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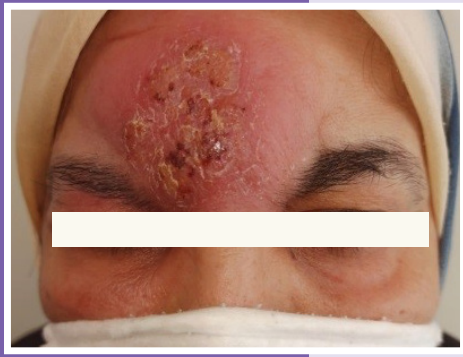

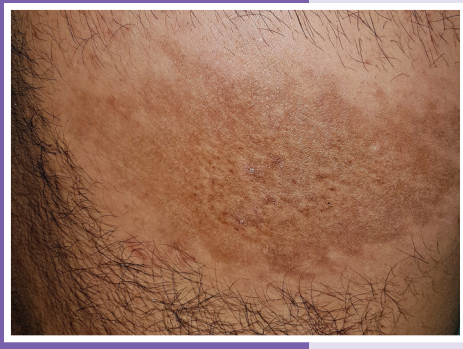

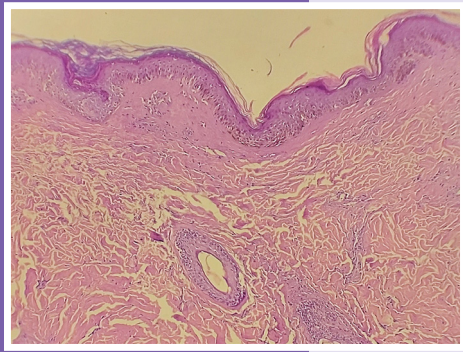

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CONTENTS

ORIGINAL ARTICLE

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The Efficacy of Omalizumab Therapy in Chronic Inducible Urticaria

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

ABSTRACT

Background: Immunoglobulin E antibody omalizumab is an effective and safe treatment option in patients with chronic urticaria and evidence is lacking in patients with chronic inducible urticaria (CindU). In this study, it was aimed to determine the efficacy of omalizumab in patients with CindU.

Materials and Methods: Patients treated with omalizumab resistant to second-generation antihistamine therapy were included in the study. Demographic characteristics, duration of disease, duration of omalizumab use and comorbidities of the patients were obtained from health records.

Results: We enrolled 27 patients ranging in age from 17 to 55 years, 9 patients had cholinergic, 2 aquagenic, 7 symptomatic dermographism, 4 cold, 4 pressure, 3 solar urticaria. Complete response was observed in 20 patients, partial response in 3 patients, and no response in 4 patients treated with omalizumab.

Conclusion: A higher percentage of patients had a complete response with 300 mg of omalizumab treatment.

Keywords: Urticaria, Inducible, Treatment

Introduction

Urticaria is a dermatologic disease which presents with recurrent wheals and/or angioedema. The disease seriously affects the quality of life of patients. Although there is no identified trigger associated with the appearance of signs and symptoms for chronic spontaneous urticaria (CSU), the appearance of symptoms in chronic inducible urticaria (CindU) is associated with a specific inducing factors. The types of CindU are physical (symptomatic dermographism, cold and heat urticaria, delayed pressure urticaria, solar urticaria, and vibratory angioedema) urticaria and non-physical urticaria (cholinergic urticaria, contact and aquagenic urticaria) [1,2].

Second-generation H1-antihistamines are the first-line treatment recommended for disease control in the treatment of CSU. Recent guidelines recommend increasing the dose up to four times when the standard dose is inadaquate to control symptoms [3]. Omalizumab, anti-Immunoglobulin E monoclonal antibody, is an effective and safe treatment option in patients with chronic urticaria who are resistant to antihistamine therapy. The efficacy of omalizumab in the treatment of CSU has been demonstrated in numerous randomized controlled trials and meta-analyses [4]. CindU often presents a major treatment challenge due to their resistance to first-line therapy with H1-antihistamines. Studies showing the efficacy of omalizumab in the treatment of CindU are limited [5]. In this study, we aimed to demonstrate the efficacy of omalizumab in CindU patients retrospectively.

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Materials and Methods

A total of 27 patients with CindU were treated with omalizumab in the dermatology department of Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine between January 1, 2018 and May 31, 2021 (approval number: A-09, date:03.08.2021). Patients with CindU who were resistant to second-generation antihistamines and other conventional treatments were included in the study. We reviewed the health records of patients for demographic characteristics, duration of disease, duration of omalizumab use, and comorbidities. Disease severity was assessed using urticaria activity score; UAS7 score of ≤6 is well-controlled, 7-15 is mild, 16-27 modarate, 28-42 is severe urticaria. After omalizumab treatment, 50% or more improvement in UAS7 score was considered as complete response, less than 50% improvement as partial response, and those who did not show any change or showed an increase in disease severity were considered as non-responders. In addition, the efficacy of omalizumab treatment on the UAS7 score was evaluated by the change from baseline UAS7 to after UAS7 score. The ethical approvement was obtained from Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine Institutional Review Board. Patients who denied research authorization were excluded. Omalizumab was used at a dose of 300 mg and repeated every month.

Statistical Analysis

Analyzes were performed by the use of the Statistical Package for the Social Sciences 2.0 version. The effiacy of treatment on symptom control was evaluated with the Wilcoxon test. A p-value of less than 0.05 was considered clinically significant.

Results

The mean age of 27 patients was 36.3 (17-55) and the mean disease duration was 4.8 years (Table 1). The types of CindU of parients included in the study were demonstrated in Table 2. There was no significant relationship between treatment response and disease onset severity, disease duration and age. It was observed that the duration of the disease was significantly higher in patients who received steroid therapy compared to those who did not receive steroid therapy (median duration 2 years and 3.75 years p=0.009). The mean duration of omalizumab use was 11 months. Before treatment, 20 patients had severe urticaria, 7 patients had moderate and 1 patient had mild urticaria. In 20 of 27 patients, complete treatment response was obtained. Three of 27 patients showed partial response while four patients showed no response to omalizumab treatment. Among non-responders, three patients had cholinergic urticaria and 1 had symptomatic dermographism. A significant difference was observed in baseline and post-treatment

Table 1. Demographic characteristics and features of patients

		n=27	%
Age*		36	17-55
Sex	Female	12	(44.4)
	Male	15	(55.6)
Disease duration (year)*		2	0.5-20
Type of inducible urticaria	Cholinergic	8	(29.6)
	Aquagenic	2	(7.4)
	Dermographism	7	(25.9)
	Cold	2	(7.4)
	Solar	2	(7.4)
	Pressure	4	(14.8)
	Cholinergic and cold	1	(3.7)
	Cold and solar	1	(3.7)
Duration of omalizumab use (month-dosage)*		8	2-39
Disease severity before treatment	Well controlled	0	(0)
	Mild	1	(3.7)
	Moderate	7	(25.9)
	Severe	19	(70.4)
Treatment response	No response	2	(7.4)
	Partial	10	(37.0)
	Complete	15	(55.6)

*n is the median values the % is the minimum and maximum values

UAS7 scores with omalizumab treatment (p<0.0001). The efficacy of omalizumab treatment on UAS7 score was shown in Table 2. No significant difference change was found between male and female patients in smyptom severity with omalizumab treatment (p=0.26). There was no significant difference in the change of disease severity in patients who used systemic steroids as previous treatment compared to patients who did not use systemic steroids (p=0.4) (Figure 1 and Table 3).

Discussion

In our study, omalizumab treatment was shown to be effective in patients with CindU. The efficacy of omalizumab in patients with cold urticaria, symptomatic dermographism and solar urticaria were demonstrated in placebo controlled randomized trials and phase 2 studies, respectively. The efficacy of omalizumab in pressure urticaria and cholinergic urticaria have been demonstrated in retrospective studies. Data showing the efficacy of omalizumab treatment on vibratory angioedema, aquagenic and contact urticaria were limited [6].

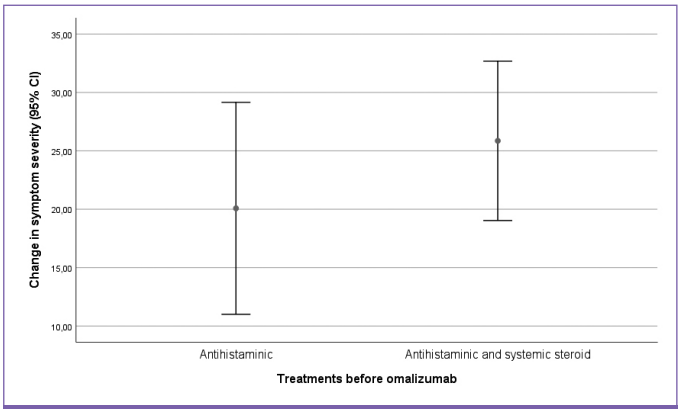

Figure 1. No significant difference in the change of disease severity in between previous treatments

Our study was showed that the duration of the disease was significantly higher in patients treated with steroids. The factors associated with longer disease duration; late-onset disease, relapsing course, concomitant CIndU, functional serum autoactivity, and insufficient response to a standard dose of antihistamine [7,8].

Symptomatic dermatographism is the most common type of physical urticaria, which presents as linear wheals in areas of friction or itching, such as collars and cuffs of clothes [9]. Our study showed a complete response in 6 of 7 patients with symptomatic dermographism. The efficacy of omalizumab in patients with symptomatic dermographism was demonstrated in a placebo-controlled randomized study involving 55 patients. Significant improvement in symptoms and dermatological quality of life index scores were observed with 150 and 300 mg omalizumab treatment compared to placebo after 10 weeks of treatment [10]. Metz et al. [11] showed complete response to omalizumab treatment in 86% of the patients with symptomatic dermatographism. In a another study, one of the two patients with symptomatic dermographism showed achieved complete/almost complete response to omalizumab treatment [12]. In a study of 25 patients treated with omalizumab, after 8 week treatment 3 patients with symptomatic dermographism had complete symptom control (defined as ≥90% improvement) [13].

Cold urticaria is itching, burning and wheals that develops within minutes in areas exposed to cold [14]. In our study, complete response was observed in 2 cold urticaria patients and partial response was observed in 2 patients with cold urticaria. In a placebo randomized controlled trial, the efficacy of 150 mg and 300 mg omalizumab were compared with placebo in 31 cold urticaria patients. After 4 weeks of treatment, significant improvement in symptoms was observed with omalizumab 150 mg and 300 mg compared to placebo and no significant difference was observed between these 2 doses of omalizumab [15]. In the case series of Kitsiolus et al. [16] in which 5 adolescent patients with cold urticaria were treated with

Table 2. The efficacy of omalizumab treatment on UAS7 score

		n	Mean score	Total score	z	p
UAS7 after - UAS7 baseline	Negative change	25[a]	13.92	348.00	-4.387	<0.0001
	Positive change	1[b]	3.00	3.00		
	Equal	1[c]				
	Total	27				

[a]UAS7 after<UAS7 baseline, [b]UAS7 after>UAS7 baseline, [c]UAS7 after=UAS7 baseline

Table 3. Relationship between previous treatments and changes in symptom severity with omalizumab treatment

	Change in symptom severity			p
	Percentile 25	Percentile 75	Median	
Antihistaminic	14.00	30.00	21.00	0.40
Antihistaminic and systemic steroid	21.00	35.00	25.50	

omalizumab 300 mg, a significant improvement in CDLQI score of 41.46% were reported in all patients after 5 months of treatment. Metz et al. [11] were reported complete response with omalizumab treatment in 3 of 6 cold urticaria patients. In a case series report, all 6 cold urticaria patients showed significant improvement in symptoms with omalizumab treatment [17].

Solar urticaria occur within minutes of exposure to ultraviolet or visible wavelengths of solar radiation [18]. In our study, complete response was obsorved with omalizumab treatment in 3 patients with solar urticaria. In a phase 2 multicenter study, the efficacy of omalizumab in solar urticaria was researched in 10 patients. At the end of 12 weeks of treatment with 300 mg omalizumab, 40% of patients achieved a DLQI score of less than 6 and 40% had a 50% improvement in severity of symptoms (measured on a visual analog scale) [19]. In a case series, significant improvement in symptoms was observed in 3 solar urticaria patients with omalizumab at varying doses of 150 mg to 450 mg [20].

Delayed pressure urticaria is characterized by the development of ıtchinng and wheals at sites of pressure to the skin [21]. In 3 of 4 delayed pressure urticaria patients, a complete response was obtained with omalizumab treatment in our study. The efficacy of omalizumab in delayed pressure urticaria was demonstrated in 2 retrospective studies. In the study of Ghazanfar et al. [12], 3 of 5 delayed pressure urticaria patients achieved a complete response with omalizumab treatment. In another study, complete response was observed in 7 of 8 pressure urticaria patients treated with omalizumab [11].

