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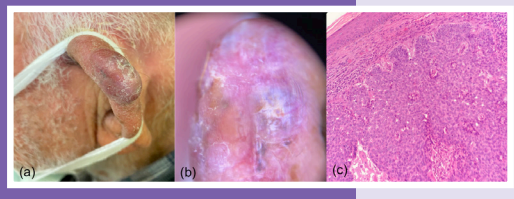

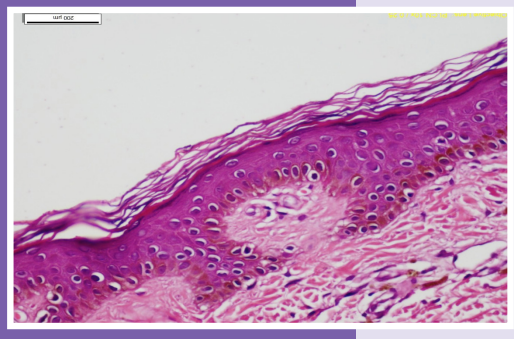

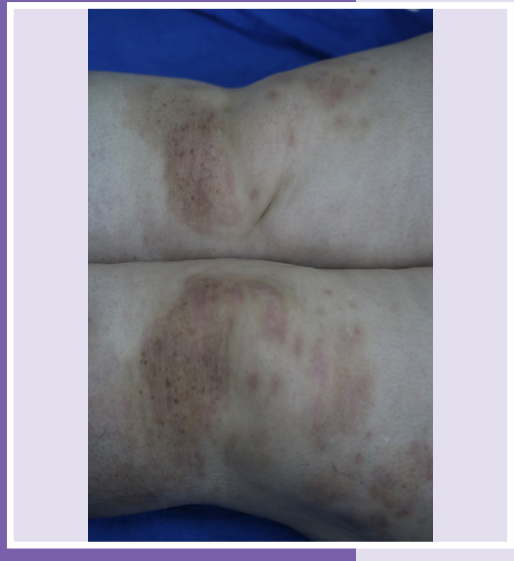

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II:Methods

III:Results

IV:Conclusions

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the appendices

FIGURE LEGENDS

TABLES

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

Doger FK, Dikicioglu E, Ergin F, Unal E, Sendur N, Uslu M. Nature of cell kinetics in psoriatic epidermis. J Cutan Pathol 2007; 34: 257-263. PMID: 17302610

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CONTENTS

REVIEW

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The Treatment Options for Generalized Pustular Psoriasis

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ABSTRACT

Generalized pustular psoriasis is an uncommon variant of pustular psoriasis that includes many different treatment options. First line treatment options include acitretin, cyclosporine, methotrexate and infliximab. Besides these treatment options, there are many upcoming new molecules that are candidates for the treatment.

Keywords: Pustular psoriasis, Treatment, Immunosuppressant

Introduction

Generalized pustular psoriasis (GPP) is an uncommon variant of pustular psoriasis. The age of onset is usually within fifth decade. Although various medications and infections have a role in the disease process, the etiology is uncertain. The pregnancy form of the GPP is known as impetigo herpetiformis.

Multiple sterile pustules on erythematous skin are the most characteristic skin lesions. In addition, systemic symptoms including lymphadenopathy, fever, malaise can be seen in patients. There are many treatment options for GPP. First line treatment options include acitretin, cyclosporine, methotrexate and infliximab. Besides these treatment options, there are many upcoming new molecules that are candidates for the treatment.

Systemic retinoids are among the first line treatment of GPP. Acitretin is drug of choice for GPP and found to be effective in 85% of patients. It has the highest efficacy among first line treatment options. The optimal dosage for initial therapy is 0.75 to 1 mg/kg/day with the maintenance dose of 0.125 to 0.25 mg/kg/day [1]. Retinoids in general, should not be used in any patient who is pregnant or likely to become pregnant. Systemic retinoids may lead capillary leak syndrome in dose dependent manner [2]. Isotretinoin is inferior to acitretin in the treatment of GPP. It has shorter half life compared to acitretin [3]. Therefore, it is more suitable for the patients whose retinoid side effects are not desired.

Methotrexate is recommended for the patients with GPP who do not respond to systemic retinoids. It may take weeks to reach an effective dose since it has slow onset. The optimal dose for initial therapy is 5-15 mg/week with dose increment of 2.5 mg per week [4]. The most common side effects are gastrointestinal symptoms including diarrhea, nausea and vomiting. Periodic monitoring for complete blood test, liver and renal function tests is needed.

Cyclosporine, immunosuppressive calcineurin inhibitor, has rapid onset of action in GPP treatment. It is effective at doses of 2.5 to 5 mg/kg/day. Dose can be decreased gradually by 0.5 mg/kg every 2 weeks. The resolution of symptoms usually seen after 2 to 4 weeks [5].

Monoclonal antibodies have been approved for many inflammatory conditions in dermatology. Infliximab, anti-tumor necrosis factor (TNF) molecule, is highly effective and lead to dramatic improvement in GPP symptoms. The most of the studies supporting the use of infliximab in GPP are case reports [6,7,8]. It is known that the antichimeric antibodies to infliximab may decrease the

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effectiveness and increase the risk of transfusion reactions [9]. The addition of methotrexate to the treatment increases the efficacy of infliximab since methotrexate leads decrement in antibodies formed against infliximab [10]. The dosage of infliximab is 5 mg/kg at weeks 0, 2, 6 followed by maintenance dose every 8 weeks thereafter. Secukinumab is an anti-IL17A monoclonal antibody that can also be used in GPP treatment. Multiple case reports showed clinical improvement with secukinumab in GPP patients [11,12]. In one open-label study, clinical improvement was seen in 10 of 12 patients with GPP treated with secukinumab [13]. Ixekizumab, another anti-IL17A agent, may also be effective in the treatment of GPP patients. In an opel-label study with 78 GPP patients including plaque, erythrodermic and pustular psoriasis, 4 patients with GPP and 3 patients with GPP showed 75% and 90% clinical improvement respectively [14]. Brodalumab, anti-IL-17 monoclonal antibody, also lead clinical remission in GPP patients [15]. In addition to anti-IL17 molecules, guselkumab, directed against p19 subunit of IL-23, showed efficacy at week 16 in 7 of 10 patients with GPP [16]. Patients were treated with 50 mg guselkumab at weeks 0.4 and every 8 weeks thereafter.

Beside first line therapies, there are also other treatment options for GPP. PUVA photochemotherapy is among the second line therapies. It has slow onset of action, therefore usually considered for the patients whose acute symptoms were controlled. One of the disadvantages of PUVA photochemotherapy is the requirement of frequent clinical visits. In an uncontrolled study, PUVA 4 times/wk with mean 13.5 treatment session lead complete resolution of lesions [17].

As an TNF inhibitor adalimumab also showed clinical efficacy in some case control studies for GPP patients [18]. In one retrospective study, the symptoms of two-thirds of patients treated with adalimumab regressed in 4 week [19]. It should be noted that adalimumab can also trigger TNF-alpha induced pustular psoriasis. Therefore, careful monitoring is needed during adalimumab treatment.

Another biologic agent, ustekinumab has conflicting results in GPP treatment. In one case report, all 4 patients responded well to ustekinumab treatment. Three of four patients in this study were also taking low dose acitretin treatment. However, another case study reported flare of pustular psoriasis after ustekinumab treatment [20]. Therefore, the efficacy of ustekinumab treatment in GPP is debatable and further studies are needed to evaluate efficacy of ustekinumab in GPP treatment.

Anakinra, an interleukin (IL)-1 receptor antagonist, has shown clinical efficacy in GPP treatment in several case reports [21,22]. Canakinumab, another anti-IL-1-beta antagonist, may be also treatment option in GPP. In one case study, a patient with GPP responded well to anakinra treatment, developed hypersensitivity reaction to anakinra at the end of week 8. Therefore, the anakinra treatment was switched to canakinumab treatment. Patient received 150 mg subcutenous canakinumab injections every month over 1 year and the lesions resolved completely [23].

As for the novel drugs, anti-IL-36 receptor antagonists can also be used in GPP treatment since IL-36 is one of the main cytokines having a key role in pathophysiology of GPP. IL-36 is a member of proinflammatory cytokines that have a role in innate immunity. It was shown that mutations in IL-36R antagonist gene have been found in 40% to 80% of GPP cases [24]. Spesolimab, an anti IL-36R antibody, is a novel candidate for the treatment of GPP. In one study, 7 patients with the diagnosis of GPP had received single dose of 10 mg/kg spesolimab an followed for 20 weeks. Of those 7 patients, 3 patients had IL-36RN mutation and 1 patient had CARD14 mutation. At the end of week 4, all patients achieved efficacy endpoint GPP Physician Global Assessment GPPGA score of 0 or 1.

Mycophenolate mofetil (MMF), an inhibitor of inosine monophosphate dehydrogenase, is one of the widely used immunosuppressants. Several case reports support use of MMF in GPP [25,26]. Dapsone, 4,4'-diaminodiphenylsulfone, is anilin derived sulfone antibiotic which has anti-inflammatory and bacteriostatic effects. It inhibits neutrophil recruitment via inhibiting neutrophil myeloperoxidase and beta-2 integrin mediated adherence. Several case reports showed efficacy of dapsone in GPP treatment [27,28].

