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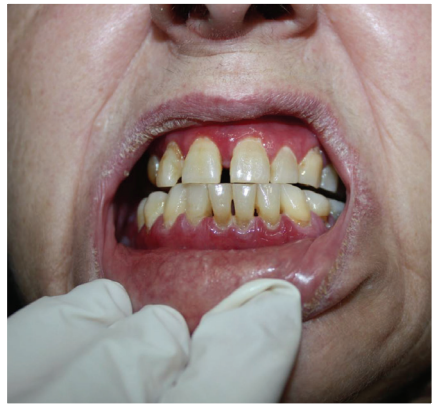

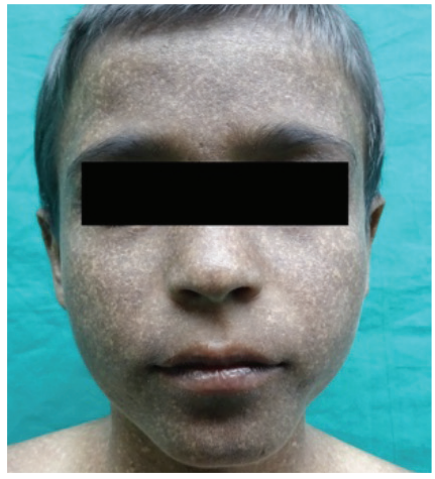

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II:Methods

III:Results

IV:Conclusions

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the appendices

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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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REVIEW

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Morphea: Clinical Considerations and Management

Muazzez Çiğdem Oba, Özge Aşkın, Burhan Engin

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ABSTRACT

Morphea, also known as localized scleroderma, is a sclerosing disease of unknown etiology that involves mainly dermal and subcutaneous layers of skin. Several types of morphea exist and various clinical manifestations are encountered. Early clinical diagnosis is crucial to minimize functional and cosmetic sequelae. Treatment choice depends on activity, extent of disease and depth of involvement. In this review, we aimed to review clinical features and current treatment options for morphea.

Keywords: Localized scleroderma, Morphea, Treatment

Introduction

Morphea, also known as localized scleroderma, is a sclerosing skin disease that mainly affects dermal and subcutaneous layers of the skin without internal organ involvement. Histologically, there is increased collagen deposition in dermis. Depending on subtype, adjacent sites such as muscles, bones and joints can be affected. Morphea can severely impact quality of life by causing cosmetic and sometimes functional problems. Early diagnosis and treatment is crucial to minimize potential sequelae.

Clinical features

Depending upon the severity, extent and depth of involvement, five main clinical variants of morphea are described: limited, generalized, linear, deep, and mixed (Table 1) [1].

Plaque type morphea is the most common presentation of morphea [1,2,3]. Initially, oval or round erythematous indurated plaques are seen, mostly on the trunk. Central sclerosis develops with time, which is surrounded by an active liliac halo. Hyperpigmented plaques that show central depression are features of late lesions (Figure 1). Guttate morphea and atrophoderma of Pasini and Pierini are variants of limited morphea characterized by truncal sclerotic lesions measuring less than 1 cm in diameter [1,2].

Generalized forms include generalized morphea and disabling pansclerotic morphea. Generalized morphea is diagnosed when four or more plaques, measuring larger than 3 cm involve two or more anatomical sites (Figure 2) [4]. Pansclerotic morphea is a very rare variant presenting with extensive full-thickness skin involvement sparing acral skin. It is more commonly observed in children compared to adults [4]. Some authors also consider eosinophilic fasciitis (Shulman's syndrome) to be part of generalized forms of morphea [1]. Pseudo-cellulitis appearance

Table 1. Classification of morphea

Limited morphea	- Plaque morphea - Guttate morphea - Atrophoderma of Pasini and Pierini
Generalized morphea	- Generalized morphea - Disabling pansclerotic morphea
Linear	- Linear morphea of the extremities - Linear morphea of the face ("en coup de sabre" and Parry Romberg syndrome)
Deep	-
Mixed	-

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of proximal extremities and blood eosinophilia are features of eosinophilic fasciitis.