Study Limitations

The main limitations of our study are its retrospective nature and small sample size.

Conclusion

In conclusion, this retrospective analysis demonstrated the efficacy of omalizumab in different types of CindU. In addition, no relationship was found between omalizumab treatment and previous treatments in the change of disease severity to obtain more trustable results, there is need for more studies researching the efficacy of omalizumab in CindU.

Ethics

Ethics Committee Approval: The ethical approvement was obtained from Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Institutional Review Board (approval number: A-09, date:03.08.2021).

Informed Consent: Retrospective study.

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A Cross Sectional Investigation of the Effect of Eczema on Life Quality and its Comparison with Psoriasis

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ABSTRACT

Background: Eczema and psoriasis are inflammatory skin diseases that negatively affect patients' quality of life. In this study, we aimed to evaluate the dermatology life quality index (DLQI) scores in patients diagnosed with eczema and psoriasis.

Materials and Methods: A total of 797 patients, 410 (51.4%) female and 387 (48.6%) male, 202 (25.3%) of whom were diagnosed with mild to moderate psoriasis and 595 (74.7%) with eczema less than 10% of the body surface area were included in this retrospective study. The differences between the demographic data of psoriasis and eczema patient groups and factors affecting the DLQI score were evaluated.

Results: The median age of the patients in our study was determined to be 33 (28/41) years, while those patients with eczema were younger and had lower body mass index (BMI) values ($p<0.001$ and $p=0.034$, respectively). Seborrheic dermatitis (59.1%) was the most common type of eczema, while psoriasis vulgaris was the most common type among psoriasis group. The total DLQI score was 7 (4/13) in the eczema group and 6 (3/11) in the psoriasis group, respectively. Higher total DLQI scores were found in patients with eczema, women, patients with allergic diseases, patients with sinopulmonary disease, and in people with genital, upper and lower extremity involvement ($p<0.05$). There was a positive low-power correlation between the increase in BMI and the total DLQI scores of patients with psoriasis and eczema.

Conclusion: We found that the DLQI life quality of patients diagnosed with eczema and psoriasis was affected negatively in a similar way. We found that this deterioration increased in both groups in parallel with levels of obesity.

Keywords: Eczema, Psoriasis, DLQI

Introduction

Eczema and psoriasis are inflammatory skin diseases that have a negative impact on the quality of life of patients [1]. Although there are significant differences between these diseases, both are characterized by erythematous, and epidermal lesions, varying in density and affected body surface area [2].

Psoriasis is a chronic inflammatory disease that can occur at any age, affecting both genders at a similar rate, affecting the skin, nails and joints [3]. The clinical pattern is very varied among several types of eczema. Whatever the type of eczema, the histopathological processes are similar and can be seen as a stereotyped reaction pattern to a variety of different stimuli [4].

A multidimensional disease burden can be described in adult patients diagnosed with eczema (mainly atopic dermatitis) and psoriasis, including not only disease-related skin symptoms, but also sleep disturbances, impaired mental health, impairment in life quality and work productivity [5-7].

The Dermatology Life Quality Index (DLQI) scale is a tool that is frequently used to assess the impact of dermatological diseases on life quality [8]. We have previously shown that psoriasis negatively

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affects the life quality of Turkish patients via using DLQI [9]. In this study, we aimed to compare the effect of eczema on the life quality with psoriasis patients in whom this effect is best known and to reveal the factors affecting life quality.

Materials and Methods

Design of the Study

This study was conducted at the Bahcesehir University Faculty of Medicine Hospital, Dermatology Clinic from October 2017 to March 2020. Seven hundred ninety-seven patients with a clinical diagnosis of psoriasis were enrolled in the study. After the selection criteria were met, all patients were informed about the study and informed consent was obtained.

Patients

Socio-demographic characteristics of the patients (age, gender, educational status, marital status, income level, alcohol and smoking habits, and comorbid diseases), psoriasis and eczema-specific data (disease subtype, involvement area, disease duration, and presence of psoriatic arthritis) were recorded. The researcher, a dermatologist, collected socio-demographic and clinical data. Inclusion criteria for the study were that the patients be older than 18 years of age, have the ability to give informed consent, be literate in Turkish, and have clinically and/or laboratory-defined psoriasis or eczema with less than 10% body surface area involvement. Patients younger than 18 years of age, those who were unable to evaluate the DLQI form and did not agree to participate in the study, and those with two dermatological diseases were excluded from the study. Ethical permission for conducting this study was obtained from the Ethics Committee of Kocaeli University in the province where the relevant institution is located (approval number: 2016/172, date:17.02.2016).

Measurements

Independent variables included demographic, socio-economic, and clinical characteristics. Patients who signed the informed consent form were asked to complete the DLQI.

DLQI Score

DLQI is a questionnaire created for patients with skin diseases and consists of 10 items (emotions, daily activities, leisure time, work, personal relationships and treatment) that are filled out by the patients themselves. The overall DLQI score is the sum of the individual answer scores and ranges from 0 [meaning the skin disease has no effect on health-related quality of life (HRQoL)] to 30 (meaning the maximum effect on HRQoL). A DLQI score of 0-1 points indicates no impact on the patient's life; 2-5: a slight impact on the patient's life; 6-10: a moderate impact on the patient's life; 11-20: a significant impact on the patient's life; and a score of 21-30 is defined as one in which the patient's life is severely impacted. Score increase is associated with decreased quality of life. The Turkish version of this questionnaire was prepared by Ozturkcan et al. [10] and a study of its accuracy and validity has been conducted.

Statistical Analysis

The Statistical Package for the Social Sciences 26.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of variables. The suitability of univariate data to normal distribution was evaluated by Kolmogorov-Smirnov test and Shapiro-Wilk Francia test. The Mann-Whitney U test was used with the Monte Carlo simulation technique in comparing two independent groups with each other according to the quantitative data. Spearman's rho tests were used to examine the correlations of variables with each other. In the comparison of categorical variables with each other, the Pearson chi-square test was used with exact results and the column proportions were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. Odds ratio was used with 95% confidence intervals to show how many times those with a risk factor were higher than those without. Linear Regression, Random Forest, and Neural Network (Multilayer Perceptron-Radial Basis) were used to find and predict the variable with the highest significance in the DLQI total score. Since none of these methods could create a meaningful and valid model, their results were not reported. Quantitative variables were explained in tables as mean±standard deviation, median±interquartile range and median (minimum/maximum), categorical variables were shown as n (%). Variables were analyzed at a 95% confidence level and a p-value of less than 0.05 was considered to be significant.

Results

Demographic Characteristics

Our study included 410 (51.4%) females and 387 (48.6%) males, of whom 202 (25.3%) were mild to moderate psoriasis and 595 (74.7%) were eczema patients with less than 10% body surface area involvement. The most common type of eczema found in eczema group was seborrheic dermatitis (59.1%), while psoriasis vulgaris was the most common type in the psoriasis group (67.8 %) (Table 1).

While the median age of the patients in our study was 33 (28/41) years, patients with eczema were younger (32 vs. 37) and had lower body mass index (BMI) values (25.4 vs. 26) ($p<0.001$ and $p=0.034$, respectively) (Table 2).

Comparison of Eczema and Psoriasis Groups

While there was no difference between genders in the eczema group, it was found that psoriasis was more common in women than men (F/M: 1.7). The frequency of involvement in the truncus, genital area and extremities was found to be higher in patients with psoriasis than in those in the eczema group. On the other hand, the

Table 1. Demographic findings		
	n	%
Group		
Psoriasis	202	25.3%
Eczema	595	74.7%
Gender		
Female	410	51.4%
Male	387	48.6%
Eczema type		
Seborrheic dermatitis	351	59.0%
Nummular dermatitis	91	15.3%
Dyshidrotic Ezcema	20	3.4%
Irritant contact dermatitis	52	8.7%
Allergic contact dermatitis	26	4.4%
Atopic dermatitis	26	4.4%
Lichen simplex chronicus	17	2.9%
Other	12	2.0%
Psoriasis type		
Psoriasis vulgaris	137	67.8%
Palmoplantar pustulosis	6	3.0%
Guttate psoriasis	6	3.0%
Psoriatic arthritis	2	1.0%
Pustular psoriasis	1	0.5%
Other	50	24.8%

involvement frequency on face was found to be higher in patients who have eczema compared to the ones with psoriasis (Table 2). While additional skin diseases are more common in patients with eczema, the presence of other systemic diseases in the history of patients with psoriasis, sinopulmonary disease, continuous drug use, metabolic disease, cardiovascular disease, neurological disease, musculoskeletal disease, psychiatric disease, female-male hormonal diseases are statistically more likely (Table 3).

DLQI Results

While the total DLQI score was found to be 7 (4/13) in the eczema group, it was 6 (3/11) in the psoriasis group. When the DLQI effect status of the patients was evaluated, it was found that 252 (31.6%) of the patients were affected at a mild level, 230 (28.9%) of them were moderately severe, and 190 (23.8%) were affected at a very severe level (Table 2). It was found that approximately half of the patients with a diagnosis of psoriasis (none=15.8%, mild=32.2%) had very low DLQI levels. Symptoms, emotions and leisure time scores were found to be significantly higher in the eczema group (p=0.012 and p=0.034, respectively) (Table 2).

Comparison by Psoriasis and Eczema DLQI Scores

When the patients were evaluated according to their psoriasis and eczema DLQI total scores, it was found that among eczema patients; females (p=0.003), patients with allergic disease (p=0.025), patients with sinopulmonary disease (p=0.022), and patients with genital (p=0.023), upper extremity (p=0.001) and lower extremity (p=0.016) involvement had higher total DLQI scores than others. It was found that in patients with psoriasis only those with lower extremity (p=0.045) involvement had higher DLQI scores than those without lower extremity involvement.

DLQI Total Correlation Analysis

A positive low-strong correlation was found between increased BMI and DLQI total scores, leisure time activities and disrupted friendship scores in patients with psoriasis. In patients with eczema, a positive low-strong correlation was found between increased BMI and DLQI totals, leisure activity, symptoms, level of deterioration in friendships and effect on feelings (Table 4).

Discussion

Chronic dermatological diseases have a significant impact on patients' psychological health, self-esteem, and body image. Chronic stress and associated loss of positive self-image can also lead to social disability, which will likely exacerbate psoriatic and eczema symptoms [5,11]. In our study, we found that the life quality of patients diagnosed with eczema and psoriasis was similarly affected in a negative way.

DLQI is a reliable and valid tool for measuring quality of life and is widely used in psoriasis clinical investigations to assess life quality [6,12]. Studies on psoriasis patients in the United States of America have shown that an increase in disease severity is associated with a decrease in HRQoL, more hospital admissions, decreased self-confidence, and treatment-related frustration [13,14]. Quality of life is significantly affected in patients with eczema, but DLQI measurement is not used routinely in daily clinical practice.

Psoriasis affects both sexes in equal frequency and can occur at any age, whereas eczema starts at an earlier age and, similar to psoriasis, does not differ in distribution between genders [15,16]. In our study, there was no difference found in the frequency of incidence between genders in the eczema group, while it was found that psoriasis was more common in women than men (F/M: 1.7). The higher prevalence of female patients diagnosed with psoriasis was thought to be related to the fact that the patient cohort in our study consisted of younger patients compared to those in the literature.

