-19 [19,20,21]. The results of our study may be related to the small population size when compared with the multicenter study of Kartal et al. [6].

Study Limitations

Our study was a single center study which included a relatively small number of patients. A specific comparison with the same month and season of the previous year was not performed.

Conclusion

In conclusion, COVID-19 outbreak caused some changes in the distribution of some dermatological diseases. These changes give information about the effect of pandemic conditions on the administration of the patients to the hospital and the role of stress and COVID-19 as triggers of the diseases. Experiences in dermatology practice during pandemic period will enable the physicians to cope with such pandemics more successfully in the future.

Ethics

Ethics Committee Approval: Ethical approval for this retrospective study was gained from Kirsehir Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee (decision number: 2021-02/24, date: 26.01.2021).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.M.A., K.Ö., B.U., Ö.F.E., Concept: K.Ö., Design: K.Ö., Data Collection or Processing: E.M.A., B.U., Ö.F.E., Analysis or Interpretation: E.M.A., K.Ö., Literature Search: E.M.A., K.Ö., Writing: E.M.A., K.Ö.

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CASE REPORT

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Secukinumab-induced Behçet's Disease in a Patient with Ankylosing Spondylitis Successfully Treated with Certolizumab: A Case Report

Yusuf Karabulut

Doruk Private Hospital, Clinic of Internal Medicine, Division of Rheumatology, Bursa, Turkey

ABSTRACT

Interleukin (IL)-17A is pro-inflammatory cytokine and plays a vital role in the pathogenesis of a range of immune-mediated diseases, including psoriasis, psoriatic arthritis, and ankylosing spondylitis (AS). Moreover, IL-17A plays protective roles in immune defense against certain pathogens at epithelial and mucosal barriers. Blocking IL-17A may be efficient to treat those immune-mediated diseases, but on the other hand it may trigger other immune related diseases such as Behçet's disease (BD) or Crohn's disease (CD). IL-17A blockers are newly introduced alternative treatment for AS patients but careful clinical assessment of comorbidities and patient history are required before making therapeutic choice. This case presentation reports a secukinumab induced BD in patient diagnosed with AS successfully treated with certolizumab pegol. IL-17A blockage is important in the treatment of AS. However, patients having comorbid disorders including BD, CD or other inflammatory bowel diseases must be treated with anti-TNFs rather than IL-17A blocker treatment.

Keywords: Ankylosing spondylitis, Behçet's disease, Interleukin (IL)-17A, Certolizumab, Case report

Introduction

Interleukin (IL)-17A is pro-inflammatory cytokine [1] and plays a vital role in the pathogenesis of a range of immune-mediated diseases, including psoriasis (PsO), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) [2]. PsO, PsA, and AS having considerable overlapping genetic features in pathogenesis [2]. Due to common etiologic heritage, treatment related adverse events and complications may occur in the same manner.

IL-17's pro-inflammatory and damaging effects have also been linked to pathogenic processes of other autoimmune diseases like rheumatoid arthritis (RA), Crohn's disease (CD) and Behcet's disease (BD) [3]. Blocking IL-17 was regarded as an alternative pathway and secukinumab was first in class molecule. As an IL-17A blocker, safety and efficacy of secukinumab are clinically tested in PsO, PsA, AS, RA, CD and BD [3].

Pivotal studies revealed clinical success in AS, PsO and PsA and as a fully human monoclonal antibody, secukinumab received Food and Drug Administration approval for moderate-to-severe plaque PsO, PsA, and AS [3].

However, clinical studies in RA, CD and BD were not successful, secukinumab failed to demonstrate clinical improvement in these disorders. Besides there are recent case reports demonstrating potential triggering role of secukinumab in PsO, CD and BD [4,5,6]. Existing data prove benefit of targeting IL-17 therapeutically, however clinicians should consider paradoxical reactions and risks related with secukinumab. This case study reports a secukinumab induced BD patient successfully treated with certolizumab pegol (CZP).