Linear form of morphea presents with longitudinal streaks of sclerosis. It may be located on upper or lower extremities sometimes causing flexion contractures and limb length discrepancies (Figure 3). Other typical location of linear morphea is scalp or the face, also known as "en coup de sabre" variant. Paramedian depression on the forehead and scarring alopecia of the scalp are the most common clinical features (Figure 4). Parry Romberg syndrome is the severe subtype of "en coup de sabre" lineer morphea. There is loss of subcutaneous fat in entire hemifacial region resulting in facial asymmetry. Ocular and neurologic abnormalities may accompany linear morphea of the face [1,4].

Deep form of morphea affects deeper tissues such as subcutaneous fat, fascia and muscle. Mixed type is the combination of more than one morphea subtypes, combined linear and plaque type being the most common [1,2].

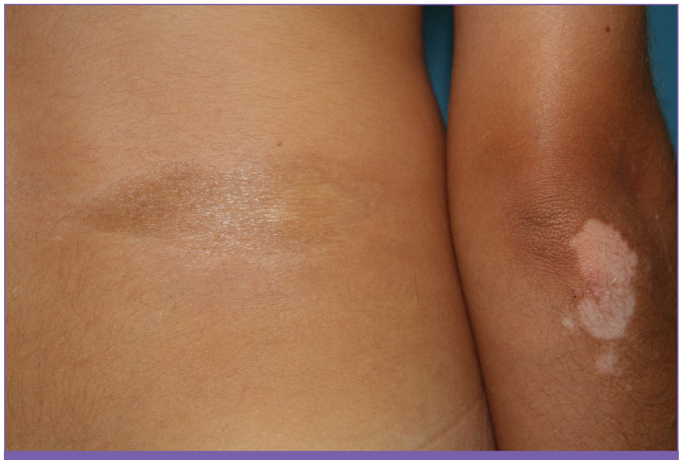

Figure 1. Hyperpigmented sclerotic plaque morphea is seen on lumbar region along with vitiligo patch on the elbow

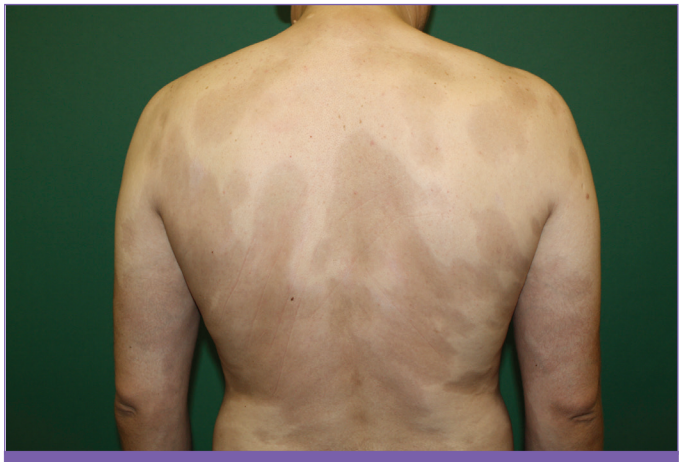

Figure 2. Generalized morphea

Extracutaneous involvement may be seen in morphea. In a multinational study involving seven hundred fifty juvenile patients with morphea, up to one forth of the children had extracutaneous manifestations, articular, neurologic, vascular and ocular findings being more common [5]. Arthritis is the most common extracutanous finding, seen especially in linear and generalized morphea. Arthritis frequently affects the joints underlying morphea plaques, however distant involvement may also occur [6]. In some cases,