It has been shown that the negative effects of psoriasis on life quality can be as severe as heart failure, diabetes, cancer and major

Table 2. Table in which patient groups are compared

	Total	Eczema	Psoriasis	p
	(n=797)	(n=595)	(n=202)	
Age, Median (Q1/Q3)	33 (28/41)	32 (27/38)	37 (29/49)	**<0.001[u]**
Complaint duration (months), Median (Q1/Q3)	12 (2/36)	6 (1.5/36)	12 (4/60)	**<0.001[u]**
Smoking (absent), n(%)	244 (30.6)	172 (28.9)	72 (35.6)	0.136[fe]
Alcohol use (absent), n(%)	118 (14.8)	90 (15.1)	28 (13.9)	0.731[pe]
Presence of allergies, n(%)	173 (21.7)	134 (22.5)	39 (19.3)	0.375[pe]
BMI (kg/m^2), Median (Q1/Q3)	25.5 (22.4/28.2)	25.4 (22.3/27.9)	26 (22.9/30)	**0.034[u]**
	n (%)	**n (%)**	**n (%)**	
Gender				**<0.001[pe]**
Female	410 (51.4)	284 (47.7)	126 (62.4)	
Male	387 (48.6)	311 (52.3)	76 (37.6)	
Face	367 (46.0)	320 (53.8)	47 (23.3)	**<0.001[pe]**
Truncus	153 (19.2)	89 (15.0)	64 (31.7)	**<0.001[pe]**
Genital	73 (9.2)	30 (5.0)	43 (21.3)	**<0.001[pe]**
Upper extremity	375 (47.1)	193 (32.4)	182 (90.1)	**<0.001[pe]**
Lower extremity	245 (30.7)	104 (17.5)	141 (69.8)	**<0.001[pe]**
DLQI effect				**0.002[pe]**
None	78 (9.8)	46 (7.7)	32 (15.8)[A]	**0.001**
Small	252 (31.6)	187 (31.4)	65 (32.2)	ns.
Moderate	230 (28.9)	179 (30.1)	51 (25.2)	ns.
Very large	190 (23.8)	153 (25.7)[B]	37 (18.3)	**0,033**
Extremely large	47 (5.9)	30 (5.0)	17 (8.4)	ns.
	Median (Q1/Q3)	**Median (Q1/Q3)**	**Median (Q1/Q3)**	
DLQI total	7 (3/12)	7 (4/13)	6 (3/11)	**0.017[u]**
Symptoms and feelings	3 (2/4)	3.3 (2/5)	2.8 (2/4)	**0.012[u]**
Daily activities	1 (0/2)	1 (0/2)	1 (0/2)	0.097[u]
Leisure	1 (0/2)	1 (0/2)	0 (0/2)	**0.034[u]**
Work and school	0 (0/1)	0 (0/1)	0 (0/1)	0.055[u]
Personal relationships	1 (0/2)	1 (0/2)	0 (0/1)	0.135[u]
Treatment	0 (0/1)	0 (0/1)	0 (0/1)	0.957[u]

[u] Mann-Whitney U Test (Monte Carlo), [fe] Fisher Exact Test(Exact), [pe] Pearson chi-square Test (Exact), Q1: Percentile %25, Q3: Percentile %75

depression [17]. Patients struggle with the disease and face various psychosocial problems during daily life activities highlighting the need for psychosocial strategies to treat patients diagnosed with psoriasis and to help them improve their overall quality of life. In our previous study conducted with 154 patients with psoriasis in 2011, we found the average DLQI score to be 9.3 (0-29) [9]. In this current study, the median DLQI score was found to be 6 (3/11) in patients diagnosed with psoriasis. We believe that the lower average DLQI score found in the current study is due to the fact that the psoriasis patients included in the study had milder disease activity, received adequate local therapies, and participated in standard clinic follow-ups.

In this current study, we aimed to reveal the life quality status of people diagnosed with two different skin diseases that are similar in appearance by evaluating their DLQI score, and we noticed that the eczema patient group had higher average DLQI scores. Another remarkable finding was that patients with eczema had very severe DLQI scores at a higher rate (36.7% vs. 26.7%) than those with psoriasis. Similar to our study, Lundberg et al. [18] found that patients with psoriasis had lower mean DLQI scores than those with atopic dermatitis. Face, hand and forearm involvement in patients with eczema significantly affects the patient's life quality and comfort during the day, both cosmetically and functionally. In addition, the fact that eczema affecting the face area is resistant

Table 3. Comparison of the groups in terms of comorbid conditions of the patients

	Total (n=797) n (%)	Eczema (n=595) n (%)	Psoriasis (n=202) n (%)	p
Family history	251 (31.5)	197 (33.1)	54 (26.7)	0.096[pe]
Additional skin disease	294 (36.9)	237 (39.8)	57 (28.2)	**0.003[pe]**
Disease in medical history	351 (44.0)	234 (39.3)	117 (57.9)	**<0.001[pe]**
Sinopulmonary disease	86 (10.8)	61 (10.3)	25 (12.4)	0.431[pe]
Cancer	10 (1.3)	6 (1.0)	4 (2.0)	0.284[fe]
Continuous drug use	226 (28.4)	156 (26.2)	70 (34.7)	**0.024[pe]**
GIS disease	33 (4.1)	24 (4.0)	9 (4.5)	0.838[pe]
Metabolic disease	68 (8.5)	43 (7.2)	25 (12.4)	**0.029[pe]**
Cardiovascular disease	73 (9.2)	40 (6.7)	33 (16.3)	**<0.001[pe]**
Urogenital disease	14 (1.8)	7 (1.2)	7 (3.5)	0.056[fe]
Neurological disease	18 (2.3)	9 (1.5)	9 (4.5)	**0.025[fe]**
Musculoskeletal disease	33 (4.1)	15 (2.5)	18 (8.9)	**<0.001[pe]**
Hepatobiliary disease	17 (2.1)	12 (2.0)	5 (2.5)	0.778[fe]
Thyroid disease	46 (5.8)	30 (5.0)	16 (7.9)	0.161[pe]
Psychiatric illness	17 (2.1)	9 (1.5)	8 (4.0)	**0.048[fe]**
Female/Male hormonal disorders	121 (15.2)	74 (12.4)	47 (23.3)	**<0.001[pe]**

[fe] Fisher Exact test (exact), [pe] Perason chi-square test (exact)

to conventional treatments emerges as an significant challenge [18,19]. In our study, we think that the acute and widespread occurrence of face involvement in patients with eczema may be associated with higher DLQI scores in the patients, and the increase in the symptoms-emotions and leisure time sub-criteria is due to this psychosocial influences and treatment difficulty.

In a study conducted by Araya et al. [20], the mean DLQI score of patients diagnosed with seborrheic dermatitis was found to be 8.1 (0/27). In the same study, it was emphasized that people with scalp lesions are more severely affected than those where other body parts are affected. Szepietowski et al. [21] found the mean DLQI score of 7.73±5.3 in a study in which patients with seborrheic dermatitis were evaluated, and it is similar to the results of our study involving patients with predominantly seborrheic dermatitis. Holm et al. [22] found the median DLQI score to be 5 (3-9) in a study in which they evaluated the life quality of patients with AD in 2006. In this study, they emphasized that AD has a significant effect on HRQoL, and that mental health, and the social and emotional functioning of patients are affected more than physical function. Similarly, in our study, it was found that symptoms and emotions and leisure time scores were significantly higher than those for physical activity in the patient group with eczema ($p<0.005$).

There are not sufficient data in the literature regarding the presence of asthma and sinopulmonary disease in eczema or psoriasis patients that result in deterioration in DLQI scores. In our study, in addition to the literature, it was determined that patients with eczema who had allergic diseases ($p=0.025$) and those with sinopulmonary disease ($p=0.022$) had higher DLQI scores. This situation may be thought to be related to additional factors (such as continuous drug use, atopic structure, and disease burden brought by additional comorbidity) that negatively contribute to the life quality of patients with chronic allergic diseases.

The relationship between eczema and obesity has been described especially in children, and the effect of this condition on the life quality of patients is controversial. Xuan et al. [23] found that BMI affects the life quality of patients with seborrheic dermatitis. Silverberg and Simpson [24] found that obesity was associated with an increased frequency and severity of eczema in adolescents aged 10-17 years, and a deterioration in the general health status of eczema patients. However, measurements were not made with the DLQI in this study. In our study, obesity was found to be correlated with the DLQI total, leisure activity and symptom-feeling effects in patients with eczema, similar to those in psoriasis patients. In our study, we think that the relationship between BMI and DLQI deterioration in eczema patients is an important finding, in contrast to those in the literature.

Study Limitations

There are some limitations to our study. Some of which are due to the fact that patients were followed up in a single center, as

Table 4. Correlation analysis for factors affecting DLQI increase in patients with psoriasis and eczema					
			Age	**BMI**	**Complaint duration**
Psoriasis	DLQI total	r	0.034	0.161	0.054
		p	0.630	0.022	0.445
	Symptoms and feelings	r	0.024	0.050	-0.017
		p	0.739	0.478	0.808
	Daily activities	r	0.052	0.118	0.112
		p	0.466	0.093	0.111
	Leisure	r	0.015	0.194	0.078
		p	0.831	**0.006**	0.270
	Work and school	r	0.004	0.103	0.075
		p	0.959	0.145	0.289
	Treatment	r	0.135	0.222	0.101
		p	0.055	**0.002**	0.154
	Personal relationships	r	0.058	**0.173**	-0.021
		p	0.410	**0.014**	0.768
Eczama	DLQI total	r	0.034	0.086	-0.004
		p	0.413	**0.037**	0.923
	Symptoms and feelings	r	0.046	0.103	-0.004
		p	0.258	**0.012**	0.923
	Daily activities	r	0.022	0.064	-0.002
		p	0.590	0.122	0.956
	Leisure	r	0.087	0.09	-0.021
		p	0.033	**0.027**	0.615
	Work and school	r	0.010	-0.002	-0.036
		p	0.810	0.953	0.384
	Treatment	r	-0.008	0.072	0.000
		p	0.843	0.080	0.997
	Personal relationships	r	0.104	0.116	-0.036
		p	**0.011**	**0.004**	0.385

Spearman's rho test, r: Correlation coefficient

patient selection causes numerical differences between the groups, and there was no information about the patients' education levels, employment and income status. In addition, the relationship between disease severity and DLQI could not be clearly evaluated because scoring systems that evaluate the disease severity of the patients (Psoriasis Area Severity Index and Eczema Area and Severity Index) were not used. We think that the fact that the DLQI scores of the patients in our study are at a higher level compared to the literature can be explained by this situation.

Conclusion

In conclusion, in our study, we found that the DLQI life quality of patients diagnosed with eczema, was affected in a moderate-negative way, similar to that in those with psoriasis. We found that this deterioration increased in both groups in parallel with obesity. Follow-up of these diseases in a multidisciplinary manner, in which comorbid conditions are considered, optimal treatments are performed and weight control is addressed is very important in terms of improving the social, psychological and cognitive conditions of patients.

Ethics

Ethics Committee Approval: Ethical permission for conducting this study was obtained from the Ethics Committee of Kocaeli University in the province where the relevant institution is located (approval number: 2016/172, date:17.02.2016).

Informed Consent: All patients were informed about the study and informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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The Optimal Reading Time for Patch Testing: A Retrospective, Cross-sectional, Single Center Study Over 8 Years from Turkey

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ABSTRACT

Background: Controversy still exists concerning the optimal reading time of patch testing, and the lack of analysis after day seven might result in missing late positive reactions in rare cases. We aimed to describe our experience with patch test reading and the frequency of early and late positivity, with particular attention to detecting delayed reactions.

Material and Methods: This is a retrospective study on 791 patients who were consecutively patch tested with the extended European baseline series and gold salts, between January 2004 and December 2012. Test sites were evaluated on day D2, D3, and D4, and since 2010, on D7 as well, according to the European Society of Contact Dermatitis patch-test guideline. Positivity on D2 or D3 was identified as early reaction, and on D4, D7 and later as late reaction.

Results: Of the total 791 patch-tested patients, 773 (97.7%) had at least one positive patch test reaction of which 651 (84.2%) were classified as early (on days 2 or 3), and 122 (15.8%) were classified as late (on day 4 or later). The early and late reaction groups were similar in terms of age, sex and atopy; however, metal hypersensitivity was significantly more frequent in the late reaction group. The substance with the most number of late positive tests was nickel sulfate (16.3%). In terms of relative frequency of positivity on D7 or even later, the most notable substances included neomycin sulfate, gold salts, epoxy resin and polyethylene glycol.

Conclusion: The results of our study promote the value of an additional late patch test reading on D4 and D7 or even later in the presence or suspicion of allergy caused by nickel sulfate, cobalt chloride, gold salts, epoxy resin, polyethylene glycol, and neomycin.

Keywords: Patch test, Allergic contact dermatitis, Late reactions, Reading time, Delayed, Early

Introduction

Patch testing is a routinely used standardized protocol for investigation of contact allergy resulting from type IV hypersensitivity [1,2].

The European baseline series (EBS) of contact allergens is preferred throughout Europe as a standard patch test screening [3]. According to the European Society of Contact Dermatitis (ESCD) guidelines, the results of diagnostic patch testing is advised to be assessed through at least two readings which may be performed on day D2, D3 or D4, and around D7, after application. A reading at D3 or D4 is considered obligatory [4]. The morphological criteria for visual assessment has been described by the International contact dermatitis research group (ICDRG) [5].

It has been previously shown that approximately 30% of negative results at the D2 reading became positive at D4, which has denoted that D4 may be an optimal time-point for the second reading [6].

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Late readings between D7-D10 is accepted to be optional, but it is known that some allergens, such as corticosteroids, antibiotics and some metals, may manifest late reactions on D7 and later. Lack of late readings might cause that 7-30% of positive reactions are missed [7]. On the contrary, some authors have concerns on late readings. Saino et al. [8] found that there was a 3% increase in the number of positive reactions after D3 and they suggested that patch-test evaluation after D3 would be too time-consuming to be used routinely. It is well-known that some allergens are "late reactors", or delayed reactions may be sensitized from the patch test itself (patch test sensitization, active sensitization), or they might be a result of the varying reaction characteristics of different individuals [9].