Address for Correspondence: Yusuf Karabulut, MD, Doruk Private Hospital, Clinic of Internal Medicine, Division of Rheumatology, Bursa, Turkey
Phone: +90 532 221 14 92 E-mail: yusufkarabulut.dr@gmail.com ORCID ID: orcid.org/0000-0003-2690-6196
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Case Report

A thirty-four-year-old female was admitted to rheumatology outpatient service with gradually increasing pain in April 2019. Her widespread complaints of low back pain, morning stiffness (more than 1 hour), hip pain, night pain, and sleeping disorder were present with 12 months history. During her painful periods she took non-steroidal anti-inflammatory drugs (NSAID). Chosen medication had limited effect on pain, her morning stiffness and sleeping problems progressively worsened. On admission, her physical examination revealed increased sensitivity at both Achilles tendon. She had also limited spinal mobility and cervical rotation. Considering the patient history, ten years ago she was referred to dermatology clinic due to erythema nodosum and genital ulcers. In her comprehensive assessment she had accompanying oral ulcers and was diagnosed with BD. Her pathergy test and human leukocyte antigen (HLA) B51 test results were positive. After diagnosis, she took steroid and colchicum dispert for five years. Once her complains disappeared then all medication terminated because of remission. During this remission period there were no relapses or attacks related with BD. Radiographic and serologic evaluation were also consistent with preliminary physical examination findings (Figure 1A, B). Her HLA-B27 was positive and C-reactive protein levels were elevated. Her magnetic resonance imaging findings showed inflammatory lesions and regarded as grade II sacroiliitis. However, her x-ray findings were clear and there were no radiologic changes. First day Bath Ankylosing Spondylitis Disease Activity index score was 6.8 and patient diagnosed as AS and BD in remission medication regimen planned.

Treatment

On the second day of diagnosis, following a detailed evaluation with division of infectious diseases and radiology, biologic treatment was planned. From patient history we knew she took NSAID during painful periods and it was not efficient to heal pain or lower disease activity. Because of high titers of acute phase reactants, absence of any biologic treatment and HLA-B27 positivity, IL-17 blocker secukinumab (Verxant/Cosentyx) treatment planned. In May 2019, secukinumab treatment initiated. The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. At the fifth initial dose, there were observable improvement in her complaints of inflammatory back pain and enthesitis in Ascilles tendon. Following fifth dose, patient applied to clinic with mono-arthritis and oral ulcers. Due to BD reactivation, colchicum dispert and prednisone added to treatment. Three days later, she was re-admitted to clinic with widespread erythema nodosum in lower extremity. Following BD reactivation, prednisolone dose increased to 0.5 mg/kg/day and secukinumab treatment terminated.

Because of gradually progressing back pain, mono arthritis and difficulties in mobility, patient was prescribed CZP along with prednisone. At the second week of CZP treatment, we have added indomethacin 75 mg/day and pantoprazole 40mg/day. Following the first cure of anti-TNF treatment, all clinical findings related with AS and BD showed significant improvement. Our patient is under follow-up without low diseases activity under CZP maintenance treatment, prednisone 2.5 mg/day and colchicum dispert.