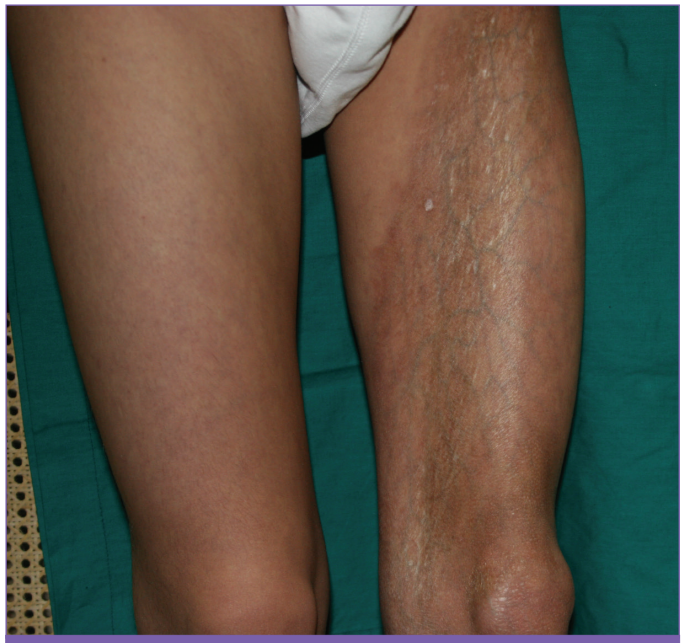

Figure 3. Linear morphea of the extremities

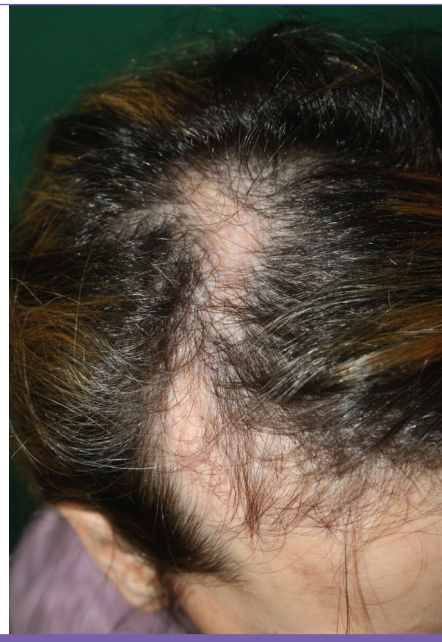

Figure 4. Linear morphea of the scalp causing cicatricial alopecia

arthritis may lead to limb length discrepancies and limited range of motion [5]. Patients with linear scleroderma of the face have the most considerable risk for neurologic involvement, including seizures and headache. Vascular involvement was reported as deep vein thrombosis and Raynaud's phenomenon. Ocular involvement consisting of uveitis, episcleritis, acquired glaucoma, xerophthalmia and keratitis were exclusively seen in patients with linear scleroderma of the face [5]. Patients with linear scleroderma of the face should be monitored with periodic eye examinations [5].

Laboratory changes

Unlike systemic sclerosis, there are no reliable laboratory markers for the diagnosis of morphea. Increased sedimentation rate and eosinophilia can occur in active disease and during relapses [7]. In patients with deep involvement leading to myositis, serum creatine kinase and aldolase levels may increase [2]. Prevalence of antinuclear antibodies and rheumatoid factor (RF) is higher in patients with extracutaneous involvement [5]. RF is considered as a significant marker for articular involvement [5]. However, routine screening for these autoantibodies is not recommended. Likewise, routine blood screening for Borrelia burgdorferi is not recommended [2].

Imaging

Patients with severe linear scleroderma of the face, especially the Parry Romberg variant may have associated neurologic disturbances. Some authors include magnetic resonance imaging (MRI) among standard diagnostic procedures of such patients [8]. MRI can also help confirm musculoskeletal manifestations such as joint effusion, synovitis, bone marrow involvement etc [9].

Differential diagnosis

Lipodermatosclerosis, especially the acute form may be misdiagnosed as morphea. Lipodermatosclerosis typically involves the lower extremities and there is accompanying findings of venous hypertension [10].

Lipoatrophy following intraarticular steroid injections may be misdiagnosed as morphea [11]. The lack of erythema, dyspigmentation and induration in a linear plaque points to lipoatrophy rather than morphea.