Controversy still exists with regard to the optimal reading time of patch testing. Such inconsistencies would inevitably affect correct interpretation of patch test results, and therefore, the detection of allergens associated with late positive reactions. In this study, we aimed to define the optimal reading time for patch testing, especially to detect late positive reactions.

Materials and Methods

Study Group

We conducted a retrospective analysis on patch test data from January 2004 to December 2012, which included 791 consecutive patients meeting the inclusion and exclusion criteria who had undergone routine patch testing in the Allergy Unit of the Department of Dermatology and Venereology, Istanbul Faculty of Medicine. Ethics committee approval of this study was carried out by Istanbul Faculty of Medicine Ethics Committee (07.06.2013/2013/700). All tests had been conducted via the same method as described below, with our extended EBS allergens and gold sodium thiosulfate.

Informed oral/written consent was obtained from all patients (or the parents or legal guardians of children) before their inclusion in the study. Any patients using prescribed medications that could affect patch testing, those who had applied topical corticosteroids/calcineurin inhibitors to the test site within 4 weeks and those with excessive sun exposure within 4 weeks were excluded.

Study Design, Patch Testing and Data Analysis

Test allergens were provided by Chemotechnique Diagnostics (Vellinge, Sweden), Brial Allergen (Greven, Germany), and AllergEAZE (Calgary, Canada), and in the earlier years by Hal-Brial (Leiden, The Netherlands). The allergens were applied on the upper part of the back using IQ chambers (Chemotechnique Diagnostics) for 48 hours under occlusion. Patients' files were evaluated with regard to demographic features (gender, age, atopy), history of metal hypersensitivity, patch test findings, and the strength of reaction. Patients who had been diagnosed with atopic dermatitis according to the criteria put forth by Eichenfield et al. [10] and those with mucosal atopy or atopic skin diathesis were recorded as atopic.

The readings were made by the International ICDRG criteria, after awaiting 20-30 minutes following removal of patch test plasters [4,11]. Test sites were assessed by experienced dermatologists on day D2, D3, and D4, and since 2010, on D7 as well. Weak (+), strong (++) and extreme (+++) patch test reactions were categorised as positive reactions. In addition to definite negative results (-), reactions classified as irritant, or doubtful were also counted as negative [12].

According to the onset of positive patch test reactions, patients were divided into "early and late" reaction groups. The early reaction group included patients in whom positive reactions were observed at D2 or D3. Patients whose positive reaction started at D4 or later were included in the late reaction group. For patients with a positive reaction beyond D7, a second patch testing was performed to differentiate between late positive reaction and active sensitization. Early positive patch test reaction on D2 or D3 in the second patch testing indicated an active sensitization with the suspected allergen.

Statistical Analysis

All analyses were performed on Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS, Inc., an IBM Company, Chicago, Illinois). For the normality check, the Kolmogorov-Smirnov test was used. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables, depending on the normality of distribution. Quantitative variables were compared using the independent samples t-test (parametric) or the Mann-Whitney U test (non-parametric), and qualitative variables were compared using chi-square tests, including McNemar's test or Fischer's exact test. $P<0.05$ values were accepted as statistically significant results.

Results

A total of 791 patients (416 females, 375 males, mean age 37.7 years) who had undergone patch testing with the 27 allergens of the extended EBS and gold salts were included in this study. Patients' demographics are shown in Table 1.

Out of these 791 patients, 773 (97.7%) had at least one positive patch test reaction. Among these, 478 reactions occurred on D2, 173 occurred on D3, 80 occurred on D4, 28 occurred on D7 and 14 occurred after D7. Therefore, among the overall number of positive tests, 651 (84.2%) were classified as early reaction, and 122 (15.8%) were classified as late reaction (Table 1). The early and late reaction groups were similar for age, sex, atopy ($p>0.05$). Nevertheless, the frequency of metal hypersensitivity in the history was significantly higher among patients with late reaction ($p=0.001$). In addition, subjects with a positive reaction on D7 or later ($n=42$) were similar

Table 1. The demographic characteristics of the patch tested patients between 1996-2012

		Overall (n=791)
Age, mean ± SD		37.7±15.8
Sex, n (%)	Female	416 (52.6%)
	Male	375 (47.4%)
Atopy (atopic dermatitis/ atopic skin diathesis/allergic rhinoconjunctivitis), n (%)	Yes	159 (20.1%)
	No	420 (53.1%)
	No data	212 (26.8%)
Year of patch testing, n (%)	2004	110 (13.9%)
	2005	88 (11.1%)
	2006	98 (12.4%)
	2007	98 (12.4%)
	2008	118 (14.9%)
	2009	32 (4%)
	2010	67 (8.5%)
	2011	104 (13.1%)
	2012	76 (9.6%)
Onset of positive patch test reactions	Early	651 (82.3%)
	Late	122 (15.4%)
	None	18 (2.3%)
Metal hypersensitivity in the history, n (%)	Yes	732
	No	451
	No data	426

to those with a positive reaction on D4 regarding age, sex, atopy and metal hypersensitivity (n=80) (p>0.05).

Among 122 patients with a late reaction, 28 (23%) had a positive reaction on D7 and 14 (11.5%) after D7. The strength of positive patch test reactions was (+) in 85 (69.7%), (++) in 34 (27.9%), and (+++) in 3 (2.5%). One hundred and twenty-two late positive reactions consisted of: nickel sulfate 16.3%, cobalt chloride 9%, thimerosal 8.2%, both neomycin sulfate and palladium chloride 7.3%, polyethylene glycol 6.6%, potassium dichromate 4.9%, and other less frequent allergens. On the other hand, if the ratio of late positivity (reacting on D4 and/or D7) according to the total number of positive reactions for each allergen was determined as "relative incidence", the following rates were obtained: budesonide (100%, 1/1), neomycin sulfate (69.2%, 9/13), gold sodium thiosulfate (50%, 2/4), epoxy resin (42.9%, 3/7) and polyethylene glycol (42.1%, 8/19). Contact allergens with the greatest "relative incidence" regarding positive reactions on D7 or later were budesonide (100%), neomycin sulfate (38.5%), gold sodium thiosulfate (25%), lanolin alcohols (22.2%), epoxy resin (14.3%), Euxyl® K400 (14.3%), cobalt chloride (12.5%), polyethylene glycol (10.5%), and thimerosal (10.2%). Only one patient showed late reactions to methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) on D7, not reacting on D4. Additional patch testing to ascertain whether active sensitization had occurred was performed on 14 subjects out of the 42 individuals with a late positive reaction on D7 or later. Among them, two patients (14.3%) were found to have active sensitization (one to cobalt chloride, the other to p-phenylenediamine). Any late positive reaction was reacted with benzocaine, clioquinol/quinoline mix, mercapto mix, 4,4'-diaminodiphenylmethane, quaternium-15, carba mix, toluene sulfonamide formaldehyde resin (TSF), hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®), methyl dibromo glutaronitrile, zinc diethyldithiocarbamate.

Discussion

Determination of the optimal reading time is essential for patch testing, both in terms of the reliability of the patch test results and the accuracy of detecting allergens yielding late-positive reactions. In the current study, 97.7% of patients had at least one positive patch test reaction of which 651 (84.2%) appeared as early positive reactions and 122 (15.8%) as late positive reactions. Findings of the present study show that the great majority of patients with a positive reaction can be detected on days 2 and 3. However, our data showed that if D3 was designated as the final analysis time point, 15.8% of the positive reactions would have been missed. That underlined the necessity of readings on D4 and later. Moreover, if D7 and later readings had not been performed, 5.4% of the positive reactions would have been missed.

It is difficult to compare our results with those of other studies because different "reading time" protocols have been used for patch testing of contact allergens. Moreover, the assigned days for "late" reading may vary considerably. Late readings are commonly characterized as occurring after D3 or D4 in certain research based on late patch-test reactions [13]; while the delayed reading period is defined as beginning at D7 in other [14,15].

Van Amerongen et al. [16] reported that, in patients tested with T.R.U.E. Test® panel 1 and 2 (including additional allergens), 13.5% of positive reactions could not be detected if D7 reading had not been performed, supporting the value of an additional late patch test reading on D7. Geier et al. [17] reported that, when compared to D3 readings, the rate of new positive reactions was 14.8% at D4 and 22.7% at D5. However, readings on days 3 and 5 may be problematic as at least one of the reading days would be on the weekend. In another study, the rate of new positive reactions (compared to D3 and D4) was found to be 13.5% at the second reading on days 6 or 7 [18]. In an interesting analysis by Wolf et al. [19] it was suspected that very late reactions could be associated with active sensitization caused by the patch test, or could reflect a slow response with respect to individual reaction patterns. In the present study, active sensitization was found to have been present in two of the 14 subjects who had undergone a second patch testing. Despite the fact that this is a small ratio, we must note that only 14 of the 42

Table 2. Positive patch test results obtained with the baseline series and gold salts between 2004-2012

	Number of tested patients	Total number of positive reactions	Total number of early reactions	Onset of early reactions		Total number of late reactions		Onset of late reactions			P***
Allergen	N	n (%)	n (%*)	D2, n	D3, n	n, (%*)	%**	D4, n	D7, n	>D7, n	
Potassium dichromate, 0.5% pet.	785	63 (8)	57 (90.5)	49	8	6 (9.5)	0.8	3	2	1	0.125
p-phenylenediamine (PPD), 1.0% pet.	779	34 (4.5)	31 (91.2)	26	5	3 (8.8)	0.4	2	0	1	1.000
Thiuram mix, 1.0% pet.	782	41 (5.2)	39 (95.1)	33	6	2 (4.9)	0.3	2	0	0	0.500
Neomycin sulfate, 20.0% pet.	788	13 (1.6)	4 (30.8)	1	3	9 (69.2)	1.1	4	2	3	**0.004**
Cobalt (II)chloride hexahydrate, 1.0% pet.	786	40 (5)	29 (72.5)	23	6	11 (27.5)	1.4	6	3	2	**0.001**
Benzocaine, 5.0% pet.	788	6 (0.7)	6 (100)	4	2	–	-	-	-	-	1.000
Nickel (II) sulfate hexahydrate, 5.0% pet.	786	160 (20.3)	140 (87.5)	109	31	20 (12.5)	2.5	18	2	-	**0.000**
Clioquinol 5.0%/Quinoline mix, 6.0%, pet.	774	5 (0.6)	5 (100)	3	2	–	-	-	-	-	1.000
Colophonium, 20.0% pet.	788	24 (3)	18 (75)	14	4	6 (25)	0.8	4	1	1	**0.03**
Paraben mix, 16.0% pet.	781	3 (0.4)	2 (66.7)	2	-	1 (33.3)	0.1	1	-	-	1.000
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD), 0.1% pet.	774	6 (0.8)	5 (83.3)	5	-	1 (16.7)	0.1	1	-	-	1.000
Lanolin alcohol, 30.0% pet.	780	9 (1.2)	6 (66.7)	3	3	3 (33.3)	0.4	1	1	1	0.250
Mercapto mix, 2.0% pet.	780	8 (1)	8 (100)	8	-	–	-	-	-	-	1.000
Epoxy resin, 1.0% pet.	783	7 (0.9)	4 (57.1)	4	-	3 (42.9)	0.4	2	1	-	0.250
Peru balsam (myroxylon pereirae resin), 25.0% pet.	788	32 (4)	27 (84.4)	20	7	5 (15.7)	0.6	2	2	1	0.063
4-tert-Butylphenolformaldehyde resin (PTBP), 1.0% pet.	783	7 (0.9)	5 (71.4)	3	2	2 (28.6)	0.3	2	-	-	0.500
2-Mercaptobenzothiazole (MBT), 2.0% pet.	787	12 (1.5)	11 (91.7)	7	4	1 (0.8)	0.1	1	-	-	1.000
4,4'-Diaminodiphenylmethane, 0.5% pet.	787	17 (2.2)	17 (100)	10	7	–	-	-	-	-	1.000
Fragrance mix I, 8.0% pet.	789	35 (4.4)	32 (91.4)	27	5	3 (8.6)	0.4	1	2	-	0.250
Sesquiterpene lactone mix, 0.1% pet.	775	10 (1.3)	7 (70)	6	1	3 (30)	0.4	3	-	-	0.250
Quaternium-15, 1.0% pet.	760	4 (0.5)	4 (100)	2	2	–	-	-	-	-	1.000
Carba mix, 3.0% pet.	545	22 (4)	22 (100)	17	5	–	-	-	-	-	1.000
Toluenesulfonamide formaldehyde resin (TSF), 10.0% pet.	788	9 (1.1)	9 (100)	9	-	–	-	-	-	-	0.125
Mercury (II) amidochloride, 1.0% pet.	781	25 (3.2)	21 (84)	16	5	4 (16)	0.5	3	1	-	0.125
Palladium (II) chloride, 2.0% pet.	789	54 (6.8)	45 (83.3)	24	21	9 (16.7)	1.1	6	3	-	**0.004**
Thimerosal, 0.1% pet.	788	49 (6.2)	39 (79.6)	18	21	10 (20.4)	1.3	5	2	3	**0.002**
Euxyl K 400, 0.5% pet.	654	14 (2.1)	10 (71.4)	7	3	4 (28.6)	0.6	2	2	-	0.125
Fragrance mix II, 14.0% pet.	176	5 (2.8)	4 (80)	3	1	1 (20)	0.6	1	-	-	1.000