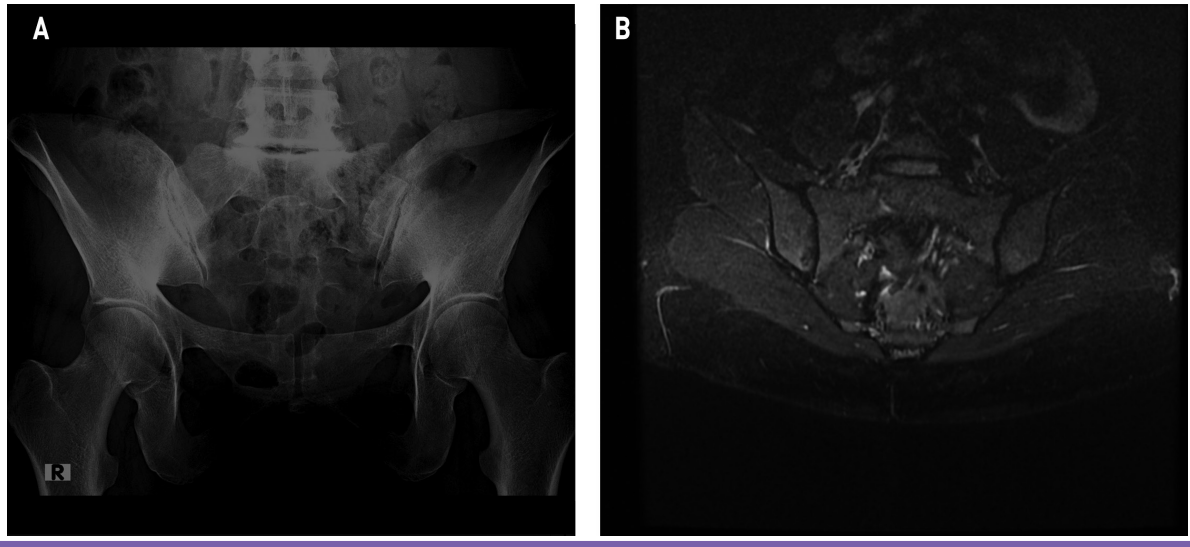

Figure 1. X-ray (a) and MRI (b) findings of patient. Radiographic findings were consistent with ASAS diagnosis criteria. Bilateral Grade II sacroileitis seen in MRI (b)

MRI: Magnetic resonance imaging, ASAS: Assessment of Spondyloarthritis International Society

Discussion

IL-17A is pro-inflammatory cytokine [1] and plays a vital role in the pathogenesis of a range of immune-mediated diseases. Moreover, IL-17A play protective roles in immune defense against certain pathogens at epithelial and mucosal barriers. It has also been reported that IL-17A-producing cells are detected upon infection with intracellular bacteria such as *Mycobacterium tuberculosis, Listeria monocytogenes* and *Salmonella typhimurium* [1]. Recent case reports demonstrating potential triggering role of secukinumab in PsO, CD and BD [4-6] are linked to IL-17A's protective roles in bacteria.

Secukinumab as an IL-17A blocker, clinically tested both in BD and CD. The multicenter Phase II trial on secukinumab in 59 patients with moderate-to-severe CD was prematurely terminated. Secukinumab did not help in improving conditions of patients with CD; moreover, worsening of the disease was reported as reflected in the high rate of serious adverse events as well as fungal infections [3].

Accordingly, elevated levels of IL-17A have been also found in the peripheral blood of patients with Behçet uveitis and as such it has been considered important in disease mechanisms [4]. With this hypothesis, a 24-week, randomized, double-blinded, placebo-controlled phase III trial was conducted in 118 Behçet's patients with posterior and pan-uveitis to assess the efficacy of secukinumab versus placebo adjunctive to standard-of-care immunosuppressive therapy [3]. This study also failed to demonstrate clinical improvement. Secukinumab showed a similar rate of recurrent ocular exacerbations with placebo during 24 weeks of treatment [3]. Further investigational studies with larger groups with secukinumab were halted.

This article is one of the first case presentations reporting potential role of Secukinumab in BD. IL-17A blockage is important in the treatment of AS. However, patients having comorbid disorders including BD, CD or other inflammatory bowel diseases must be treated with anti-TNFs rather than IL-17A blocker treatment. Since we have alternatives in the treatment of AS, such cases must be disregarded for IL-17A therapy.

Ethics

Informed Consent: Written consent obtained from patient for the case preentation.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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CASE REPORT

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Cutaneous Leishmaniasis with Unusual Psoriasiform Presentation

Icim Komurcugil[1], Esra Kiratli Nalbant[1], Nermin Karaosmanoglu[1], Eylem Pinar Eser[2]

[1]Ankara Training and Research Hospital, Clinic of Dermatology, Ankara, Turkey
[2]Ankara Training and Research Hospital, Clinic of Pathology, Ankara, Turkey

ABSTRACT

Cutaneous leishmaniasis (CL) is still an important public health problem in many countries, especially in developing countries. The disease can manifest itself in a broad spectrum of clinical presentations. In this case report, we describe a 3-year-old patient with a 12-month history of non-healing psoriasiform lesions on her right leg. It was diagnosed as CL and the lesion almost completely resolved after 5 sessions of intralesional glucantime.