Radiation induced fibrosis (RIF) usually develops in the first 3 months after radiotherapy and may mimic morphea. RIF has insidious onset and there is no erythema and induration. Of note, localized morphea following radiotherapy has been reported in literature with an incidence of 2 out of 1,000 patients [12].

Early lesions of linear morphea of the face show erythema without sclerosis and thus may be misdiagnosed as a vascular malformation including an acquired port-wine stain [13,14].

Carcinoma en cuirasse is a rare form of cutaneous metastasis that occurs mostly due to breast cancer. In patients with sclerotic plaques involving the chest wall, malignancy should be ruled out by skin biopsy if the patient has any risk factors for breast cancer [15].

Cutaneous T cell lymphomas, especially early stage mycosis fungoides, may resemble morphea. Immunohistochemistry is a helpful adjunct to differentiate the two entities [16].

Generalized morphea and pansclerotic morphea should be differentiated from scleroderma, which is a complex connective tissue disease with multi-system involvement. Clinical findings are essential to distinguish the two entities histopathologic examination of the skin shows similar findings. Raynaud phenomenon, acrosclerosis and sclerodactyly are typically absent in morphea and nail capillaroscopy is normal [6,17]. Anti-centromere antibodies and anti-Scl-70 antibodies are also absent in sera of patients with morphea [18].

Treatment

There is a wide range of therapeutic options available for the treatment of morphea. The choice of treatment modality depends on the depth and extent of involvement and the clinical activity of the disease [2].

Topical steroids are the most commonly preferred first line treatment for cases of morphea with limited involvement [19]. Despite the lack of randomized controlled studies, active disease without deep inflammation is first treated by a 3-month course of moderate- to high-potent topical corticosteroids. Occlusion may be applied in selected patients for better results. Intralesional steroid injections are also appropriate to halt lesion progression in localized active disease [2,6].

Topical tacrolimus 0.1% ointment with or without occlusion can be considered for treatment of active plaque morphea [20,21,22]. In a small double-blind placebo controlled study 10 patients were treated with tacrolimus 0.1% ointment and petrolatum for 12 weeks. Significant improvement was seen in active plaque morphea lesions treated with tacrolimus [22].

Topical calcipotriol 0.005% was shown to effectively improve morphea lesions previously not responsive to topical steroids. The ointment was applied twice daily under occlusion. Weekly calcipotriol dose should not exceed 50 g/m^2 [23,24].

Topical imiquimod 5% has also been proposed as an alternative therapeutic option for the treatment of plaque morphea. The mechanism of action of imiquimod is thought to involve the induction of T helper1 cytokine response [25]. However, currently, topical imiquimod cannot be recommended for morphea as there is limited data [2].

Efficacy of fractional carbon dioxide laser was assessed for the treatment of localized morphea. Compared with local low-dose ultraviolet A1 (UVA1) phototherapy, fractional carbon dioxide laser led to better improvement of lesional skin clinically, histopathologically and by ultrasound [26].

Phototherapy is the first-line treatment option for extensive or rapidly progressing disease without deep involvement and can also be considered for patients with limited involvement that are unresponsive to topical treatment [6]. The long wavelength of UVA radiation affects the culprit fibroblasts and inflammatory cells at the level of deep dermis [27]. Ultraviolet light also induce the matrix metalloproteinases and promote neovascularization [28]. Different from topical treatments, phototherapy not only improves existing lesions but it also prevents formation of new ones [6]. Among various modalities, UVA1 phototherapy has the highest level of evidence. It can be administered at low (10-29 J/cm^2), medium (30-59 J/cm^2) and high (60-130 J/cm^2) dose, all of which might be effective to improve sclerosis [2,6]. Most patients receive low to medium dose UVA1 for a total of 20 to 40 sessions [27]. Eighteen out of 20 patients with severe morphea had at least 80% clearance of their lesions when treated with low dose UVA1 (20 J/cm^2) for 30 sessions [29]. Medium dose UVA1 is also effective in treatment of morphea with better long-term results compared with low-dose UVA1 [30,31,32]. Broadband UVA, PUVA phototherapy (oral, bath and cream) and narrowband UVB can be considered as alternatives when UVA1 phototherapy is not available [27].