Ethics

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Authorship Contributions

Concept: S.N.Y., B.E., Data Collection or Processing: S.N.Y., B.E., Analysis or Interpretation: S.N.Y., B.E., Literature Search: S.N.Y., B.E., Writing: S.N.Y.

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ORIGINAL ARTICLE

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Social Media Use in Patients with Alopecia Areata

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ABSTRACT

Background: Alopecia areata (AA) is an autoimmune disease that significantly affects people's quality of life. Today, the use of social media (SM) is a factor that substantially affects patients' knowledge and adherence to treatment, and clinicians' awareness of this issue is essential. In this study we aimed to investigate the relationship between the use of SM to obtain information about the disease and the patient's clinic and quality of life in patients with AA.

Materials and Methods: A total of 118 patients with AA were evaluated by filling in the questionnaires prepared by the authors and containing their Dermatologic Life Quality Index.

Results: It was observed that 72.6% of the patients used SM for information about the disease. 58.5% of the patients preferred Google. 31.4% of the patients chose Instagram. 30.5% of the patients preferred YouTube, and the rest picked other SM tools. It was observed that 9.3% of the patients were group members, and 66.9% made group comments. The patients said they would trust the doctor with 96.5% in case of conflict between the SM and the doctor. It has been shown that 18.2% of patients attempt to reach the doctor via SM. They frequently preferred doctor's websites for this. They most commonly asked questions about drugs.

Conclusion: Our study has shown that AA patients use SM extensively to obtain information about their disease, emphasizing the importance of clinicians' presence on these platforms to provide accurate patient information.

Keywords: Alopecia areata, Social media, Internet

Introduction

Alopecia areata (AA) is an autoimmune disease characterized by non-scarring alopecia in which the hair follicles are affected but not usually destroyed. It occurs in 2% of the population at some point in their life. Although the disease can start at any age, it often begins under 40. The fact that the disease is seen in identical twins, siblings, and many family members indicates a genetic component [1].

People think of AA as a cosmetic disorder rather than a medical problem. As a result, stigmatization and social, economic, and psychological problems occur in patients [2]. It has been determined that half of the patients with AA have impaired quality of life, and 66-74% have psychiatric diseases at any stage of their lives [3]. One study showed that 72% of internet users use the internet to obtain health-related information [4].

Social media (SM) is an internet-based communication platform that allows more than 3 billion users to interact with video, picture, and audio content [5]. The SM platforms patients use most frequently for information are Facebook, Twitter, Instagram, and YouTube [4]. SM has been used in every field and has attracted significant attention in dermatology [5]. The fact that dermatology is a visual field substantially impacts this interest [6]. In a study, it was seen that 82.4% of dermatology patients used the internet to obtain

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information, and 65.4% used SM [7]. When we look at the most searched hashtags about skin diseases on Instagram, alopecia is in the second place, showing that AA patients use SM intensively [8].

Objectives

In the literature, there are no studies on the use of SM in AA patients so far. In our study, we aimed to investigate the use of SM to obtain information about their disease and to explore the expectations of the patients in AA patients who applied to our clinic.

Materials and Method

Patients

Patients followed in the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Skin and Venereal Diseases Hair Diseases outpatient clinic between November 15, 2020, and May 15, 2021, were included in our study. Written informed consent was obtained from themselves in adult patients and from the participants' parent/legal guardian/next to kin to participate in the study for every minor patient. The patients were divided into two groups according to age (4-16, 17≤).

Procedure

This study protocol was reviewed and approved by the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Clinical Research Ethics Committee (decision number: 14429, date: 22.01.2021). The patients were filled with questionnaires prepared by the researchers who planned to study. Parents' help was received for the 4-16 age group. Demographic characteristics of patients, Severity of Alopecia Tool (SALT) scores, clinical characteristics, comorbidities, SM use and participation in patient groups, reputation for information on SM, and Dermatologic Life Quality Index (DLQI)/child Dermatologic Life Quality Index (CDLQI) scores were noted by their physicians. Written informed consent was obtained from themselves in adult patients and from the participants' parent/legal guardian/next to kin to participate in the study for every minor patient.

Statistical Analysis

The study gives descriptive statistics as mean, standard deviation, percentage, and frequency. In the survey, Mann-Whitney U and Kruskal-Wallis tests were used to examine the difference in DLQI levels in patient groups according to patient characteristics and SM use. The all-pairwise method was used to determine the different groups. In the study, a chi-square analysis was performed to examine the rates of patients' SM use status according to age groups. In the analysis, the critical decision value was taken as 0.05. Analyzes were finalized with the SPSS 25.00 package program.

Results

Sociodemographic and Clinical Characteristics of the Patients

One hundred eighteen patients (67 males, 51 females) were included in the study, and it was determined that 58.5% of the patients were 17 years and older, and 41.5% were in the 4-16 age group. The SALT scores of the patients were determined as follows; 17.8% (S1), 16.9% (S2), 13.6% (S3), 15.3% (S4), 36.4% (S5). In Table 1, demographic and clinical characteristics of the patients are summarized.

Using SM to Get Information about the Disease, Search Topics, Group Membership

It was determined that 72.6% of the patients used SM for information about the disease. No significant correlation was found between the use of SM and gender, age, education, SALT score, site of involvement, disease duration, another disease, and family history. Although not significant, the rate of people with university and higher education levels in the group with SM use related to the disease was 3 times that of the other group. Again, although not significant, the rate of those with a SALT score of 100 in the group using SM was 41.2%, while this rate remained at 25% in those who did not use SM (Table 2).

Patients using SM are distributed as follows; 58.5% Google, 31.4% Instagram, 30.5% YouTube, 19.5% patient blocks, 14.4% Facebook, 6.8% other SM channels, 5.1% Twitter. No significant relationship

Table 1. Demographic and clinical characteristics of the patients

Features		n	%
Gender	Male	67	56.8%
	Female	51	43.2%
Group	17≤ age	69	58.5%
	4-16	49	41.5%
SALT score	S1	21	17.8%
	S2	20	16.9%
	S3	16	13.6%
	S4	18	15.3%
	S5	43	36.4%
Location	Scalp	116	98.3%
	Eyebrow	93	78.8%
	Eyelash	53	44.9%
	Beard	25	21.2%
	Trunk	37	31.4%
Comorbidities	No	98	83.1%
	Vitiligo	6	5.1%
	Thyroid disease	14	11.9%
Family history	Yes	17	14.4%

SALT: Severity of Alopecia Tool

Table 2. Relationship between SM use and other variables

Patient characteristics		Using SM to learn about the disease				p-value
		Yes		No		
		n	%	n	%	
Gender	Male	48	56.5%	19	59.4%	0.21
	Female	37	43.5%	13	40.6%	
Age (X + SD)		21.06	10.58	18.75	12.03	0.09
Education	No	4	4.7%	4	12.5%	0.13
	PE	25	29.4%	11	34.4%	
	HS	25	29.4%	13	40.6%	
	U	27	31.8%	4	12.5%	
	PG	4	4.7%	0	0.0%	
SALT score	S1	12	14.1%	8	25.0%	0.06
	S2	14	16.5%	6	18.8%	
	S3	13	15.3%	3	9.4%	
	S4	11	12.9%	7	21.9%	
	S5	35	41.2%	8	25.0%	
Scalp involvement	No	2	2.4%	0	0.0%	0.16
	Yes	83	97.6%	32	100.0%	
DD (months) (X + SD)		66.21	58.07	79.56	82.72	0.26
Comorbidities	No	72	84.7%	25	78.1%	0.53
	Vitiligo	5	5.9%	1	3.1%	
	Thyroid disease	8	9.4%	6	18.8%	
Family history	Yes	14	16.5%	2	6.3%	0.10
	No	71	83.5%	30	93.8%	

SALT: Severity of Alopecia Tool, SM: Social media, PE: Primary education, HS: High school, U: University, PG: Postgraduate, DD: Disease duration, SD: Standard deviation

was found between the types of SM used and gender, age, education, SALT score, site of involvement, disease duration, another disease, and family history. The topics the patients searched for on SM were 61% disease, 46.6% drugs, 39% patient comments, and 47.5% doctors. It was observed that 9.3% of the patients were group members, and 66.9% made group comments. It was observed that 34.7% of the patients searched for what was mentioned in the group, 28% only read, 14.4% thought that doctors and products were advertised, and 8.5% were happy to be together with those with the same disease.

Trust in Doctors and Expectations of Patients

We asked patients a few different questions about trust. Other results were obtained in response to these questions. Patients stated that they would trust the doctor with a rate of 96.5% (82/85) in case of conflict between the SM and the doctor.

The patients stated that they would trust the answers 37.1% (13/35) if they had the chance to ask a question with a photograph. According to 60.6% (20/33) of the patients, the doctor does not have to answer the patients via SM.

Using SM to Reach Doctors

18.2% of the patients made attempts to reach the doctor via SM. Patients trying to get the doctor preferred 40% doctor sites, 20% telephone, 20% Instagram, 10% search engines, and 10% health sites.

Patients who reach the doctor ask questions about AA 28.6% and questions about drugs 71.4%. It was observed that all patients (6/6) trusted the answers, and 83.3% (5/6) acted per these answers. Since this last data were obtained from six patients, it cannot draw safe conclusions.