Keywords: Antimony compounds, Cutaneous leishmaniasis, Intralesional therapy, Psoriasiform

Introduction

Leishmaniasis is caused by protozoa of genus Leishmania through the bite of the female phlebotomine sand fly. Depending on the type of Leishmania species and the host's immune response, infection results in cutaneous, mucocutaneous or visceral disease. Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis; affecting 600,000-1 million people each year [1]. The disease can manifest itself in a broad spectrum of clinical presentations. Classical CL lesions evolve from papules to nodules to ulcerative lesions, with a central depression and a raised, indurated border, and eventually, over months to years, to atrophic scars [2]. Most cases do not cause any diagnostic difficulties; however, some patients present with very unusual morphological forms of CL, which make the diagnosis even more challenging.

Case Report

A 3-year-old girl presented to our clinic with a growing lesion on her right thigh and leg. The patient's mother reported that the lesion started as a small papule 12 months earlier and grew without any response to topical or systemic antibiotics. She also did not complain about pain or pruritus. Her personal history of illness and family history was unremarkable. The patient's family was residing in Ankara, Turkey and had a history of travel only to Corum province 18 months ago. Dermatological examination revealed multiple slightly erythematous scaly papuloplaques arranged in a linear and annular pattern (Figure 1).

A 4-mm punch biopsy was performed considering granuloma anulare, zosteriform lichen planus and inflammatory linear verrucous epidermal nevus as the differential diagnosis. Histological examination showed orthohyperkeratosis, focal parakeratosis and focal atrophy; dense lymphoplasmacytic infiltration accompanied by giant cells and histiocytes. Infiltrates and histiocytes contained small oval parasitic organisms known as amastigotes (Figure 2). Giant cells along with lymphohistiocytic cell infiltration were observed (Figure 3).

In accordance with the findings, the patient received a diagnosis of CL and treated with intralesional meglumine antimoniate injections weekly. After 5 sessions, a noticeable improvement was noted (Figure 4). Informed consent was taken from the patient's mother for possible case report publication.

Address for Correspondence: Icim Komurcugil MD, Ankara Training and Research Hospital, Clinic of Dermatology, Ankara, Turkey
Phone: +90 312 306 50 00 E-mail: icim.komurcugil@yahoo.com ORCID ID: orcid.org/0000-0002-1753-7571
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Discussion

CL is a serious public health problem in the eastern Mediterranean region including Turkey. The disease had been widespread in our country before 1950; then it became limited to the Southeastern Anatolia region with the use of intense dichlorodiphenyl trichloroethane against malaria [3]. Unfortunately, there have been increased number of CL cases reported from both endemic and non-endemic regions, mainly due to the immigrants from Syria, recently [4]. Besides, it is noticed that there are also inhabitant CL cases reported from non-endemic regions in Turkey [5]. While travelling to endemic regions is considered to be the major reason for inhabitants, ecological studies have revealed some phlebotomine species that can be carriers for Leishmania species, living in non-endemic regions as well. For example, although Corum and Ankara province are located in Central Anatolia and regarded as non-endemic regions for CL, according to these studies, Phlebotomus transcaucasicus and Phlebotomus tobbi were found in Corum and Phlebotomus perfiliewi was reported in Ankara [6,7]. Interestingly, our patient's mother gave a history of visit to Corum province 18 months ago. The patient may have contracted this disease in Ankara or during this trip; this situation remains uncertain.

The typical presentation of CL is ulcerations on the exposed areas of the body such as face, arms and legs. However, it may present to our clinics as the 'great imitator' on occasion. The resemblance to other skin diseases, such as verruca vulgaris (warty), herpes zoster (zosteriform), psoriasis (psoriasiform), lupus (lupoid), erysipelas (erysipeloid) and sporotrichosis (sporotrichoid) may cause a challenge for an accurate clinical differentiation.