Table 2. continued

	Number of tested patients	Total number of positive reactions	Total number of early reactions	Onset of early reactions		Total number of late reactions		Onset of late reactions			P***
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®), 5.0% pet.	181	3 (1.7)	3 (100)	2	1	–	-	-	-	-	1.000
Budesonide, 0.01% pet.	183	1 (0.5)	–	-	-	1 (100)	0.5	-	1	-	NA
Methyl dibromo glutaronitrile (MDBGN), 0.5% pet.	256	3 (1.2)	3 (100)	1	2	–	-	-	-	-	1.000
Methylisothiazolinone/ Methylchloroisothiazolinone -, 0.01% aq.	779	11 (1.4)	10 (90.9)	8	2	1 (9.1)	0.1	-	1	-	1.000
Formaldehyde, 2.0% aq.	747	11 (1.5)	9 (81.8)	4	5	2 (18.1)	0.3	2	-	-	NA
Gold sodium thiosulfate, 0.5% pet.	109	4 (3.7)	2 (50)	2	-	2 (50)	1.8	1	-	1	0.500
Zinc diethyldithiocarbamate, 1.0% pet.	265	3 (1.1)	3 (100)	3	-	–	-	-	-	-	1.000
Polyethylene glycol, 100%	515	19 (3.7)	11 (57.9)	4	7	8 (42.1)	1.6	6	2	-	**0.008**
Propylene glycol, 5.0% pet.	514	4 (0.8)	3 (75)	1	2	1 (25)	0.2	1	-	-	1.000
Total number		773 (100)	651	478	173	122		80	28	14	

*: Percentage with respect to all positive reactions to the substance, **: Percentage of positivity with respect to patients tested for the substance, *** Statistical significance of late positive reactions (McNemar analysis) †: Euxyl K 400: methyldibromo glutaronitrile/phenoxyethanol, NA: Not applicable

patients with a late reaction had undergone this analysis. Therefore, future studies could benefit from performing this analysis in all subjects with late positivity beyond D7.

In the current study, consistent with the literature reports, metals were the most common allergens leading to late-positive reactions, including nickel sulfate, cobalt chloride, palladium chloride and gold salts [7,14,20,21]. Jonker and Bruynzeel [21] had also come upon the conclusion that the most common allergen leading to late positive reaction was nickel sulfate.

Chaudhry et al. [7] showed that a patch-test reading after D7 is particularly useful to assess reactions to metals, specific preservatives and the topical antibiotic neomycin. For other patients, a patch test schedule concluding with a D5 reading was reported to be able to identify reactions to most allergens, with the inclusion of topical corticosteroids that are known to manifest delayed reactions [7]. D6 readings were found to be particularly useful by other researchers due to the higher frequency of newly positive reactions to nickel, colophonium, and potassium dichromate [22]. A total 607 patients reacted positively to nickel sulfate in another cohort study, with 104 (17.1%) of these reactions being new positive D7 reactions [16]. However, some authors reported no late reactions with nickel sulfate [23]. In the present study, among a total of 160 positive reactions with nickel sulfate, 18 (11.3%) had developed after D4, and 2 (1.3%) after D7 (Table 2).

Our results showed that other contact allergens associated with late positive reactions were thimerosal, neomycin, polyethylene glycol and colophonium. Madsen and Andersen [18] reported a high rate of late positive reactions to neomycin (57%) which was in accordance with the results of the current study, since 9 reactions out of the 13 positive reactions to neomycin (69.2%) were detected after D4, while 5 of them (38.5%) were detected on D7 or later. According to the literature, neomycin sulfate has been the most frequently reported allergen related to new positive reactions at late readings [7,24]. Macdonald and Beck [25] reported slow local absorption of neomycin entirely the skin and slow local immunological reactivity as contributors to late positivity, while the possibility of neomycin storage in the epidermis for a long time was also suggested as a factor causing the late manifestation of positivity. Furthermore, similar to our findings, thimerosal and colophonium have also been reported to be allergens causing late positivity [21].

In the present study, polyethylene glycol was responsible for 6.6% of 122 late-positive patch test reactions. In agreement with our results, Özkaya and Kılıç [26], in their retrospective study, showed that more than one-third of the patients (34.3%, n=12) with polyethylene glycol sensitivity showed late positive patch test reactions starting on D4 or later. They concluded that late positive reactions on D7 are frequent and that late readings are essential to accurately detect positive patch test reactions.

Budesonide and tixocortol are known as late allergens which are suggested to mask the clinical signs of a positive patch test reaction due to their anti-inflammatory activities. As this effect diminishes over time, the test site becomes eczematous at subsequent readings [27]. In the present study, budesonide was positive in only one patient presenting with a late positive reaction after D7. Although the value of these extended readings was limited, some studies reported delayed reactions to corticosteroids [28,29]. However, Higgins and Collins [14] found no additional positive corticosteroid reactions in late readings in their study of 203 patients. Despite the fact that only 183 patients had been tested for budesonide, the relative incidence of late reactivity for budesonide was identified as %100 (a single case). Other late-positive allergens exhibiting a high relative incidence were neomycin sulfate, gold salts, epoxy resin and polyethylene glycol. A comparative analysis with prior studies focusing on late reactivity to patch testing is given in Table 3. In a recent study, Ozkaya et al. [30] reported two late positive reactions in 77 positive reactions with MCI/MI.

Table 3. An overview of previous studies evaluating late positivity in patch testing

	Macfarlane et al. (24)	Geier et al. (17)	Jonker and Bruynzeel (21)	Davis et al. (20)	Madsen and. Andersen (18)	Present study
Publication year	1989	1999	2000	2008	2012	
Number of patients	403	1096 (Group I) 1243 (Group II) 1136 (Group III)	760	372	9997	791
Allergen	Neomycin, potassium dichromat, cobalt chloride	European baseline series	European baseline series	European baseline series, metal and corticosteroid series	European baseline series	Extended European baseline series allergens and gold salts
Time of late positivity	4th day and after	4. day (Group I) 5. day (Group II) 6. day (Group III)	6th or 7th day and after	5th day and after	6th or 7th day and after	4th day and after
Number of late positive reactions	Not available	255 (Group I) 355 (Group II) 279 (Group III)	77	30 817	881	122
Percent of late positive reactions	Not available	12.9 (Group I) 18.5 (Group II) 15.2 (Group III)	Not available	Not available	13.5	15.8
Percent of patients with a late positive reaction	7.2	12.9 18.5 15.2	8.2	Not available	Not available	12.6
Contact allergens with a late positive reaction among all tested patients	Neomycin sulfate Potassium dichromat Cobalt chloride	Nickel sulphate Neomycin sulfate Cobalt chloride Thimerosal Peru balsam	Nickel sulphate Neomycin sulfate Tixocortol-21-pivalate PTBF-FR Methylisothiazolinone/ Methylchloroisothiazolinone Potassium dichromate	Gold sodium thiosulfate Dodecyl gallate Palladium chloride Neomycin sulfate	Not available	Nickel sulphate† Gold sodium thiosulfate Polyethylene glycol Cobalt chloride Neomycin sulfate
Contact allergens with a late positive reaction among positive patch test reactions					Neomycin sulfate Budesonide Hydrocortisone Tixocortol-21-pivalate Thimerosal	Budesonide Neomycin sulfate Gold sodium thiosulfate Epoxy resin Polyethylene glycol

†: Nickel sulphate was tested at 2.5 concentration. PTBP: 4-tert-Butylphenolformaldehyde resin

Study Limitations

The retrospective nature is one of the limitations of this study. It is difficult to compare publications on delayed positive patch test reactions due to differences in terminology and day of the patch test reading (which may vary from D5 to D9). Also, test materials and concentrations do not always match in comparable studies. Some evidence also suggests that the positive reactions on D7 or later may be related to the vehicle used, rather than the primary allergen itself.

Conclusion

The results of our study supported the importance of an additional late patch test reading on D4 and D7 or later, particularly for metals such as nickel sulfate, cobalt chloride, palladium chloride, and neomycin. Therefore, we would recommend to perform a D4 and D7 reading routinely and later patch test readings for those with suspect of contact sensitivity to aforementioned substances.

Ethics

Ethics Committee Approval: Ethics committee approval of this study was carried out by Istanbul Faculty of Medicine Ethics Committee (approval number: 700, date: 07.06.2013).

Informed Consent: Informed oral/written consent was obtained from all patients (or the parents or legal guardians of children) before their inclusion in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.Ö.A, E.Ö., Concept: T.Ö.A, E.Ö., Design: T.Ö.A, E.Ö., Data Collection or Processing: T.Ö.A, E.Ö., Analysis or Interpretation: T.Ö.A, E.Ö., Literature Search: T.Ö.A, E.Ö., Writing: T.Ö.A, E.Ö.

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Association of Hidradenitis Suppurativa and Ulcerative Colitis in a 14-Year-Old Patient

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent disease of the hair follicle and the lesions are most commonly located in axillary, inframammary, inguinal and anogenital regions. HS is associated with several comorbidities including psychiatric disorders, diabetes, metabolic syndrome, spondyloarthropathies and inflammatory bowel diseases (IBD). In recent literature the association of HS with IBD has emerged as a new research area. Common genetic susceptibility loci, certain cytokine abnormalities and altered microbiota of skin and gut are the factors which have been suggested to play role in both HS and IBD. However, less data is available on HS in pediatric patients and associated IBDs compared to adult population. Here we present an association of HS and ulcerative colitis in a 14-year-old patient to emphasize the importance of regular assessment of gastrointestinal symptoms in children with HS as the evidence to date supports a link between HS and IBD.

Keywords: Hidradenitis suppurativa, Ulcerative colitis, Pediatrics

Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent disease of the hair follicle and the lesions are most commonly located in axillary, inframammary, inguinal and anogenital regions [1]. The disease typically begins after puberty, most commonly between 20-24 years of age, and the onset before 13 years of age is rare [2,3]. The association of HS with the chronic, inflammatory, relapsing diseases of the intestinal tract, inflammatory bowel diseases (IBD), is emerging as a new research area and recent literature indicates the shared genetic susceptibility and immunologic features [4,5]. Less data is available on HS in pediatric patients and associated IBDs compared to adult population. Herein, we report an association of HS and ulcerative colitis (UC) in a pediatric patient.

Case Report

A 14-year-old female patient applied to our outpatient clinic with complaints of recurrent painful nodules and abscesses in the axillary region for more than a year. She reported that she had similar lesions on the umbilical area three months ago which were diagnosed as omphalitis and she had received multiple antibiotic regimens for her condition. Her medical history revealed that she was diagnosed with UC four months ago. Since then, she has been treated with azathioprine 100 mg/day, mesalazine 4 gr/day and prednisolone 10 mg/day for UC and she was in remission.