SM-DLQI/CDLQI Relationship

Investigation of Variables Affecting DLQI Levels of Patients 17 Years and Older

SALT scores and involvement sites ($p>0.05$) and the presence of another disease ($p=0.11$, $p>0.05$) did not significantly affect the DLQI scores of the patients (Table 3).

It was determined that patients with a family history of the disease had significantly higher DLQI scores ($p=0.01$, $p<0.05$) (Table 3).

It was determined that the SM usage status of the patients ($p=0.12$, $p>0.05$) and searching for the disease in the SM ($p=0.09$, $p>0.05$) did not significantly affect the DLQI scores. It was determined that the patient's use of SM channels such as Facebook, Instagram, YouTube, Google, Patient blocks, and other media did not significantly affect their DLQI scores ($p>0.05$). It was determined that the patients using Twitter had significantly higher DLQI scores ($p=0.01$, $p<0.05$) (Table 3).

It was determined that the topics searched on SM, group memberships, comments in groups, and patients' opinions about groups did not affect DLQI scores ($p>0.05$). If the SM contradicts the doctor, it was observed that the DLQI levels of the patients who preferred the doctor were higher ($p=0.01$).

It has been determined that DLQI levels do not differ according to whether they have the chance to ask a question with a photograph, trust the answers, think that doctors are obliged to answer, and try to reach doctors through SM ($p>0.05$).

Examination of Variables Affecting the CDLQI Levels of Patients Aged 4-16

CDLQI levels of the patients did not differ according to the SALT scores, the sites of involvement ($p>0.05$), and the presence of other diseases ($p=0.23$, $p>0.05$) (Table 3).

Patients with a family history did not significantly affect their DLQI scores ($p=0.11$, $p>0.05$). It was determined that the patient's use of SM ($p=0.32$, $p>0.05$) and searching about the disease on SM ($p=0.42$, $p>0.05$) did not significantly affect CDLQI scores (Table 3).

The patient's use of SM channels such as YouTube, Twitter, Patient blogs, and other media did not significantly affect their CDLQI scores ($p>0.05$). CDLQI scores of patients using Facebook,

Table 3. Examination of variables affecting the DLQI levels of patients

Patient characteristic		17≤ DLQI		p-value		4-16 CDLQI		p-value
		X	SD			X	SD	
SALT score	S1	5.91	7.70	0.13	S1	5.00	5.50	0.17
	S2	4.77	5.02		S2	6.86	9.70	
	S3	4.38	7.31		S3	5.86	5.46	
	S4	4.31	2.87		S4	7.20	4.71	
	S5	4.91	5.03		S5	7.25	5.50	
Scalp	No	4.00	5.66	0.22	No	5.49	5.88	0.43
	Yes	4.89	5.43		Yes	6.53	5.98	
Eyebrow	No	4.45	5.30	0.24	No	6.85	4.75	0.49
	Yes	5.41	5.56		Yes	6.43	6.73	
Eyelash	No	5.02	5.89	0.16	No	6.30	5.94	0.13
	Yes	4.44	3.81		Yes	8.60	6.62	
Beard	No	4.50	4.96	0.26				
	Yes	5.48	6.10					
Trunk	No	4.50	4.96	0.26	No	7.66	5.79	0.43
	Yes	5.48	6.10		Yes	7.55	5.91	
Comorbidities	No	4.87	5.15	0.11	No	6.68	6.29	0.23
	Vitiligo	3.80	3.42		Vitiligo	6.00	0.02	
	Thyroid	5.40	7.55		Thyroid	5.00	1.41	
Family history	Yes	10.83	9.26	0.01*	Yes	8.60	5.50	0.11
	No	4.28	4.57		No	6.00	6.05	
SM usage	Yes	5.07	5.73	0.12	Yes	6.24	5.27	0.32
	No	3.82	3.09		No	7.20	7.52	
SM usage for information about the disease	Yes	5.35	5.53	0.09	Yes	6.19	6.25	0.42
	No	3.40	4.88		No	7.18	5.57	
Facebook	No	4.91	5.56	0.36	No	5.74	4.98	0.01*
	Yes	4.56	4.42		Yes	11.29	9.29	
Instagram	No	4.43	4.72	0.39	No	5.50	4.68	0.01*
	Yes	5.60	6.40		Yes	10.09	8.53	
Twitter	No	4.73	5.43	0.01*	No	6.53	6.11	0.41
	Yes	7.67	4.04		Yes	6.50	0.71	
Youtube	No	4.02	5.16	0.18	No	6.56	6.11	0.43
	Yes	6.19	5.59		Yes	6.38	5.68	
Google	No	3.96	4.77	0.06	No	5.09	6.89	0.01*
	Yes	5.44	5.73		Yes	9.26	4.90	
Patient blogs	No	4.86	5.78	0.52	No	6.90	6.06	0.09
	Yes	4.88	4.08		Yes	4.29	5.31	
Other sites	No	4.85	5.56	0.33	No	6.65	6.13	0.11
	Yes	5.00	2.92		Yes	4.67	3.06	

SALT: Severity of Alopecia Tool, DLQI: Dermatologic Life Quality Index, CDLQI: Child Dermatologic Life Quality Index, SD: Standard deviation, *p<0.05

Instagram, and Google were found to be considerably higher ($p=0.01$, $p<0.05$) (Table 3).

DLQI scores of the patients who searched the SM about the disease, drugs, patient comments, and doctor were at similar levels ($p>0.05$).

DLQI scores of the patients were similar according to group membership, making comments within the group, and opinions about the group ($p>0.05$). It was determined that trusting the answers if there is a chance to ask a question with a photo, thinking that doctors have to answer, and trying to reach the doctor via SM did not significantly affect DLQI levels ($p>0.05$).

Discussion

Clinical Features

AA is a disease that is frequently seen together with vitiligo and thyroiditis because it originates from autoimmunity [1]. In a meta-analysis, vitiligo was found in 2.3% of AA patients, and autoimmune thyroid disease was found in 13.9% [9]. Similarly, our study found that 5.1% of the patients had vitiligo, and 11.9% had thyroiditis.

It has been shown that 20% of AA patients have a family history [10]. In our study, it was observed that 14.4% of the patients had a family history. Having a family history is considered a poor prognostic factor [10]. In our research, DLQI scores were significantly higher in those over 17 years of age than those with a family history, but no significant increase was found in the 4-16 age group.

Using SM to Obtain Information about the Disease

In a study by Gantenbein et al. [7], it was seen that 82.4% of dermatology patients used the internet to obtain information, and 65.4% used SM. Similarly, our study found that 78% of the patients used SM, and 72.6% used SM for information about the disease.

In a recent SM study on acne vulgaris patients, patients most frequently preferred Google, Instagram, and YouTube to obtain information [11]. Similarly, most SM patients chose Google, Instagram, and YouTube in our research. A study conducted with acne patients found that the use of SM related to the disease was higher in women with shorter disease duration and more advanced disease [11]. In our study, no significant relationship was found between the use of SM, the selected SM platforms, personal characteristics, and the patients' clinics. This data may be due to the larger patient population in the acne study, but 118 patients in our study.

Information Searched by Patients

In a previous study the most frequently searched information by patients online was the treatments (24.1%), followed by doctor's recommendations (11.5%), information about the disease, and information about diet. Another study on Facebook, the most frequently searched information was found to be side effects, treatment options, and drug interactions [12]. In the survey conducted with acne vulgaris patients, the patients most commonly searched for information about the disease, followed by drugs, treatment options, and cosmetics [11]. Similarly, our study found that patients most frequently searched for information about the disease, followed by doctors, medications, and patient comments. These results show that the most commonly searched information includes similar topics, although it varies.

Patient Support Group Membership

There are many hidden and open patient support groups on SM. With over 1 billion users, most patient groups seem to be on Facebook [13]. A study conducted in the USA showed that 5% of internet users are members of patient support groups [14]. Again, in a survey conducted with acne vulgaris patients, 4.3% were members of support groups [11]. In our study, it was determined that 9.3% of the patients were group members, and the majority of these groups were on Facebook. It was observed that the vast majority of patients made comments in groups. A study conducted with acne patients showed that 47% of the patients read the words in the groups [11]. In our research, it was observed that 62.7% of the patients read or searched the information in the groups, and this result shows that the patients give importance to SM information. However, here, doctors should not advertise their clinics while providing information [13]. In our study, 14.4% of the patients think that doctors and products are advertised in patient groups, emphasizing that doctors should pay attention to this issue.

Trust in Doctors

A study conducted with acne vulgaris patients showed that 84.4% of the patients preferred doctors in case of conflict between the SM and the doctor [11]. Similarly, in our study, 96.5% of the patients stated that they would trust the doctor in case of disagreement between the SM and the doctor. In addition, it was determined that 36.6% of the patients who preferred the doctor had a university or higher education level, and 41.5% had a SALT score of 100 (Table 4). These results suggest that patients with more severe diseases and high sociocultural levels prefer doctors. While these high preference rates show that we still have a strong hand as doctors, it shows the importance of the presence of doctors in SM to avoid conflicts between patients.

In a study conducted with acne vulgaris patients, it was determined that 41.1% of patients would not trust the answers if they had the chance to ask questions with photographs [11]. In our study, 62.9% of the patients stated that they would not trust the answers if they had the opportunity to ask a question with a photograph, and they were found to be insecure at a higher rate. These rates show that patients still find clinics and face-to-face examinations more reliable than online.