There may be multiple erythematous nodules mimicking cutaneous lymphoma or pseudolymphoma [8]. To our best knowledge, there are four cases of CL with psoriasiform presentation, reported in the literature. In 1997, a 28-year-old, human immunodeficiency virus-positive visceral leishmaniasis patient with widespread psoriasiform plaques was reported [9]. Moreover, Schepis et al. [10] reported a 68-year-old CL patient, with erythema and desquamation on

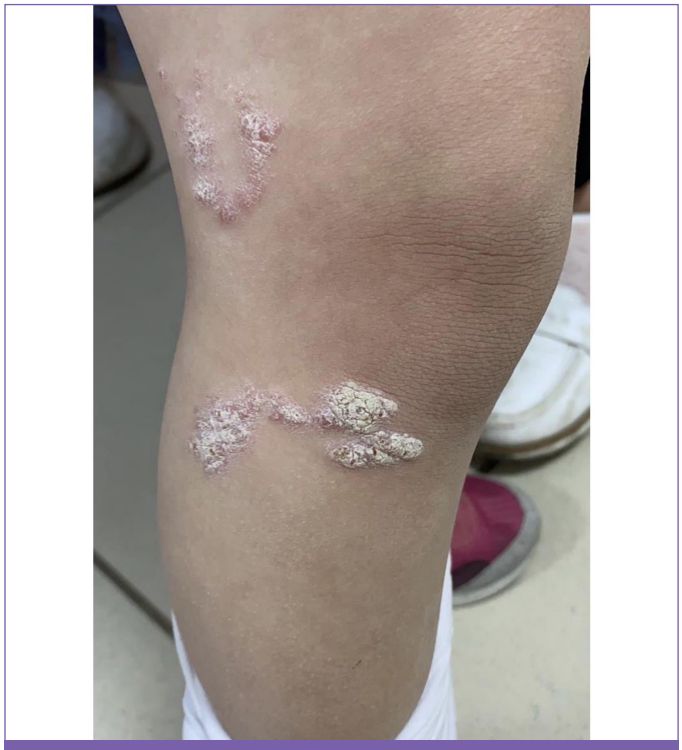

Figure 1. Linear and annular psoriasiform papules

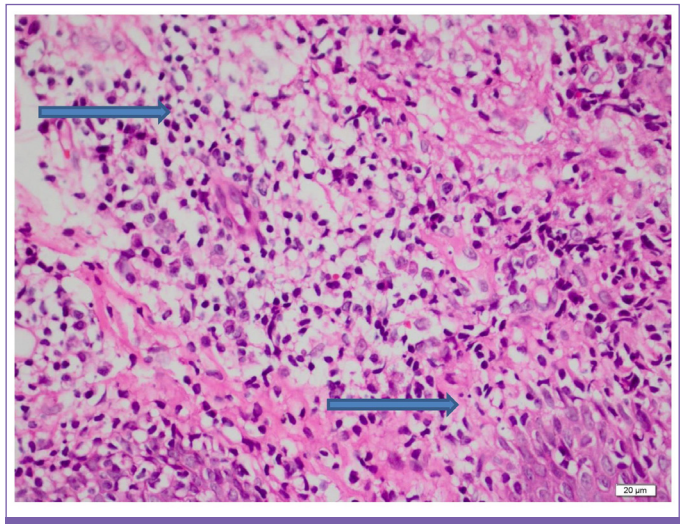

Figure 2. Circular, crumb-shaped structures compatible with leishmania are observed, in the cytoplasm of histiocytic cells (H&E x400)