Morphea lesions with deep involvement or lesions causing functional impairments should be treated with systemic therapies [6]. Methotrexate (MTX) has the most evidence for efficacy, proven by randomized controlled studies. For the first 2 to 3 months of MTX therapy, systemic corticosteroids may be added to treatment in case of rapidly progressing disease or functional impairment. In a placebo controlled study involving 70 pediatric patients with morphea, rates of clinical efficacy was significantly higher and the likelihood of relapse was significantly lower with MTX (15 to 20 mg weekly) treatment as compared to placebo [33]. Of note both groups were treated with systemic corticosteroids for the first 3 months of therapy. In management of juvenile morphea, "Childhood Arthritis and Rheumatology Research Alliance" workgroup compared effectiveness of three different treatment regimens in a 1-year observational cohort study: MTX alone, or in combination with intravenous (30 mg/kg/dose for 3 months) or oral corticosteroids (2 mg/kg/day). Their results showed that are all three regiments are effective in more than 75% of patients [34].

In case of intolerance to or ineffectiveness with MTX, mycophenolate mofetil may be used as a safe alternative treatment option [35].

Two cases of children with pansclerotic morhea and five pediatric patients with refractory morphea were treated with intravenous tocilizumab, an anti-interleukin-6 receptor antibody [36,37]. All patients improved without any adverse events, however further studies are needed to confirm effectiveness and safety of tocilizumab therapy for morphea.

Autologous fat grafting is currently considered as ideal treatment for inactive linear morphea of the face [38]. Soft tissue fillers such as hyaluronic acid may also be used in selected patients where there is less tethering to underlying tissues [39].

Ethics

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Authorship Contributions

Concept: M.Ç.O., Ö.A., B.E., Design: M.Ç.O., Ö.A., B.E., Data Collection or Processing: Ö.A., B.E., Literature Search: M.Ç.O., Ö.A., B.E., Writing: M.Ç.O., Ö.A., B.E.

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ORIGINAL ARTICLE

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Effects of Narrow-band UVB Alone and in Combination with Isotretinoin on Apoptosis and Its Clinical Implications in Early Stage Mycosis Fungoides

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ABSTRACT

Background: Mycosis fungoides, one of the most common subtypes of cutaneous T-cell lymphomas, is characterized by uncontrolled T cell proliferation, apoptosis resistance, and consequent chronic cutaneous inflammation. This study aims to show the effects of narrow-band ultraviolet B (UVB) alone and narrow-band UVB + isotretinoin treatments on the expression of fas, fas ligand, Bcl-2, STAT-3 and galectin-3 proteins which are responsible for apoptosis regulation, and also assess the relationship between this regulatory functions and clinical improvement.

Materials and Methods: The first group received narrow-band UVB alone and the other group received narrow-band UVB combined with 0.5 mg/kg/day oral isotretinoin. After 30 sessions of treatment, biopsies from the patient groups were examined immunohistochemically for the expression of fas, fas ligand, Bcl-2, STAT-3 and galectin-3 protein.

Results: In the narrow-band UVB only group, the intensity of epidermal Bcl-2 staining was found to be increased in the post-treatment samples when compared to the pre-treatment. On the other hand, epidermal staining intensities and diffuseness for fas, fas-ligand, Bcl-2, STAT-3, and galectin-3, and also the intensities and diffuseness of epidermal lymphocyte staining and presence of epidermal cells were similar between pre and post-treatment samples within each group separately, and between the two treatment groups overall.

Conclusion: In the treatment of early stage mycosis fungoides, darband UVB and retinoic acid are used. In our study, the effects of these treatments on apoptosis could not be demonstrated. Larger series studies are needed in this regard.