Table 4. Characteristics of the doctor-preferred group in the SM-doctor conflict			
Patient characteristics		**The group that chooses the doctor if SM contradicts the doctor**	
		n	**%**
Gender	Male	47	57.3%
	Female	35	42.7%
Age (X + SD)		20.59	10.47
Education	No	4	4.9%
	PE	25	30.5%
	HS	23	28.0%
	U	26	31.7%
	PG	4	4.9%
SALT score	S1	11	13.4%
	S2	14	17.1%
	S3	12	14.6%
	S4	11	13.4%
	S5	34	41.5%
Scalp involvement	No	2	2.4%
	Yes	80	97.6%
DD (X + SD)		65.41	57.44
Comorbidities	No	69	84.1%
	Vitiligo	5	6.1%
	Thyroid	8	9.8%
	DM type I	0	0.0%
Family history	Yes	13	15.9%
	No	69	84.1%

SALT: Severity of Alopecia Tool, SM: Social media, PE: Primary education, HS: High school, U: University, PG: Postgraduate, DD: Disease duration, SD: Standard deviation
*no p-value because there is only one group (who chose the doctor)

In a previous study, more than 40% of patients discontinued their treatment based on the recommendations in SM [15]. In our research, it was seen that 83.3% of the patients who reached doctors from SM followed the advice here. Interestingly, although the patients express that they do not trust the answers to the questions they ask from the SM, they follow the recommendations here at a high rate.

Reaching a Doctor via SM

Since patients see online consultations as more convenient and time-independent than face-to-face consultations, they ask doctors various questions in this way. Although it is possible to ignore these messages, it is evident that doctors have an ethical responsibility towards a person who asks for help [16]. In the study conducted with acne vulgaris patients, 40.7% of the patients stated that the doctors did not have to answer the patients via SM [11]. In our study, 60.6% of patients said doctors do not have to answer patients via SM. These results indicate that the patient's expectations differ, and some want to see their doctors as always available.

SM Choice to Reach the Doctor

In a study, 41% of the patients stated that they were affected by SM in choosing a doctor or health institution [17]. In the study by Albeshri et al. [18], 21% of dermatology patients found doctors from SM and received information most frequently from Twitter and Instagram. Similarly, in our study, 18.2% of the patients reached the doctors via SM. They most preferred doctor sites and then Instagram. These results show that SM is an effective platform in health research.

Relationship Between SM and DLQI/CDLQI

It was observed that the DLQI levels of the patients who preferred the doctor if the SM conflicted with the doctor in the over 17 age group were higher. To our knowledge, this has not been shown in the literature before; it can be explained by the fact that patients with high DLQI, whose disease has a significant impact on their lives, are more conscious about their diseases and trust the professionals of the job.

Usually, the increase in SALT should be related to the rise in DLQI but did not occur. The reason for this may be the uneven distribution

of SALT score groups in the patient population included in the study and the differences in education levels and genders of the patients in these groups. A study showed a positive correlation between education level and disease compliance, and men were stronger in personal control than women [19].

Study Limitations

The small number of patients in some parameters (ex. trust) is not capable of drawing safe conclusions.

Conclusion

SM is being used more and more in health research in every field. It is crucial in branches such as dermatology, where visuality is at the forefront. AA patients are affected both physically and mentally due to the loss of hair, which has a vital role in the person's appearance. The data in our study show that dermatologists and dermatology associations should keep up with this change and exist on the Internet and SM, along with changing conditions. This way, disinformation will be prevented by ensuring that patients get the correct information from the right source.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Clinical Research Ethics Committee (decision number: 14429, date: 22.01.2021).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgial and Medical Practices: S.G., Concept: T.K.U., Ö.A., Design: S.G., Ö.A., Data Collection or Processing: S.G., Analysis or Interpretation: S.G., T.K.U., Ö.A., Literature Search: S.G., Writing: S.G.

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Body Composition Parameters, Carotid Intima Media Thickness and Epicardial Fat Thickness in Male Patients with Androgenetic Alopecia

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ABSTRACT

Background: Androgenetic alopecia (AGA) is a noncicatricial alopecia that happens under the stimulus of androgens in genetically predisposed individuals. Previous studies have shown that bioelectrical impedance analysis (BIA) is an objective indicator of body composition. Measurement of carotid intima-media thickness (CIMT) and epicardial fat thickness (EFT) indicates the risk of cardiovascular disease and subclinical atherosclerosis. In this study, we aimed to examine body composition parameters, CIMT and EFT values and to correlate these parameters with each other.

Materials and Methods: Sixty-four male patients with AGA who had no history of chronic disease and 67 age-matched healthy men were included as the control group. Subjects were separated into two groups (mild/moderate and severe) based on the Hamilton baldness scale modified by Norwood. BIA and body composition parameters and echocardiographic CIMT and EFT values were evaluated in all individuals included in the study.

Results: BIA; fat percentage, degree of obesity, metabolic age, body mass index (BMI) and visceral fat were higher than the controls. In echocardiographic measurements; LA diameter, interventricular septal thickness and posterior wall thickness averages were statistically significantly higher in the patients than in the controls. In the correlation analysis, a strong positive correlation was tracked between EFT and fat mass, obesity degree, BMI, visceral fat, and CIMT. On the other hand, strong negative correlation was tracked between EFT and fat free mass, muscle mass and body water.

Conclusion: In the study, obesity parameters measured by BIA were higher in patients with AGA compared to the control group, but there was no difference between the groups in terms of CIMT and EFT in echocardiographic measurements.

Keywords: Androgenetic alopecia, Bioelectrical impedance, CIMT, EFT, Visceral fat

Introduction

Androgenetic alopecia (AGA) is a noncicatricial alopecia that happens under the stimulus of androgens in genetically predisposed individuals [1]. In AGA, the anagen phase is shortened, resulting in miniaturization of the follicles. Dark and thick hairs are replaced by thin, short and light colored vellus hairs [2]. Its frequency varies between communities. It usually begins in the 3rd and 4th decades and its incidence raises with age [3,4]. It is the most frequent cause of hair loss in men during their lifetime [5]. In the dermatological examination, thinning of the hair in the vertex and

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bilateral temporal regions and regression of the anterior skin line are observed in men [2]. Although its pathophysiology is not openly reported, androgens, especially dihydrotestosterone (DHT), play a crucial part in the development of AGA. DHT is the main metabolite of testosterone found in the skin and is the most potent androgen in human blood [6].

Muscle tissue, adipose tissue and visceral protein are the three main nutritional parts of body composition [7]. Bioelectrical impedance analysis (BIA) method is one of the most effective methods for evaluating body fat ratio. It is based on the principle of determining body composition by applying electric current at different frequencies (at a very low level) to the human body [7,8]. BIA has recently been used in the evaluation of diseases such as metabolic syndrome, obesity, insulin resistance and nutritional status [9,10]. It is stated that it is more reliable than body mass index (BMI) in the evaluation of obesity [11]. With this assessment, which is based on the difference in lean tissue mass and electrical permeability of fat, various body tissue compositions such as muscle mass, body water content, body fat mass and lean body mass can be examined [7].

Epicardial fat is the visceral fat located between the pericardium and the heart and covers 80% of the heart surface [12]. Lately, measurement of carotid intima-media thickness (CIMT) and epicardial fat thickness (EFT) as practical and noninvasive methods have become popular to point out the risk of subclinical atherosclerosis and cardiovascular disease. Various studies have shown that CIMT and EFT are increased in patients with insulin resistance, metabolic syndrome and major cardiac events [12,13,14,15]. In a recent study, it was shown that CIMT and EFT values measured echocardiographically were higher in patients with advanced stages of AGA [6].

BMI was found to be higher in men with moderate and severe AGA than in men without AGA or with mild AGA [16]. On the other hand, there are also studies reporting that there is no difference in BMI between patients with AGA and the control group [17,18]. As far as we can scan, there is no study investigating body composition parameters in patients with AGA using the BIA method. In this study, it was purposed to examine body composition parameters with BIA and to examine CIMT and EFT values echocardiographically and to correlate these parameters with each other.

Materials and Method

Study Population

The study was conducted in accordance with the Declaration of Helsinki. This study was carried out between February 2020 and January 2022. In this prospective study, male patients who applied to the dermatology outpatient clinic due to hair loss and men without AGA were included as the control group. Previously diagnosed cerebral, peripheral or coronary artery disease; presence of congestive heart failure, chronic kidney disease, diabetes mellitus, hypertension, thyroid, pituitary, or adrenal disorders or left ventricular ejection fraction (LVEF) fewer than 50%; current or previous alopecia and those using drugs like androgens, antiandrogens or glucocorticoids in the last 3 months were not included to the study. All participants were informed and their written consent was obtained. Approval was obtained for the study from Malatya Clinical Research Ethics Committee on 15.01.2020 (decision no: 2020/10).

Assessment of AGA

AGA was categorized according to the Hamilton baldness scale modified by Norwood [19]. The two doctors separately examined each subject's head from two perspectives (top and side), matching the subject's hairstyle with consensus with the Hamilton-Norwood scale of baldness. Subjects were then classified into one of two groups for comparison. According to the Hamilton-Norwood scale, AGA stage II-IIa-IIIa-III vertex subjects were group I; AGA stages IV-IVa-V-Va-VI-VII were grouped as group II.