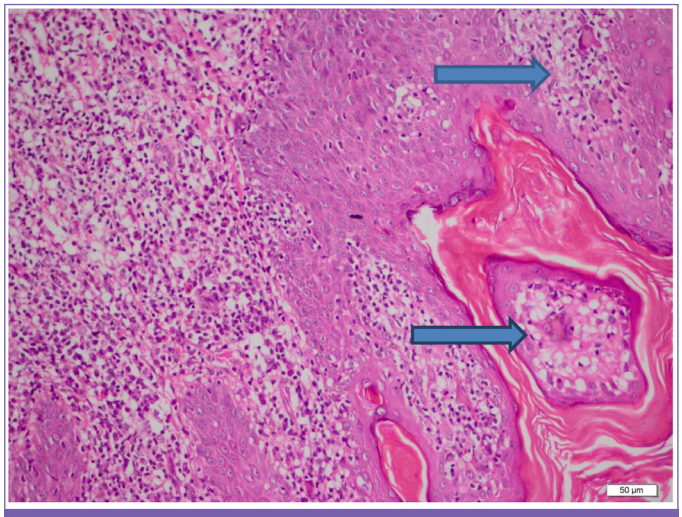

Figure 3. Giant cells indicated by blue arrows between lymphoplasmacytic cell infiltration (H&E x200)

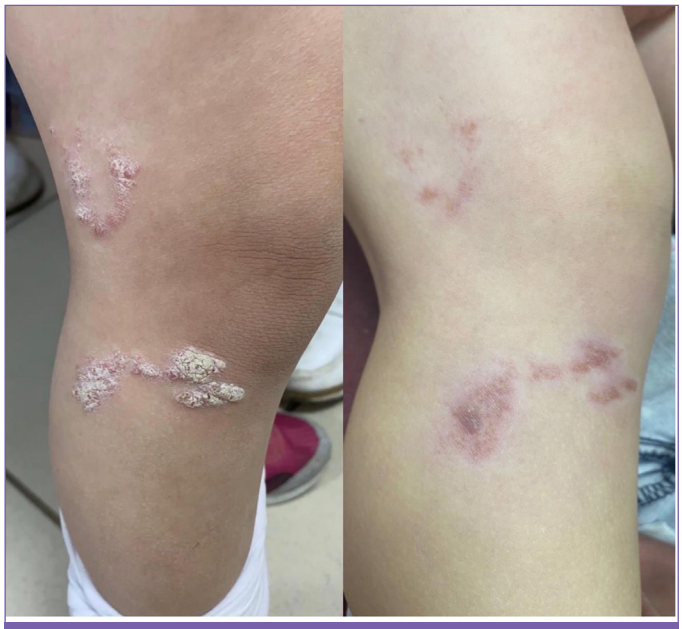

Figure 4. Before and after 5 sessions of meglumine antimoniate injections

the scalp and face resembling sebopsoriasis. Veraldi et al. [11] reported a 54-year-old CL patient who was misdiagnosed as psoriasis and was unresponsive to topical corticosteroid and vitamin D analogues [10,11]. The patient had scaly, erythematous-infiltrated lesion with well-defined borders. In addition, a study which was recently published, collected cases of CL with atypical clinical features. Out of 27 atypical CL patients, only one patient had psoriasiform lesion on the elbow [12]. Interestingly, our patient is the only pediatric case reported up to now. She was diagnosed with CL histopathologically and responded well to the intralesional glucantime treatment.

The reason for pleomorphism of CL is not fully understood; but variations in parasite virulence and host factors, abnormal host immune response, malnutrition, and immunosuppression have been suggested as the possible reasons. Although the usual clinical presentations of leishmaniasis are easily diagnosed by clinicians in endemic regions, the unusual forms may give rise to difficulties in diagnosis, delaying the diagnosis and appropriate treatment for several months. Thus, all cases of atypical CL should be confirmed by demonstration of the parasite in a Giemsa-stained smear. When the parasite cannot be demonstrated in a smear, histopathological examination should be used. If the microscopic examination result is negative, polymerase chain reaction appears to be the most sensitive diagnostic test for the identification of parasites; in the event that the microscopic examination result is negative.

These atypical forms are observed in only 2 to 5% of all affected patients and may cause a delay in the diagnosis and treatment. Although not life-threatening, it is important to diagnose and treat CL because it can be associated with permanent scarring, decreased quality of life, stigmatization and long-term psychologic consequences [1]. It also remains as an important public health problem in endemic regions. In case of an increase in cases, it is important to apply prompt therapeutic and preventive interventions. Consequently, our case is worth reporting, since it is seen in a non-endemic region, with a very rare clinical presentation.