On dermatological examination, she had erythematous nodules and sinuses with minimal discharge in the axillary region (Figure 1). Based on her medical history and clinical examination she was diagnosed with HS and started with topical clindamycin. On the

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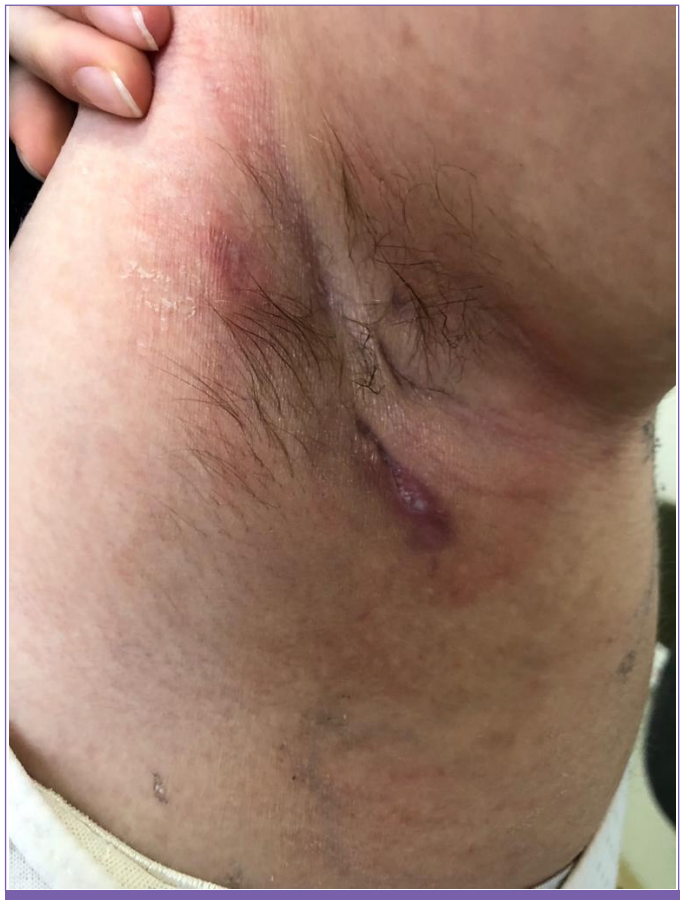

Figure 1. Axillary region with erythematous nodules and sinuses with minimal discharge

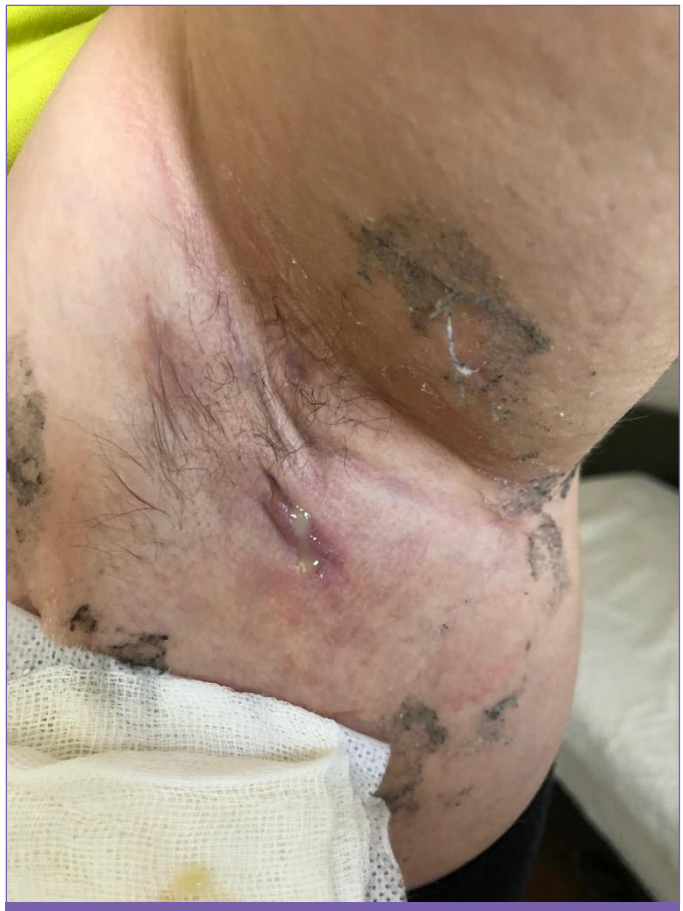

Figure 2. Prominent purulent discharge in axillary region

follow-up examination, as she had an increase in the purulent discharge (Figure 2), oral doxycycline 100 mg/day was added to her treatment.

The delay of diagnosis for HS was 1.5 year for our patient and according to her medical records, the skin lesions started approximately one year before the gastrointestinal symptoms, which then led to the diagnosis of UC.

Discussion

HS is a burdensome disease with several associated comorbidities including psychiatric disorders, diabetes, metabolic syndrome, spondyloarthropathies and IBD [6]. Lately, the link between HS and IBDs has been attributed to similar pathogenic mechanisms as both diseases are known to be chronic inflammatory diseases [4]. Common genetic susceptibility loci involving *SULT1B1* and *SULT1E1* [7], cytokine abnormalities such as increased levels of tumor necrosis factor, interleukin 1 (IL-1), IL-6, IL-17, IL-23 [8-10] and altered microbiota of skin and gut [5] are the factors which have been suggested to play role in both HS and IBD.

A recent systematic review and meta-analysis by Chen and Chi [4] showed that in patients with HS, there is a 2.12-fold increased risk for Crohn's disease (CD) and 1.51- fold increased risk for UC. Most of the studies in the literature which have shown this association included adult patients and there is less evidence available in pediatric age group. A study with 153 pediatric HS patients also demonstrated that IBDs were significantly more common than control group and affecting 3.3% of the patients [6]. In a retrospective study including 109 patients ≤18 years old diagnosed with HS demonstrated that six patients (6/109, 5.5%) had concomitant IBD, one patient classified as CD and five patients as UC [11]. Similarly, in a pediatric CD cohort with 380 patients, seven patients diagnosed with HS [12]. The peak incidence of IBD is in second to fourth decade of life [13] and the earlier onset of IBD is known to be associated with more severe disease and relatively increased risk of intestinal cancer, therefore early diagnosis is of paramount importance [14].

As the younger patients may be more prone to the risk of accumulation of comorbidities [6], children with HS should be evaluated with appropriate screening tools for associated comorbidities including IBDs. In this report, we presented a 14-year-old adolescent female with HS and UC to emphasize the importance of regular assessment of gastrointestinal symptoms including abdominal pain, chronic diarrhea and bloody stool in patients

with HS. The collaboration with gastroenterologists in symptomatic patients is an essential part of the multidisciplinary approach as the evidence to date supports an association between HS and IBD.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., E.Ad., Concept: E.A., E.Ad., Design: E.A., E.Ad., Data Collection or Processing: E.A., E.Ad., Analysis or Interpretation: E.A., E.Ad., Literature Search: E.A., E.Ad., Writing: E.A., A.Ed.

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

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CASE REPORT

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Disseminated Superficial Porokeratosis Mimicking Disseminated Discoid Lupus Erythematosus: An Unusual Presentation

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ABSTRACT

Porokeratosis is an acquired disorder of keratinization characterized by clonal expansion of keratinocytes which differentiate abnormally. All forms of porokeratosis have been reported to have familial clusters with autosomal dominant patterns of inheritance but with variable penetration. It is classified into the localized forms which include porokeratosis of Mibelli, linear porokeratosis (LP), and punctate palmoplantar porokeratosis, genital porokeratosis and perianal porokeratosis; the disseminated forms including disseminated superficial actinic porokeratosis, disseminated superficial porokeratosis (DSP), and disseminated palmoplantar porokeratosis and systematized LP. Disseminated superficial porokeratosis presents with multiple pink or red-brown finely scaly macules with a well defined raised border which appears in early adult life predominantly on extremities. The histopathology is characterized by thin column of tightly packed parakeratotic keratinocytes within a keratin filled invagination of the epidermis through stratum corneum known as cornoid lamella. It is associated with immunodeficiency or may appear spontaneously in childhood. Here we describe a young man with hyperkeratotic, hyperpigmented annular plaques distributed over extremities, trunk and face, mimicking disseminated discoid lupus erythematosus.

Keywords: Porokeratosis, Disseminated, Disorder of keratinization

Introduction

Porokeratosis is a clonal disorder of keratinization characterized by lesions with an atrophic center, prominent peripheral ridge, and a histologic hallmark in the form of cornoid lamella. Genetics, immunosuppression, and sunlight are some of the factors blamed for its occurrence. Various morphological variants have been described. Here we report a case who presented with disseminated superficial porokeratosis (DSP) resembling discoid lupus erythematosus (DLE).

Case Report

A 23-year-old man presented with brown slightly raised skin lesions over both upper extremities for last 5 years. The lesions were small to start with and then gradually increased in size with central flattening. It first appeared on face and neck then progressed to involve trunk and upper extremities. There was no history of photosensitivity, joint pain, recurrent fever or Raynaud's phenomenon. Family history was positive. Annular hyperpigmented plaque with hyperkeratotic raised margins measuring 0.5x1 cm to 1.5x2.5 cm with central atrophy and scaling "Figure 1", "Figure 2". A biopsy from margin of annular plaque, stained with hematoxylin and eosin stain, showed cornoid lamella, a parakeratotic column of keratinocytes within a keratin-filled invagination of epidermis through the stratum corneum with absent underlying stratum granulosum, perivascular lymphocytic infiltrate "Figure 3". A Periodic acid-Schiff (PAS) stain was also performed which showed no thickening of basement membrane "Figure 4".

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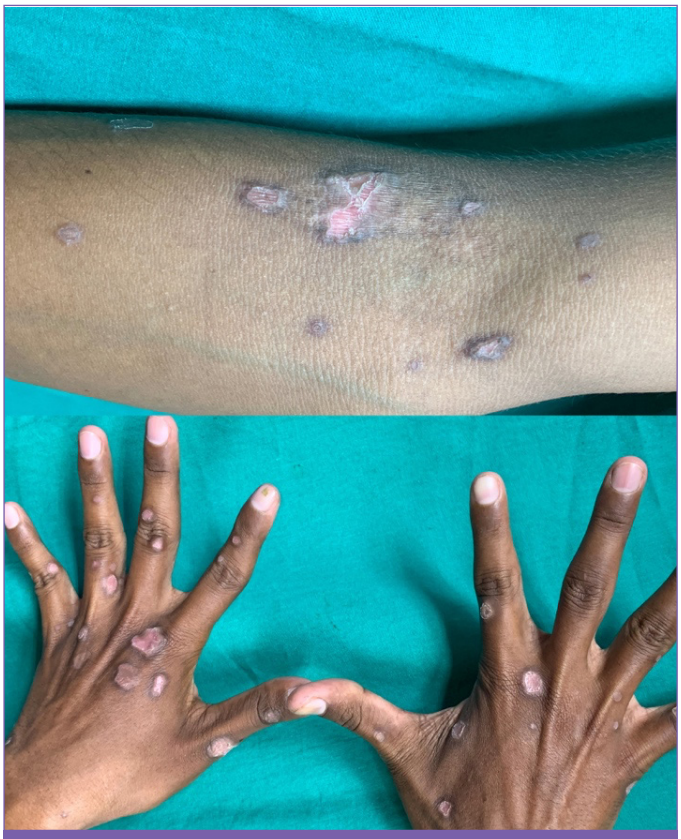

Figure 1. Annular hyperpigmented plaque with hyperkeratotic raised margins on extremities

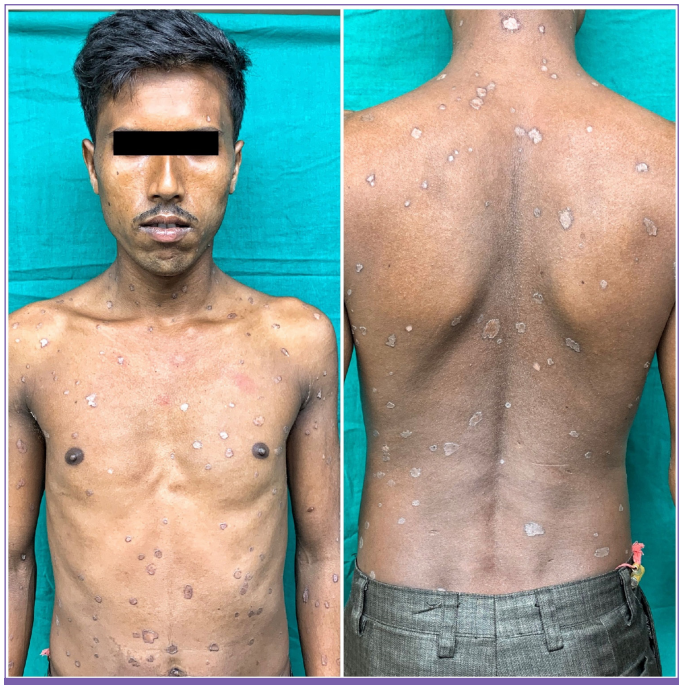

Figure 2. Annular hyperpigmented plaque with hyperkeratotic raised margins on anterior and posterior trunk