Bioelectrical Impedance Analysis

Body weight was measured using the BIA device with the least possible clothing of the individuals. The Tanta-BC 418 device was used to measure body composition. The diagnostic device works with 8 electrodes, 50 kHz constant current (hand to hand, foot to foot). It is a device that measures fat ratio, muscle mass and lean mass values for five different regions (right and left arm, right and left leg, trunk) with five separate current waves [20]. Measurements were carried out taking into account the working principles of the BIA device.

Echocardiographic Measurements

Echocardiographic examinations were applied according to the AHA and ESC Cardiac Chamber Measurement guidelines [21]. Echocardiographic evaluations of all participants were made by 2 cardiologists who were unaware of their clinical knowledge in each group using the Vivid E95 system (GE Vingmed Ultrasound AS, Horten-Norway) and an M5Sc-D (1.4-4.6 MHz) transducer probe. Two-dimensional, pulsed and continuous wave, color doppler evaluations were performed. LVEF was determined by Simpson method. Epicardial adipose tissue was defined as an anechoic space between the two epicardial layers on 2D echocardiographic images. EFT was calculated in the free wall of the right ventricle at the end of diastole on both parasternal long and short axis views. The mean of three cardiac cycles from each echocardiographic view was defined as EFT [22]. Intraobserver and interobserver variability rates for EFT were not statistically significant.

Carotis Intima Media Thickness Measurements

CIMT was calculated by a trained cardiologist who recorded ultrasonographic images of both the left and right common carotid arteries using the Vivid S6N device and a linear transducer when the participants were in the supine position. The proximal and distal walls of the artery were kept parallel to each other by applying transducer manipulation. Measurements were made 1 cm proximal to the carotid bifurcation. After visualization of the distal and proximal walls of the arteries parallel to each other in the longitudinal axis, the images were frozen. Images have been enlarged for detailed evaluation. Intima media thickness was measured from 4 different points with 1 mm distances and averaged.

Statistical Analysis

Quantitative-data were summarized as mean ± standard deviation and qualitative-data were given as number and percentage. Yates corrected chi-square tests were utilized to compare independent categorical variables. P-value <0.05 was contemplated statistically significant. The data were evaluated by using SPSS Package Statistical-Package-for-Social-Sciences software (SPSS Inc., Chicago, IL, USA, v17.0).

Results

There were 64 participants in the patient group and 67 participants in the control group. The mean age of the patient and control groups was close to each other (30.4±9.7, 28.3±8.6, respectively) and the difference was not statistically significant (p>0.05). Family history of AGA was higher in the patient group than in the controls (p<0.001). Approximately half of the patients were in groups III and IV according to the Hamilton-Norwood scale, and the disease duration in most patients was between 1 and 5 years (Table 1).

In bioimpedance analysis; lean muscle mass, muscle mass, body water percentage and body density were statistically lower in AGA patients than in the controls (p<0.001, p<0.001, p=0.002, p<0.001, respectively). Conversely, fat mass, obesity degree, metabolic age, BMI and visceral fat were higher than the control group (respectively, p<0.001, p=0.01, p=0.002, p=0.006, p=0.001) (Table 2).

In echocardiographic measurements; LA diameter, interventricular septal (IVS) thickness and posterior wall thickness (PWT) mean values were significantly higher in the patient group than in the controls (p=0.006, p=0.037, p=0.043, respectively). At the same time, IVS and PWT were statistically significantly higher in group II patients with higher AGA severity compared to the control group (p=0.010, p=0.045, respectively). No significant difference was observed between the groups in the comparison of other parameters (Table 3).

In the correlation analysis, a strong positive correlation was observed between EFT and FM, obesity degree, BMI, visceral fat, and CIMT (p<0.001, p=0.002, p<0.001, p<0.001, p=0.001, respectively). Conversely, a strong negative correlation was observed between EFT and fat free mass, muscle mass and body water (p<0.001, p<0.001, p<0.001, respectively) (Table 4).

Table 1. Demographic and clinical characteristics of the patient and control groups

		Patients	Controls	p-value
Age, mean ± SD		30.4±9.7	28.3±8.6	0.15
Family history, n (%)	Yes	58 (86.6)	29 (45.3)	<0.001
	No	9 (13.4)	35 (54.7)	
AGA severity, n (%)	II	11 (16.4)	-	-
	IIa	6 (9.0)	-	
	III	1 (1.5)		
	IIIa	8 (11.9)	-	
	III vertex	12 (17.9)	-	
	IV	15 (22.4)	-	
	Va	4 (6)	-	
	V vertex	6 (9)	-	
	VI	4 (6)	-	
	VII	-		
AGA duration, n (%)	0-12 months	5 (7.5)	-	-
	1-3 years	25 (37.3)	-	
	3-5 years	20 (29.9)	-	
	5-10 years	12 (17.9)	-	
	≥10 years	5 (7.5)	-	

AGA: Androgenetic alopecia, SD: Standard deviation

Table 2. Antropometric, BIA, and clinical parameters

	Patients			Controls	p-values*			
	Group I	Group II	All		p^1	p^2	p^3	p^4
+FFM (%)	78.2±5.5	78.3±5.3	78.2±5.4	82.4±4.8	**0.001**	**0.001**	0.99	**<0.001**
+MM (%)	74.3±5.2	74.3±5.0	74.3±5.1	78.3±4.5	**0.001**	**0.001**	0.98	**<0.001**
+FM (%)	21.6±5.5	21.6±5.3	21.6±5.3	17.4±4.8	**0.001**	**0.001**	0.99	**<0.001**
+BW (%)	55.8±3.4	56.0±4.2	55.9±3.8	58.3±3.6	**0.005**	**0.017**	0.87	**0.002**
+Obesity degree	16.7±13.0	12.1±14.3	14.5±13.7	6.9±14.6	**0.006**	0.15	0.23	**0.01**
+Protein	13.3±2.3	13.2±3.1	13.3±2.7	13.3±2.3	0.98	0.85	0.88	0.90
+Mineral	4.5±0.4	4.4±0.6	4.4±0.5	4.3±0.4	0.24	0.59	0.67	0.31
*Metabolic age (years)	25.2±6.0	32.4±9.8	28.7±8.8	24.3±7.7	0.14	**<0.001**	**0.012**	**0.002**
+BMI (kg/m^2)	25.4±2.9	25.1±3.7	25.3±3.3	23.4±3.2	**0.012**	**0.046**	0.78	**0.006**
*Body density	1.0±0.0	1.0±0.0	1.04±0.0	1.2±1.3	**0.001**	**0.002**	0.95	**<0.001**
*Visceral fat	5.1±2.6	6.7±3.5	5.9±3.2	3.9±2.5	**0.043**	**0.001**	0.10	**0.001**

*Mann-Whitney U test, +t-test, BIA: Bioimpedance analysis, FFM: Fat free mass, MM: Muscle mass, FM: Fat mass, BW: Body water, BMI: Body mass index, Group I: Subjects with AGA stages (Hamilton-Norwood scale) II, IIa, IIIa and III vertex, Group II: AGA stages IV, IVa, V, Va, VI and VII, p^1: Group I and controls, p^2: Group II and controls, p^3: Group I and group II, p^4: All patients and controls, AGA: Androgenic alopecia

Table 3. Echocardiographic and ultrasonic datas for the groups

	Patients, mean ± SD			Controls, mean ± SD	p-values*			
	Group I	Group II	All		p^1	p^2	p^3	p^4
EFT (cm)	3.3±1.0	3.4±0.8	3.4±0.9	3.2±1.0	0.75	0.34	0.49	0.46
LVEF (%)	64.6±1.3	64.6±1.2	64.6±1.3	64.4±1.5	0.49	0.44	0.87	0.36
LA (cm)	3.5±0.2	3.5±0.2	3.5±0.2	3.4±0.2	**0.012**	0.05	0.59	**0.006**
LVEDD	4.7±0.3	4.6±0.3	4.7±0.3	4.6±0.2	0.06	0.99	0.10	0.21
LVESD	3.1±0.4	3.0±0.3	3.0±0.3	3.0±0.3	0.10	0.92	0.05	0.29
IVST	0.96±0.0	1.0±0.3	0.99±0.2	0.93±0.0	0.32	**0.010**	0.11	**0.037**
PWT	0.88±0.1	0.91±0.1	0.89±0.1	0.86±0.0	0.16	**0.045**	0.52	**0.043**
sPAP	27.3±5.9	27.2±2.7	27.2±4.8	26.3±2.9	0.90	0.24	0.29	0.47
CIMT (cm)	0.05±0.0	0.04±0.0	0.05±0.0	0.05±0.0	0.78	0.68	0.58	0.63

*Mann-Whitney U test, EFT: Epicardial fat thickness, LVEF: Left ventricular ejection fraction, LA: Left atrium, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVST: Interventricular septal thickness, PWT: Posterior wall thickness, sPAP: Systolic pulmonary artery pressure, CIMT: Carotid intima-media thickness, Group I: Subjects with AGA stages (Hamilton-Norwood scale) II, IIa, IIIa and III vertex, Group II: AGA stages IV, IVa, V, Va, VI and VII, p^1: Group I and controls, p^2: Group II and controls, p^3: Group I and group II, p^4: All patients and controls, AGA: Androgenic alopecia

Discussion

AGA is the most common type of alopecia in the general population [17]. It was first stated by Cotton et al. [23] that male AGA might be a risk factor for cardiovascular disease.