Ethics

Informed Consent: Informed consent was taken from the patient's mother for possible case report publication.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: E.P.E., Analysis or Interpretation: N.K., Literature Search: İ.K., E.K.N., Writing: İ.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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COVID-19 Associated Unilateral Maculopapular Eruption: A Case Report

Zehra Aşiran Serdar[1], Zeynep Altan Ferhatoğlu[2], İnci Serdar[3]

[1]Istanbul Yeni Yuzyil University Faculty of Medicine, Department of Dermatology and Venereology, Istanbul, Turkey
[2]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Dermatology and Venereology, Istanbul, Turkey
[3]Humanitas University Faculty of Medicine, Milano, Italy

Keywords: COVID-19, Maculopapular eruption, Unilateral

Dear Editor,

Coronavirus disease 2019 (COVID-19), in addition to being a disease with mainly pulmonary involvement, can cause cutaneous pathologies in patients. Major cutaneous manifestations can be listed as maculopapular rash, urticarial lesions, pseudo-chilblain, vesicular eruptions, livedo, and necrotic lesions [1]. Recently, newly defined entities such as COVID-19-related exfoliative shock syndrome, COVID-19-induced rash and mucositis, and calciphylaxis with thrombotic vasculopathy have also been reported [2]. Here, a case of a patient who developed a unilateral maculopapular eruption after the diagnosis of COVID-19 is presented.

A 55-year-old female patient was evaluated by teledermatology method with the complaint of an itchy red rash on the left side of her body. The patient's history revealed a positive Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR test 2 days before the complaint. Medications used by the patient were Favipiravir 200 mg/day, azithromycin 500 mg/day, acetylsalicylic acid 100mg/day, acrivastine 8 mg-pseudoephedrine 60 mg/day, liposomal vitamin C, and A multivitamin tablet containing beta-glucan, astragalus extract, sambucol extract, royal jelly, vitamin D3, and zinc. In dermatological examination; painless, itchy erythematous papules and plaques of diameters ranging from 3 mm to 2 cm were observed with scattering on the left side of the patient's body on the arm, upper breast, trunk, hip, and leg. (Figures 1, 2, 3) No pathology was detected in blood tests. Cetirizine 10 mg and medium potent topical corticosteroid lotion were prescribed

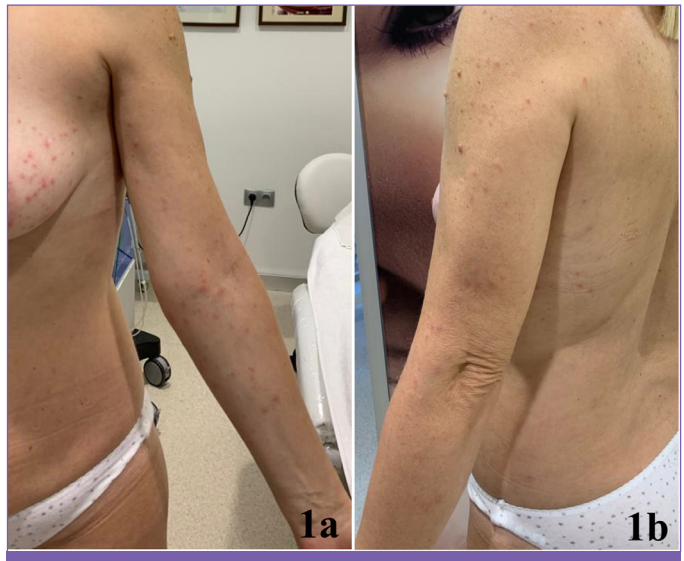

Figure 1. Anterior (1a) and posterior (1b) views of the lesions located on the left side of the patients body

Address for Correspondence: Zeynep Altan Ferhatoğlu MD, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Dermatology and Venereology, Istanbul, Turkey
Phone: +90 534 878 77 48 E-mail: zeynepaltanferhatoglu@gmail.com ORCID ID: orcid.org/0000-0003-3090-656X
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and the patient presented with regression on the lesions at 1-month follow-up.