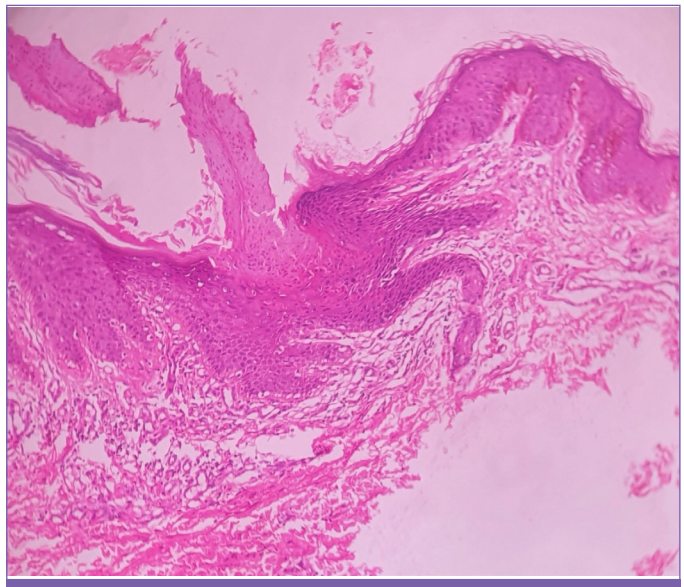

Figure 3. Biopsy from margin of annular plaque, stained with Hematoxylin and Eosin stain, showed cornoid lamella, a parakeratotic column of keratinocytes within a keratin&8208; filled invagination of epidermis with absent underlying stratum granulosum

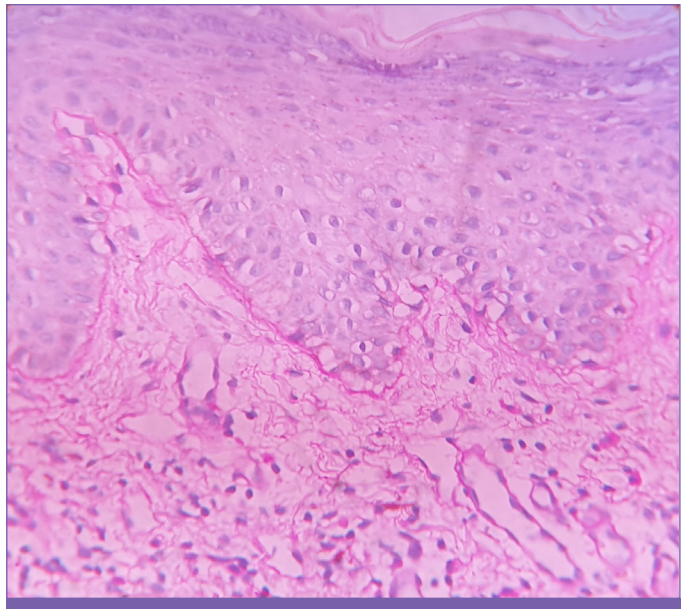

Figure 4. Periodic acid–Schiff stain was also performed which showed no thickening of basement membrane

Discussion

Porokeratosis is an acquired disorder of keratinization characterized by clonal expansion of keratinocytes which differentiate abnormally. One of its variants is DSP which presents with multiple pink or red-brown finely scaly macules with a well-defined raised border which appears in early adult life predominantly on extremities. The histopathology is

characterized by thin column of tightly packed parakeratotic keratinocytes within a keratin filled invagination of the epidermis through stratum corneum known as cornoid lamella [1]. All forms of porokeratosis have been reported to have familial clusters with autosomal dominant patterns of inheritance but with variable penetration [2]. It has been classified into the localized forms which include porokeratosis of Mibelli, linear porokeratosis (LP), punctate palmoplantar porokeratosis, genital porokeratosis, perianal porokeratosis and the disseminated forms including disseminated superficial actinic porokeratosis, DSP, and disseminated palmoplantar porokeratosis and systematized LP [3]. DSP is not necessarily related to sun exposure and will then present in both sun-exposed and sun-protected sites, including sometimes oral mucosa and genitalia. It may be associated with immunodeficiency (e.g. organ transplantation, malignancy, HIV infection) or may develop sporadically during childhood. Cutaneous malignancies particularly squamous cell carcinoma may occur as a complication of porokeratosis. All forms of porokeratosis are chronic with no tendency for spontaneous resolution. It can mimic DLE [4]. Its association with Gardner syndrome, Lichen planus, diabetes mellitus, CAP syndrome, Bloom syndrome and cystic fibrosis has also been reported. Various modalities of treatment include topical retinoids, cryotherapy, 5-fluorouracil, imiquimod, curettage and cautery, photodynamic therapy, CO_2 laser and topical vitamin D analogues such as calcipotriol has been used as first line therapy with varying degree of success. Oral retinoids such as isotretinoin and acitretin have been given to patients with porokeratosis who are immunosuppressed to reduce the risk for malignant transformation. Patient must be counselled regarding photoprotection and long term follow up. Our patient responded well to treatment.

Ethics

Informed Consent: Consent form was filled out by a participant.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.H., S.M., S.B., S.Ban., G.C., Concept: A.H., S.M., S.Ban., G.C., Design: A.H., S.M., S.B., S.Ban., G.C., Data Collection or Processing: A.H., S.M., S.B., S.Ban., G.C., Analysis or Interpretation: A.H., S.M., S.B., S.Ban., G.C., Literature Search: A.H., S.M., Writing: A.H., S.M.

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

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CASE REPORT

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Leishmaniasis: Is it Treatment Failure or Drug Resistance?

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ABSTRACT

The term leishmaniasis defines a wide range of diseases caused by leishmania parasites that are transmitted by infected sandflies while sucking blood from the skin. The World Health Organization reports that there are more than 20 million leishmaniasis patients in around 80 countries. Pentavalent antimony compounds have been the basis of anti-leishmanial therapy since the 1940s. Although primary resistance up to 15% has been reported against pentavalent antimony compounds in different geographical regions, these compounds are still the most effective drugs for many types of leishmania. Treatment failure and drug resistance are different concepts. We wanted to mention this difference in our case, which we treated with meglumine antimonate, although it did not benefit before.

Keywords: Leishmania, Treatment, Drug resistance

Introduction

The term leishmaniasis defines a wide range of diseases caused by leishmania parasites that are transmitted by infected sandflies while sucking blood from the skin. Depending on the type of the parasite and the immune response of the host, the disease may present in three basic forms: cutaneous, mucocutaneous and visceral leishmaniasis [1].

The World Health Organization reports that there are more than 20 million leishmaniasis patients in around 80 countries, and an estimated 1.5-2 million new patients of leishmaniasis, including 1-1.5 million cutaneous cases, and 500 thousand visceral and mucocutaneous cases, is observed every year [2]. The mortality and morbidity caused by Leishmaniasis lead to an estimated 2-4 million "years of unhealthy life" worldwide [3].

Pentavalent antimony compounds have been the basis of anti-leishmanial therapy since the 1940s. They include meglumine antimonate (glucantime) and sodium stibogluconate (pentostam). However, in recent years, further reports demonstrating different clinical responses to the treatment of leishmania have been submitted from various parts of the world. Such difference may be related to drug resistance or treatment failure. Although primary resistance up to 15% has been reported against pentavalent antimony compounds in different geographical regions, these compounds are still the most effective drugs for many types of leishmania [4].

Treatment failure and drug resistance are different concepts. In this case report, we aimed to place emphasis on this difference, presenting a patient whose leishmania treatment continued.

Case Report

A 61-year-old female patient. In October 2020, she presented to the Erciyes University Faculty of Medicine Skin and Venereal Diseases Polyclinic with the complaint of a 1-year wound on the forehead, hands and arms. Our patient had emigrated from Syria and she had been living in Turkey for five years. She had a history of travel to Syria one year ago and her complaints started after this travel. At first, acne occurred on the forehead. Then, it gradually spread out, and

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similar lesions appeared on the hands and arms. The lesions caused pain and sometimes itching symptoms. The patient presented to the hospital about five months ago with these complaints, but could not be diagnosed and treated because she had to be hospitalized due to chronic kidney failure. Two months ago, she presented to the hospital again with the same complaints. A pre-diagnosis of leishmaniasis was considered in the patient, and necessary samples were taken and sent to the microbiology laboratory. Then, the patient was diagnosed with cutaneous leishmaniasis upon the presence of leishmania amastigotes observed by direct microscopy. She began to receive intralesional meglumine antimonate treatment once a week. However, since the patient did not benefit from this treatment, she presented to Erciyes University.

When the patient presented to us, she had one erythematous, soft consistency, 3x4 cm nodular lesion with yellow crusts and local hemorrhagic crusts, extending from the glabella region to the right frontal area. She also had marked edema, erythema and scaling on the whole fifth finger of the right hand, along with purplish, centrally scaled plaques, two on the right forearm, and one on the left forearm (Figure 1, 2).

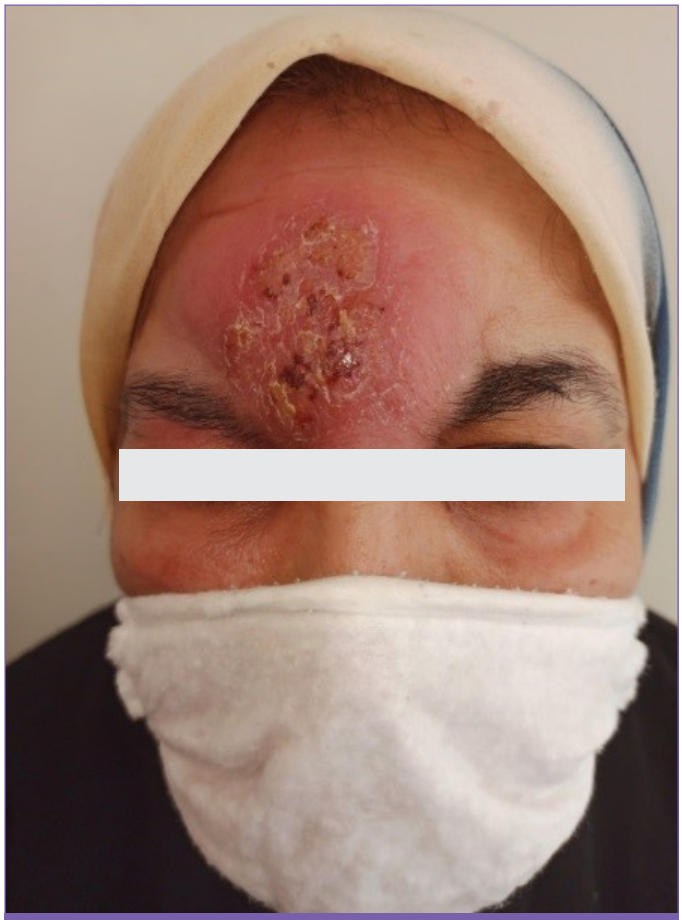

Figure 1. Lesion in the facial area before treatment

Due to the presence of amastigote forms in her samples examined in an external center and their clinical compatibility, the patient was considered to have cutaneous leishmaniasis. Seeking further details of the patient's history by the help of an interpreter revealed that she had not continued her treatment regularly. Therefore, the patient was not considered to have meglumine antimonate resistance. Since the lesions were large and numerous, systemic meglumine antimonate treatment was planned for the patient. We consulted with the nephrology department about the appropriateness of systemic treatment because the patient had chronic renal failure and underwent dialysis. Upon receiving the response that systemic therapy would not be appropriate due to the patient's existing kidney disease, intralesional meglumine antimonate treatment was initiated 3 days a week, along with additional cryotherapy for lesions on the arms and fingers. The treatment days and hours of the patient were arranged in accordance with the dialysis hours in order to ensure the continuity of the treatment. The treatment and follow-up of our patient continue and she has benefited significantly from the treatment (Figure 3, 4).

Discussion

Cutaneous leishmaniasis is a disease that can be seen all over the world except the Antarctic continent, especially with a quite high incidence in countries bordering the Mediterranean [5]. It has been a serious public health problem for many years also in Turkey, particularly in the Southeastern Anatolia region [6].

Two equivalent antimony compounds form the basis of the treatment of cutaneous leishmaniasis. These drugs can be used

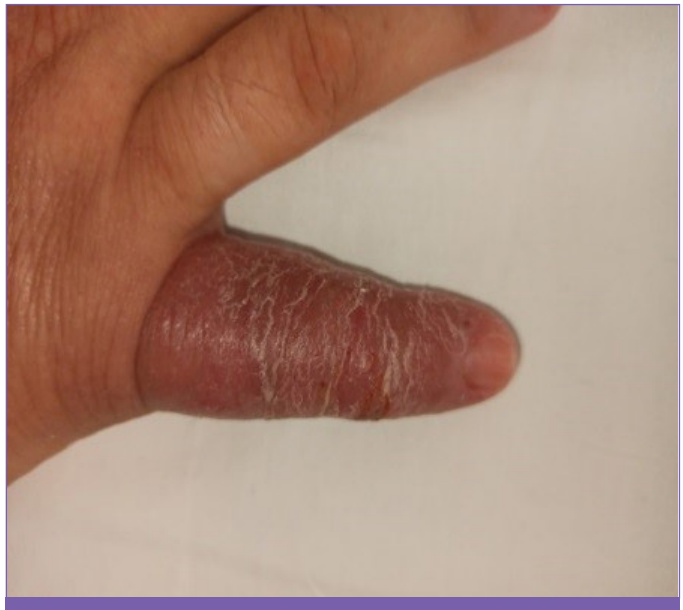

Figure 2. Lesion on the fifth finger of the right hand before treatment

systemically or intralesionally (IL). IL treatment is done using a fine-tipped syringe. The drug is applied into the lesion without any dilution. The entire lesion should become white in order for the drug to reach an effective dose within the lesion. The injection is applied 1-3 times a week until the lesion is completely healed. The descent of the lesions in the form of puffy papules, nodules or plaques to the skin level, and complete closure of ulcerated lesions are the criteria for healing, and therefore, termination of the treatment [7].