There are various studies investigating the relationship between AGA and CVD, insulin resistance and metabolic syndrome [17]. In a meta-analysis of 50,956 patients, AGA was found to be associated with hyperinsulinemia, insulin resistance, and metabolic syndrome as well as coronary artery disease. The pathological mechanism underlying the relationship between AGA, cardiovascular risk factors and coronary artery disease has not yet been openly determined [24].

In a study conducted in 126 male patients, it was shown that patients with advanced stages of AGA had higher CIMT and EFT values [6]. Although it has been indicated that the increase in CIMT and EFT in AGA patients is associated with coronary artery disease, no such evaluation was made in our study.

In a study of 189 male subjects, higher alopecia severity, higher degree of obesity were associated with higher BMI, particularly in those with early-onset male type AGA [25]. In another study, it was found that the severity of AGA rised with age in 132 male patients, but it was not found to have a statistically significant relationship with BMI [17].

Cardiovascular events such as severe myocardial infarction and fatal ischemic heart disease have been documented with early AGA, but

Table 4. Correlation of BIA parameters with echocardiography and CIMT

		EFT	LVEF	LA	LVEDD	LVESD	IVST	PWT	sPAP	FFM (%)	MM (%)	FM (%)	BW (%)	Obesity degree	BMI	Visceral fat	CIMT
EFT	r	1															
	p																
LVEF	r	-0.363**	1														
	p	0.003															
LA	r	0.392**	-0.266*	1													
	p	0.001	0.030														
LVEDD	r	0.347**	0.390**	0.719**	1												
	p	0.004	0.000	0.000													
LVESD	r	0.009	0.392**	0.347**	0.259*	1											
	p	0.942	0.000	0.004	0.022												
IVST	r	-0.032	0.178	0.095	0.038	0.262*	1										
	p	0.795	0.075	0.445	0.741	0.007											
PWT	r	0.353**	0.518**	0.432**	0.343*	0.727**	0.321*	1									
	p	0.003	0.000	0.000	0.002	0.000	0.001										
sPAP	r	0.094	0.147	-0.073	-0.032	0.093	0.019	-0.058	1								
	p	0.449	0.237	0.558	0.800	0.454	0.876	0.643									
FFM (%)	r	-0.491**	0.215	-0.381**	-0.426**	-0.167	0.256	-0.368**	-0.098	1							
	p	0.000	0.130	0.006	0.002	0.240	0.069	0.008	0.496								
MM (%)	r	-0.485**	0.212	-0.367**	-0.415**	-0.158	0.265	-0.364**	-0.096	0.999**	1						
	p	0.000	0.136	0.008	0.002	0.268	0.061	0.009	0.503	0.000							
FM (%)	r	0.485**	-0.206	0.379**	0.424**	0.170	-0.259	0.373**	0.097	-1.000**	-0.999**	1					
	p	0.000	0.147	0.006	0.002	0.232	0.067	0.007	0.498	0.000	0.000						
BW (%)	r	-0.540**	0.283*	-0.537**	-0.547**	-0.276	0.116	-0.411**	-0.069	0.873**	0.861**	-0.872**	1				
	p	0.000	0.044	0.000	0.000	0.050	0.416	0.003	0.630	0.000	0.000	0.000					
Obesity degree	r	0.420**	-0.264	0.463**	0.571**	0.298*	-0.205	0.326*	0.172	-0.693**	-0.680**	0.687**	-0.786**	1			
	p	0.002	0.061	0.001	0.000	0.034	0.149	0.020	0.228	0.000	0.000	0.000	0.000				
BMI	r	0.502**	-0.231	0.447**	0.488**	0.229	-0.168	0.342*	0.152	-0.666**	-0.654**	0.660**	-0.738**	0.850**	1		
	p	0.000	0.104	0.001	0.000	0.106	0.237	0.014	0.287	0.000	0.000	0.000	0.000	0.000			
Visceral fat	r	0.537**	0.227	0.513**	0.363**	0.122	-0.042	0.429**	0.160	-0.835**	-0.830**	0.834**	-0.768**	0.626**	0.744**	1	
	p	0.000	0.109	0.000	0.009	0.393	0.768	0.002	0.263	0.000	0.000	0.000	0.000	0.000	0.000		
CIMT	r	0.412**	-0.146	0.414**	0.302*	0.068	0.041	0.317**	0.033	-0.357*	-0.355*	0.352*	-0.306*	0.204	0.428**	0.484**	1
	p	0.001	0.240	0.001	0.013	0.585	0.744	0.009	0.793	0.010	0.011	0.011	0.029	0.151	0.002	0.000	

*<0.05, **<0.01; EFT: Epicardial fat thickness, LVEF: Left ventricular ejection fraction, LA: Left atrium, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVST: Interventricular septal thickness, PWT: Posterior wall thickness, sPAP: Systolic pulmonary artery pressure, FFM: Fat free mass, MM: Muscle mass, FM: Fat mass, BW: Body water, CIMT: Carotid intima-media thickness, BW: Body water

the mechanism underlying this relationship is not yet understood [24,26].

In our study, body composition parameters were examined by BIA in patients with AGA and in the controls, and the relationships between cardiovascular disorders and AGA were investigated by making cardiac measurements with echocardiography. Considering the correlation of BIA data with echocardiographic and CIMT data, it was seen there was a powerful and positive correlation between visceral fat, CIMT and EFT values. The relationship between visceral fat ratio and hyperinsulinemia, diabetes mellitus and atherosclerotic heart disease is known [27]. In our study, the visceral fat ratio in BIA analysis was higher in AGA patients compared to the controls, it was significantly higher in group II patients and showed a strong correlation with CIMT and EFT values, which supports this data. In the light of these data, it can be considered as an advantage that visceral fat assessment by BIA method is an easily accessible and non-invasive test, since it may show the development of subclinical atherosclerosis and prediabetes in the early period.

Study Limitation

The limited number of patients included in our study, the fact that our patient profile mostly consists of young individuals, only male patients and the absence of female patients can be expressed as limitations.

Another limitation of our study is that more sensitive methods such as tomography or magnetic resonance imaging (MRI) were not used to measure CIMT and EFT values.

Conclusion

Although it was stated that these values were significantly impaired in studies evaluating CIMT and EFT in patients with AGA, no significance was observed in our study. We believe that this may be because of the few number of patients included in our study and the fact that our patient profile is mostly composed of young individuals. In our study, a two-dimensional transthoracic echocardiography device was used to measure CIMT and EFT values, but using more sensitive methods such as tomography or MRI can provide more meaningful results in the measurement of these values.

Ethics

Ethics Committee Approval: Approval was obtained for the study from Malatya Clinical Research Ethics Committee on 15.01.2020 (decision no: 2020/10).

Informed Consent: All participants were informed and their written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.T., Ş.H., Concept: D.T., Ş.H., N.A., Design: D.T., Ş.H., N.A., Data Collection or Processing: D.T., Ş.H., S.A., M.Y.A., F.B.B., Analysis or Interpretation: D.T., Literature Search: D.T., S.A., Writing: D.T., Ş.H., S.A.

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Can We Recognize Skin Adnexal Tumours? Retrospective Evaluation of Clinical and Histopathologic Data in a Tertiary Dermatology Clinic

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ABSTRACT

Background: Clinical diagnosis of skin adnexal tumours (SATs) is challenging. In this study, we aimed to determine the compatibility rate of clinical pre-diagnoses and histopathological diagnoses in histopathologically confirmed cases of SATs examined by dermatologists.

Materials and Methods: Histopathologically confirmed cases of SATs in a single center dermatology clinic during May 2019- May 2023 were retrospectively retreived. We recorded demographic characteristics, clinical characteristics (elementary lesion type, tumour localization, when available dermoscopic features) and clinical pre-diagnoses from patient medical records.

Results: A total of 39 SATs from 38 patients (18 female and 20 male) were included in the analysis. All 38 SATs (97.4%) were benign except one trichilemmal carcinoma. Lesions were most commonly located in head and neck region in 61.5% (n=24) of patients, presenting as nodules (n=21, 53.9%) and papule/plaques (n=18, 46.1%). Dermatoscopic features included linear vessels, structureless white areas, structureless pink/purple areas and blue-gray dots. Clinical pre-diagnoses were discordant in 53.8% (n=21) of cases where SAT was not mentioned among one or more pre-diagnoses. Most common erroneous pre-diagnoses were epidermal cyst, nevi and non melanoma skin cancer.

Conclusion: With the exclusion of pilomatricoma, more than half of SATs are difficult to recognize in clinical and dermoscopic examination. Further studies with focus on clinical and dermoscopic differentiation of SATs from most common pitfall diagnoses are needed.

Keywords: Adnexal tumors, Clinicopathologic correlation, Hair follicle, Pilomatricoma, Sebaceous, Sweat gland

Introduction

Skin adnexal tumours (SATs) refer to heterogenous group of tumours arising from hair follicle, sebaceous and sweat glands [1]. From dermatologists' perspective, SATs are important for several main reasons. SATs mostly have a non-specific clinical appearance, presenting frequently as asymptomatic papules or nodules [2,3]. Some SATs may point to underlying genetic conditions [1]. Malignant SATs are rare, however they might have an aggressive course with local invasion and distant metastasis [2].