Although it does not appear to be a dermatotropic virus, cutaneous findings have been reported in 20% of patients with COVID-19. When all cutaneous findings were compiled, two groups were formed as inflammatory/exanthematous and vasculopathic in terms of pathophysiology. It is stated that the most common cutaneous finding is maculopapular exanthema (morbilliform) [3].

There are 3 cases in the literature with unilateral lesions associated with COVID-19, similar to our patient [4,5,6]. The lesions reported by Glick et al. [4] were limited to the right axillary region and the ones reported by Karaca et al. [5] were limited to the left inguinal region [4,5]. In the case reported by Shubhra et al. [6], unilateral wet gangrene located in the right lower extremity was found to be associated with pulmonary thromboembolism [6]. In our case, a diffuse unilateral maculopapular eruption was observed in nearly half of the body. The distribution of the lesions in our patient suggests cutaneous mosaicism, and it has been reported that many inflammatory polygenic diseases, including drug eruptions, may have segmental involvement [7].

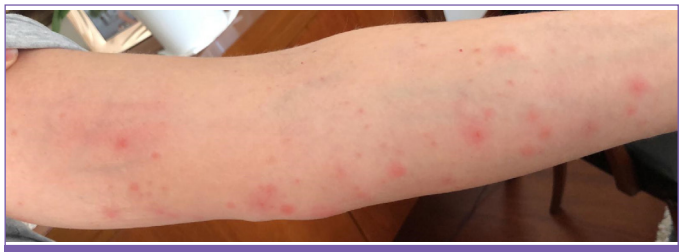

Figure 2. Close-up view of lesions on the arm volar face

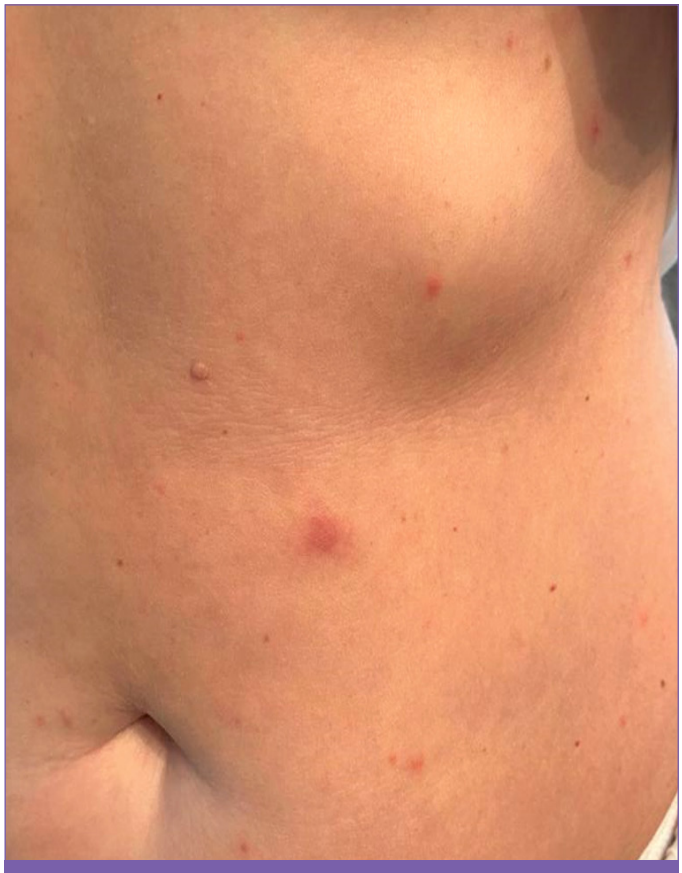

Figure 3. Close-up view of the lesions on the trunk

Due to its peculiar feature, we decided to present unilateral maculopapular exanthema in our patient during the course of COVID-19. Future studies are needed to fully elucidate the cutaneous effects of the SARS-CoV-2 virus or the drugs used in the treatment of COVID-19.

Ethics

Informed Consent: Consent form was filled out by the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.A.S., Concept: Z.A.S., Design: Z.A.F., Data Collection or Processing: Z.A.S., Analysis or Interpretation: Z.A.F., Literature Search: Z.A.F., İ.S., Writing: Z.A.F., İ.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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