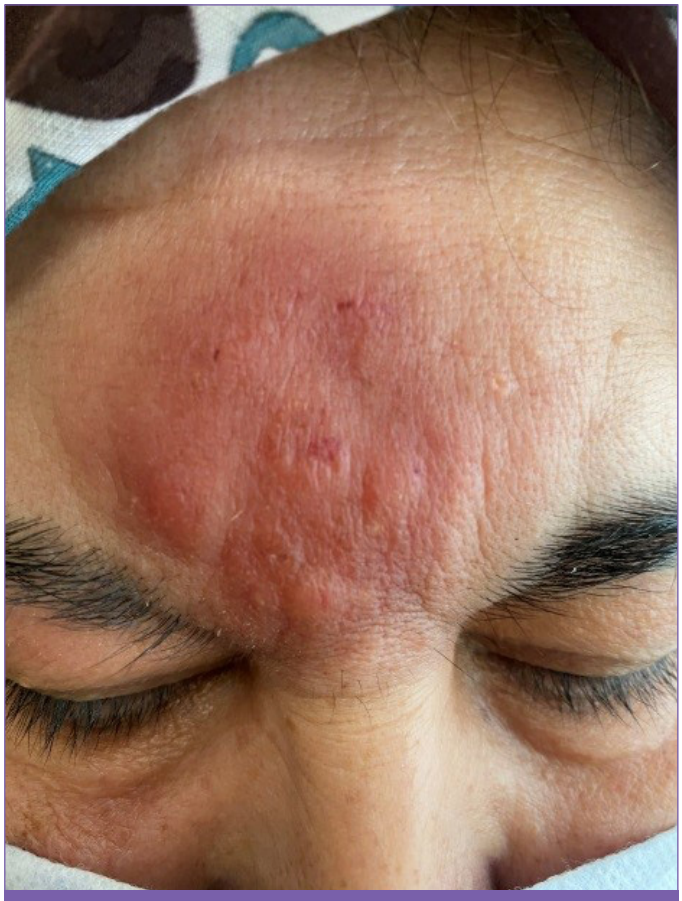

Figure 3. Lesions in the facial area during treatment

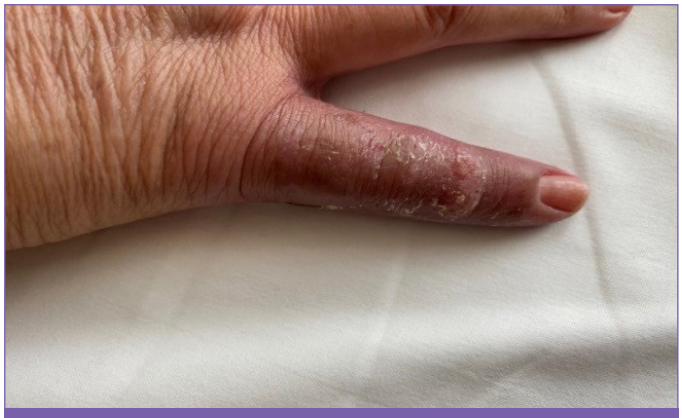

Figure 4. Lesion on the fifth finger of the right hand before treatment

Drug resistance can be defined as a decrease in the effectiveness of a drug in ameliorating a disease or a condition. In order for antimony to be effective on amastigote and promastigote forms of leishmania species, it must be reduced to the trivalent antimony form. The reduction reaction of antimony to trivalent occurs in both parasite and macrophage cells. In our country, enolase, EF-2, HSP-70, trypanothion reductase, protein kinase c receptor and metallo-peptidase genes have been found to play a role in the resistance development of L. tropica isolates against antimony compounds [8]. Treatment failure, however, is a concept different from drug resistance. Failure in treatment can occur due to several reasons other than drug resistance, depending on the host (immune status of the host, etc.), parasite (parasite settling in tissue areas where the drug cannot reach, etc.), environmental and socio-economic factors (continuity of treatment, etc.), and drug (staying below therapeutic dose or duration, etc.).

In this case, the patient did not take the initial treatment regularly. Since she did not have a good command of Turkish, this situation was initially considered to be treatment resistance. However, when the history was sought again through an interpreter, it was thought that the situation was more associated with treatment failure than drug resistance. The number of cutaneous leishmaniasis cases in Turkey has increased, especially in recent years and most of these patients are refugees. Inadequate communication causes treatment failure to be perceived as drug resistance. However, it should not be forgotten that the number of resistant strains and cases may increase rapidly if CL patients receive inadequate and incomplete treatment. In this case report, we aimed to draw attention to the need for being more careful about this distinction.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.C.A., Concept: F.C.A., D.K., Design: D.K., F.C.A., E.Ö.S., Data Collection or Processing: F.C.A., D.K., Analysis or Interpretation: F.C.A., D.K., Literature Search: F.C.A., D.K., Writing: F.C.A., D.K.

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

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Morphea Due to Waxing at a Salon: The First Case Report

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Keywords: Circumscribed morphea, Morphea, Morphea after waxing, Localized scleroderma

Dear Editor,

Morphea, a relatively rare sclerosing condition, involves skin and the tissues beneath it. It's characteristic feature is the fibrosis of the skin, the underlying subcutaneous tissue and in rare instances of the underlying fascia, muscle or bone [1-4]. In this article, we have described a unique case of circumscribed morphea following waxing at a salon. Despite a meticulous review of medical literature in English language using PubMed, we could not find any case of morphea due to waxing. This prompted us to report this case.

A 33-year-old male visited to our dermatology clinic. His chief complaint was hyperpigmentation and thickening of the skin over his back for the past two years. He had done waxing at a salon for his hypertrichosis over back as suggested by friends. Hot waxing (soft type) was done using stripping method. Day after waxing, he developed redness, itching and mild pain over the right upper back followed by the development of flat reddish skin lesion. The lesion progressed with time and in about one month turned into a brownish thickened plaque. Since then he didn't observe any enlargement of the lesion. He denied any history of similar lesions on other body parts.

Examination revealed a single well-defined brownish indurated plaque measuring 10×7 cm on the right upper back (Figure 1). The borders of the plaque were irregular. The surface of the plaque was dry with loss of hair. The skin over the lesion was indurated with slight atrophy at places. Clinical examination did not reveal any anesthesia/hypoesthesia in the plaque. The examination of nails,

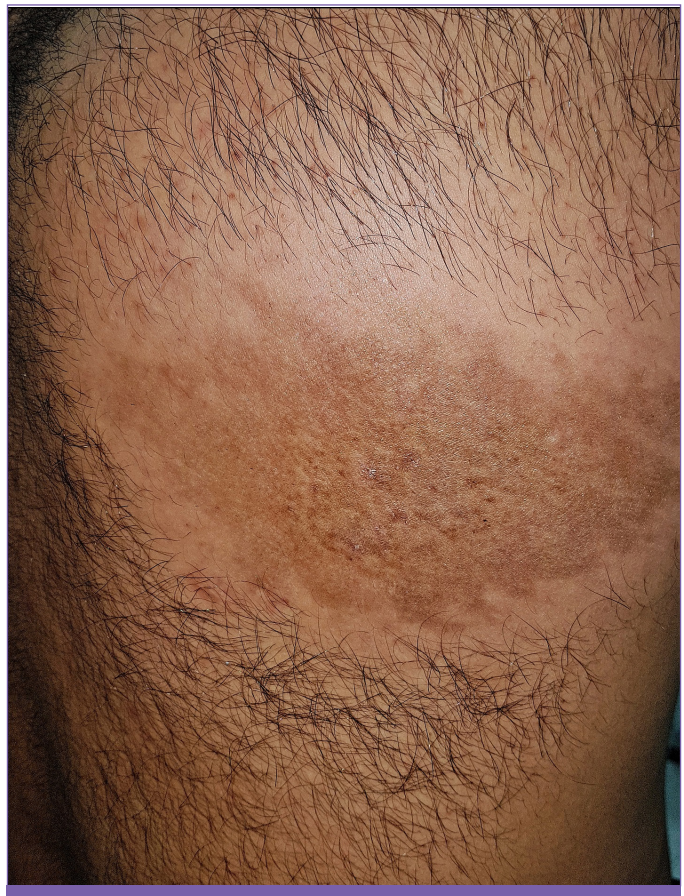

Figure 1. Brownish colored indurated plaque on the right upper back. The surface of plaque looks dry with loss of hair. Note the hypertrichosis over the unaffected skin

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mucous membranes and hair was unremarkable. Review of systems including examination of peripheral nerves was normal.

Routine laboratory tests including the test for anti-nuclear antibody and Borrelia serology were unremarkable. Skin biopsy showed epidermal atrophy with blunting of rete ridges. There was mild-moderate perivascular lymphocytic and plasma cell infiltrates in the dermis. Dense bundles of collagen were seen in deeper dermis. Loss of skin appendages was also noticed (Figure 2). Based on history and clinical examination and further supported by histopathology of skin biopsy, the diagnosis of circumscribed morphea due to waxing was made. He was prescribed topical tacrolimus 0.1% ointment, to be applied twice a day and is under follow up.

Circumscribed morphea is defined when single or multiple round or oval lesions are present, not amounting to generalized disease. It has been divided into two types: Superficial type where the disease is limited to epidermis and dermis and deep type in which inflammation and sclerosis extend up to subcutaneous tissue, fascia or muscle [1,5]. The histopathological changes in the present case extended up to the reticular dermis, suggesting the superficial type.

The etiology of morphea is not clear till date. In susceptible individuals, various predisposing factors have been proposed to cause the development of morphea. These include trauma (blunt, surgical, penetrating, persistent friction), vaccinations (measles, mumps and rubella; bacilli Calmette-Guérin, hepatitis B, diphtheria, tetanus, pneumococcus, pertussis), injections of vitamin B12 and K, immobilization, tight undergarments, previous herpes zoster infection, diagnostic X-ray, radiotherapy, several drugs, and probably Borrelia infection [2-4,6]. Waxing as an etiological factor for the development of morphea has not been described in literature. Some authors have suggested that trauma induces an aberrant wound healing response accompanied by up-regulation of endogenous toll-like receptor ligands. This causes enhancing of innate immune signal pathways thereby causing activation of fibroblasts and leading to scleroderma [7].

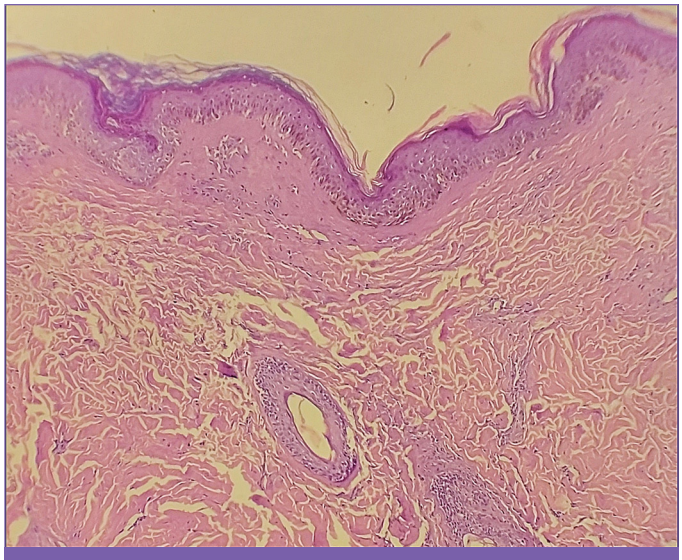

Figure 2. There is epidermal atrophy with blunting of rete ridges. Mild to moderate perivascular lymphocytic infiltrate along with dense bundles of collagen are seen in dermis (HE×10x)

A case of circumscribed morphea has been reported in a female after wearing electronic slim belt for abdominal obesity in which the authors proposed that the persistent pressure and irritation due to the wearing of slim belt together with local heat might have caused morphea [2]. We speculate that the trauma caused by stripping during waxing in collaboration with the heat generated by the hot wax might be the reason for inducing morphea in the present case. Since, morphea following waxing has not been reported before, hence we were obliged to present this novel case.

Ethics

Informed Consent: The authors confirm that they have received all appropriate patient informed consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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