In this study, we aimed to determine the compatibility rate of clinical pre-diagnoses and histopathological diagnoses in histopathologically confirmed cases of SATs. Our secondary aim was to document clinical and dermoscopic data of SAT cases.

Materials and Method

Histopathologically confirmed cases of SATs, diagnosed in the Pathology Clinic of University of Health Sciences Turkey, Istanbul Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research

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Hospital, during May 2019- May 2023 were retrospectively retreived. Hematoxylin and Eosin stained slides and immunohistochemical stains were used to establish diagnosis. Non-syndromic SAT cases who were examined by at least one dermatologist (with/without plastic surgeons, pediatric surgeons, general surgeons) were included in the study. We retrospectively noted demographic characteristics, clinical characteristics including elementary lesion type, tumour localization and when available dermoscopic features. Clinical pre-diagnoses and biopsy technique (punch/excision) were also recorded.

Before starting the study, approval was obtained from the Institutional Review Board of University of Health Sciences Turkey, Istanbul Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital (decision no: 113, date: 21.06.2023).

Statistical Analysis

Descriptive statistics were presented with mean and standard deviation values. Categorical variables such as gender, tumour diagnosis, location were expressed in percentages.

Results

A total of 39 SATs from 38 patients (18 female and 20 male) were included in the analysis. Age range was from 7 to 82 years (41±21.5 years), most patients being in their fifth decade. Demographics of the patients can be seen in Table 1.

All 38 SATs (97.4%) were benign except one trichilemmal carcinoma. Histopathological diagnoses of the SATs and their origin are given in Table 2. Lesion origin was hair follicle in 59% (n=23) and sweat gland in 41% (n=16) of cases. None of the tumours were of sebaceous origin. Histopathologic confirmation was performed with total excision in 84.6% (n=33) and with punch biopsy in 15.4% (n=6) of cases.

Table 1. Characteristics of the patients (total=38)

Characteristics	n (%)
Gender	
Female	18
Male	20
Age range	
0-10	3 (7.9%)
11-20	5 (13.1%)
21-30	5 (13.1%)
31-40	5 (13.1%)
41-50	7 (18.4%)
51-60	5 (13.1%)
61-70	5 (13.1%)
71-80	1 (2.6%)
>80	2 (5.3%)

Lesions were most commonly located in head and neck region in 61.5% (n=24) of patients, followed by extremities (n=11, 28.2%) and trunk (n=4, 10.3%). In clinical examination, lesions were described as nodular (n=21, 53.9%) and papule/plaques (n=18, 46.1%). Dermoscopic features were available in medical records of 20 patients. Linear vessels (n=15), structureless white areas (n=10), structureless pink/purple areas and blue-gray dots (n=3) were noted.

In 46.2% (n=18) of cases, SAT was suspected by examining dermatologist. Among 12 pilomatricoma cases, 58.3% (n=7) were correctly identified. Clinical pre-diagnoses were discordant in 53.8% (n=21) of cases where SAT was not mentioned among one or more pre-diagnoses. Erroneous pre-diagnoses were epidermal cyst (n=16), nevus (dermal/Spitz) (n=7), non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, n=5) and verruca vulgaris (n=1). A demonstrative case can be seen in Figure 1.

Discussion

Thirty-nine histopathologically confirmed SAT cases were evaluated in dermatology our department during a four year period. This data points to a rare diagnosis, thus SATs are difficult to recognize for both dermatologists and pathologists [2,3]. Vast majority of SATs are benign tumours, with a proportion ranging from 69.41% to nearly 100% in different studies, as observed in our study [2,3,4,5]. Consistent with existing literature, in our cohort SATs were observed in a wide age range [1,2,3,4,6] with nearly 20% of patients being in their 5th decade [3]. Although some data report female preponderance in SAT cases [2,3] which may be attributed to cosmetically unacceptable

Table 2. Histopathological diagnoses according to tumour origin

Histopathologic diagnosis	Origin	n (%)
Pilomatricoma	Hair follicle	12 (30.8)
Syringoma	Sweat gland	4 (10.2)
Proliferated trichilemmal tumour	Hair follicle	4 (10.2)
Trichofolliculoma	Hair follicle	3 (7.7)
Syringocystadenoma papilliferum	Sweat gland	3 (7.7)
Chondroid syringoma	Sweat gland	2 (5.1)
Trichoblastoma	Hair follicle	2 (5.1)
Hidrocystoma	Sweat gland	2 (5.1)
Hidroadenoma	Sweat gland	2 (5.1)
Eccrine poroma	Sweat gland	1 (2.6)
Eccrine spiradenoma	Sweat gland	1 (2.6)
Hidroadenoma papilliferum	Sweat gland	1 (2.6)
Desmoplastic trichoepitelioma	Hair follicle	1 (2.6)
Trichilemmal carcinoma	Hair follicle	1 (2.6)

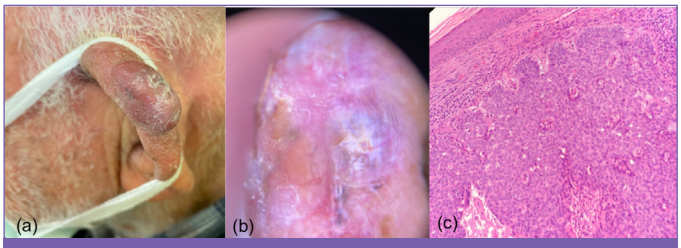

Figure 1. Clinical, dermatoscopic and histopathologic photographs of adnexal tumour (trichoblastoma) with clinical pre-diagnoses of basal cell carcinoma and Kaposi's sarcoma. (**a**): Clinically a solitary nodular lesion on the helix of a 81 year old man was observed. (**b**): Dermoscopy reveals purple structureless areas, shiny white lines, blue-gray ovoid nests. (**c**): Histopathologically a palisading uniform cellular proliferation with basaloid morphology as a dermal tumour nodule without epidermal connection was diagnosed as trichoblastoma (Hematoxylin and Eosin x200)

nature of the lesions [2], we did not observe a gender predilection in our series as Pujani et al. [5] and Bartoš [6], while other authors have reported a male preponderance [4]. Majority of the lesions are typically located in head and neck region, as this is an area rich in skin appendages [1,2,3,4,5,6,7].

In most studies, SATs arising from sweat glands outnumbered tumours with follicular or sebaceous differentiation [1,4,5,7]. However, similar to data from a Slovakian center, in our series follicular tumours were more common [6]. In the present study, the most common type of SAT was pilomatricoma as in many studies [4,8], followed by proliferating trichilemmal tumour (PTT). PTT was also reported to be frequent among SATs with hair follicle differentiation in another study [2]. Syringomas of our series was in equal number with PTTs. Of note, three out of four syringomas were located on trunk and extremities, where diagnostic difficulties are even increased. On the other hand, sebaceous SATs were not biopsied or excised in our series. SATs with sebaceous differentiation presented only 5% of a total of 1615 SATs biopsied or excised in the extensive study by Cook et al. [1] where sebaceous nevus was excluded from analysis. Similar to our results, very few cases of sebaceous SATs were reported in some series [2,6,7].

Clinically SATs present as non-specific asymptomatic papulonodules [2,3]. In addition, reported dermoscopic features of SATs were also mostly non-specific, mimicking melanocytic lesions, non-melanoma skin cancer and other benign cutaneous disorders [9,10]. Consistent with literature, dermoscopic features noted in our cohort were non-specific and even misleading. A very recent multi-center study by Longo et al. [11] better characterized dermoscopic features of trichoepitheliomas. Ivory white background color, small, unfocused vessels and grey-purple structureless areas were most common dermoscopic features of trichoepithelioma and trichobastomas, while ulceration and erosion favored diagnosis of basal cell carcinoma [11].

In studies from various institutions from different countries, correctness rates of pre-biopsy diagnoses in SATs ranged from 6.4% to 48% [1,2,3,5,12]. The study by Aslan Kayiran et al. [3] conducted in an experienced tertiary dermatology clinic in Turkey has reported a clinicopathologic compatibility rate of 45%, similar to our cohort. This relatively high concordance rate in our study and in the latter study might be attributed to study design, as these were studies conducted by dermatologists. Studies involving SATs pre-diagnosed by all clinicians report lower rates of concordance [1,2,5,12]. Aslan Kayiran et al. [3] have noted higher concordance rate for the two most common subtypes of SAT in their series, which were sebaceous hyperplasia and pilomatricoma (65.2% and 50% respectively). Diagnostic accuracy of pilomatricoma was also higher (58.3%) in our series. Similar to our series, epidermal cysts, melanocytic and nonmelanocytic tumors were among most common erroneous clinical prediagnoses [2,3].

Definitive diagnosis of SATs relies on histopathologic examination [3]. As local surgical excision is curative in most cases [2], total excision is preferred over punch biopsies in diagnostic management of SATs. In our series, majority of cases were simultaneously diagnosed and treated with total excision.

Study Limitation

Limitations of the present study include its retrospective nature, which restricts available clinical data to medical records written by one examining dermatologist.

Conclusion

With the exclusion of pilomatricoma, more than half of SATs are difficult to recognize in clinical and dermoscopic examination. Atypical localizations of commonly observed SATs also constitute a diagnostic concern. In our study, most common erroneous clinical pre-diagnoses were epidermoid cysts, nevi and non-melanoma skin cancers. Further studies with focus on clinical and dermoscopic differentiation of SATs from most common pitfall diagnoses are needed.

Ethics

Ethics Committee Approval: Before starting the study, approval was obtained from the Institutional Review Board of University of Health Sciences Turkey, Istanbul Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, (decision no: 113, date: 21.06.2023).

Informed Consent: Informed consent was waived due to retrospective design.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.Ç.O, M.Y., Design: M.Ç.O., M.Y., Data Collection or Processing: M.Y., Analysis or Interpretation: M.Ç.O., Literature Search: M.Ç.O., M.Y., Writing: M.Ç.O.

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

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CASE REPORT

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Multiple Lentigines in Resolving Psoriatic Plaques After Treatment with Secukinumab in Two Cases

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ABSTRACT

The development of lentigines in resolving psoriatic plaques has been reported in the literature after different treatment modalities including phototherapy, topical therapeutics, and recently during or after treatment with tumor necrosis factor inhibitors and ustekinumab. Herein we want to report two cases with multiple lentigines developed after healing of the plaques of psoriasis who received treatment with secukinumab for psoriasis. To our knowledge development of multiple lentigines after secukinumab treatment has not been reported in the literature before.

Keywords: Biologic agents, Dermatology, Lentigo, Psoriasis, Secukinumab

Introduction

The development of lentiginous pigmentation confined to resolved psoriatic plaques is a rare phenomenon that has been reported after different treatment regimens in the literature [1,2,3]. The pathogenesis of the melanocytic stimulation and increased melanin production over resolved psoriatic plaques after the treatment is not well-known but it was suggested that this reaction may be explained with post-inflammatory hyperpigmentation and previous history of ultraviolet (UV) light exposure, genetic predisposition, having a fair skin type and disease severity may also have a role [2].

Case Reports

Case 1

A 37-year-old male patient who was under follow-up for chronic plaque-type psoriasis for 2 years in our clinic admitted for a routine control visit. He was taking secukinumab for 6 months due to the side effects and unresponsiveness to conventional antipsoriatic agents. On dermatologic examination, marked remission was detected on hyperkeratotic and desquamating erythematous plaques over the trunk, upper and lower extremities. Also, small, 2-3 mm of light and the dark brownish hyperpigmented lentiginous macular eruption was realized over resolved psoriatic plaques (Figure 1). Patient consent form was taken before the treatment. Histologically these pigmented lesions were consistent with lentiginous proliferation (H&E, x400) (Figure 1b). He was otherwise healthy and he has no history of any other systemic or dermatologic disease and biologic agent used previously. Routine follow-up was recommended.

Case 2

A 38-year-old female patient who was diagnosed as a 4-year history of chronic plaque-type psoriasis presented to our outpatient clinic for her routine control visit. She was unresponsive to conventional therapies and due to the secondary unresponsiveness to etanercept

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and primary unresponsiveness to adalimumab, we initiated secukinumab. On her routine follow up at 3rd month, multiple millimetric brown lentiginous eruption was realized over previously psoriatic plaques on elbows and knees (Figure 2a). There was no similar lentiginous lesion on the normal skin or mucosal surfaces. She has no history of another systemic or dermatological disease. Patient consent form was taken before the treatment. Histologically lentiginous proliferation was noted on the epidermis. (H&E, x200) (Figure 2b). Routine follow-up was recommended.

Discussion

Development of lentigines on resolving psoriatic plaques is a rare phenomenon that has been reported following different topical and systemic antipsoriatic treatment modalities including topical calcipotriol, topical tar, phototherapy, apremilast, methotrexate, and some biologic agents including adalimumab, infliximab, ustekinumab, and recently after guselkumab use [1,2,3,4,5,6,7,8,9]. The occurrence of lentigines was first linked to the phototherapy and implicated as PUVA- or UVB-induced lentigo in most cases, but after they have been noted following different therapy modalities, especially patients who do not have history phototherapy, they were referred to post-inflammatory hyperpigmentation mechanisms [3,5,7]. Most of the cases had skin types of Fitzpatrick I-III and the appearance of the lentiginous lesions usually reported to develop at 2-6 months of the treatments. In some of these observations, the development of lentigines was linked to sun exposure or sunburns. None of our patients have sunburn history previously, the possible effect of biologic agents on melanocytes or melanogenesis is not well-known. Some authors suggested that the effective suppression of tumor necrosis factor (TNF)-a and other psoriasis-related inflammatory cytokines may lead to this reaction by their inhibitory effects on melanocytes and tyrosinase activity [1,8,9,10,11]. Our first patient was biologic naive, and he has also no history of phototherapy or anti-TNF agent use. Our second patient has also no history of phototherapy, she used anti-TNF agents previously but no similar lesions occurred on resolving psoriatic plaques during these therapies. They have skin types of Fitzpatrick type III and PASI scores were between 10-15 in our patients. Dogan and Atakan [1] suggested that the development of lentiginous eruption may be a clinical marker of response to the therapy. They reported almost total clearance with infliximab, which was resulted in multiple lentiginous proliferation within the resolved plaques. As Singh and Beniwal [2] mentioned, this reaction is most probably related to the level of cytokine suppression is responsible for this phenomenon rather than the drug itself.

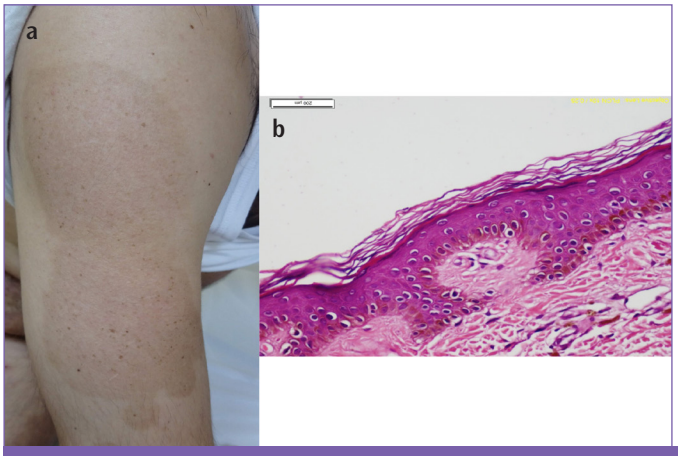

Figure 1. a) Lentiginous macular lesions over healed plaques of psoriasis on the extensor surface of the left arm, **b)** Lentiginous proliferation on basal layer (H&E, x400)

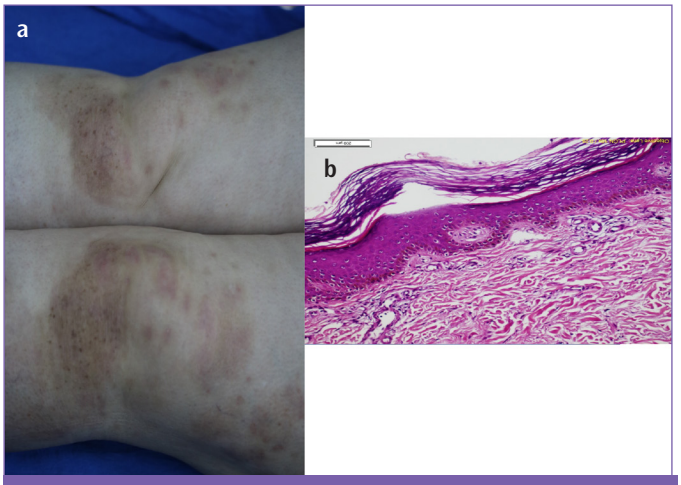

Figure 2. a) Lentiginous macular lesions over healed plaques of psoriasis on the knees (marked with red lines), **b)** Homogenous lentiginous proliferation in the epidermis (H&E, x200)

The effects of proinflammatory cytokines including TNF-alpha and IL-17 on melanocytes were investigated in previous studies and the authors underlined the synergistic stimulation of these cytokines may lead to increased expression of growth factor genes and mitogenic cytokines and seems to downregulate the melanin production and the pigmentation signaling pathway [10,11]. The blockage of IL-17 by secukinumab may be the most probable factor in the development of lentigines in our patients.

Conclusion

The development of multiple lentigines in treated lesions of psoriasis is a rare clinical manifestation that may present following different therapeutic agents. In the literature both anti-TNF agents and anti IL12/23 agents. To our knowledge lentiginous proliferation has not been reported with anti-IL-17 agents previously. The development of lentiginous proliferation with different biologic pathways may support the hypothesis of post-inflammatory hyperpigmentation mechanisms in response to effective therapy in

psoriasis. These lesions are usually permanent and laser therapies may be offered for the patients. Although long term follow-ups have not been reported in the literature, in few cases reports total clearance was reported in 4 weeks - 4 months, and persistence of the lesions for years was reported in some of the cases.

In our patients during routine follow-ups, no clinical regression was detected on the lentiginous eruption. It is also not well-known if this localized pigmentation may be a marker for cutaneous malignancy or progress into a malignancy in long term. Physicians should be aware of this entity and sun protection should be advised to prevent further formation.

Ethics

Informed Consent: Patient consent form was taken before the treatment.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.K.U., Concept: T.K.U., A.S.K., Design: T.K.U., A.S.K., B.Ç.Ş., Data Collection or Processing: T.K.U., B.Ç.Ş., Analysis or Interpretation: T.K.U., A.S.K., B.Ç.Ş., Literature Search: T.K.U., Writing: T.K.U.

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

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