Keywords: Mycosis fungoides, Narrow-band ultraviolet B, Isotretinoin

Introduction

Our skin is one of our largest organs, which we have the largest relationship with the external environment and constitutes approximately 16% of body weight [1]. While the epidermis exerts its barrier function mechanically, our skin plays an active role in the immune response to pathogens by the cellular elements it contains although it is not considered as a primary or secondary lymphoid organ. When the resident Langerhans cells are stimulated by proper signals, they turn into effective antigen presenting cells, causing an immune response against the target antigen under the control of T and B lymphocytes [2]. Although the etiology of mycosis fungoides, one of the most common subtypes of cutaneous T-cell lymphomas, is not fully elucidated, genetic, environmental and infectious causes are accused. Monoclonal proliferation of T-cells in the epidermis

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and disruption of the apoptosis process which result from diffuse inflammatory reactions induced by chronic antigenic stimulation form the basis of the disease [3,4]. Uncontrolled T cell proliferation, resistance to apoptosis and consequent chronic cutaneous inflammation are responsible for the development of lymphoma. Primary cutaneous lymphomas have an overall incidence of 0.3-1.0 / 100.000 and 54-72% of them are mycosis fungoides [5]. Clinically there are four stages of mycosis fungoides, namely patch, plaque, tumor, and erythroderma, and some cases may be characterized by atypical skin manifestations [6,7]. In the patch and plaque stage, lesions are often asymmetrical, itching is prominent and scalp involvement may result in alopecia [8,9]. These infiltrations, which begin as patches and plaques, progress into nodules and may show systemic spread when left untreated [10,11]. The gold standard for the diagnosis of mycosis fungoides is histopathological evaluation of skin biopsy. The treatment methods can be classified into three main approaches: methods targeting the skin, systemic treatment or biological agent regulators. The observation that the lesions frequently reside on the regions unexposed to sunlight led to the assumption that ultraviolet (UV) radiation may prevent the development of mycosis fungoides and thus PUVA, narrow-band and broadband UV B (UVB) treatments are used [12,13]. There are three types of retinoids: isotretinoin, acitretin and etretinate, which exert their effects via the retinoic acid receptor, and bexarotene which binds to the retinoid X receptor. All these retinoids show their therapeutic effects by inducing apoptosis [14]. The aim of this study is to investigate the effects of narrow-band UVB only and narrow-band UVB + isotretinoin treatments on the expression of fas, fas ligand, Bcl-2, bax, STAT-3 and galectin-3 proteins which are responsible for apoptosis regulation and the relationship between apoptosis regulation and clinical improvement.

Materials and Methods

This study was carried out between May 2006 and March 2010 at the Dermatology and Pathology Departments of the Faculty of Medicine and supported by the Scientific Research Project Commission of the University (project no: TT-06-34, approval no: 01/181). Twenty-one patients diagnosed as mycosis fungoides patch stage clinically and histopathologically were included in the study after receiving consent form from patients. Demographic data of all patients were recorded. Dermatological examinations of the patients were performed. The total affected body area was calculated as cm^2, and all treatments were ceased two weeks before skin biopsy. A total of two skin biopsies (i.e. pre-, and post-treatment) were obtained from the lesion area, and the diagnosis was confirmed by histopathology and immunophenotyping. Patients were randomly divided into two groups. Pre-, and post-treatment lesion size and symptom severity were evaluated. The first group was given narrow-band UVB treatment at 0.005 joules/cm^2 three days a week for a total of 30 sessions, increasing the applied dose by 30% in every third session. The second group received 0.5 mg/kg/day per-oral isotretinoin in combination with the narrow-band UVB treatment. After 30 sessions of narrow-band UVB treatment, each patient underwent a dermatological examination, in which clinical findings and symptoms were scored between 0 and 8 and lesion size between 0 and 18, and a cumulative score was calculated for each patient thereafter. Pre- and post-treatment biopsy specimens obtained from each patient in both study groups were initially examined with hematoxylin-eosin staining, followed by immunohistochemical evaluation for fas, fas-ligand, Bcl-2, bax, galectin-3 and STAT-3 expressions in malignant lymphoid cells. For each patient, pre- and post-treatment images of the lesions were taken with a digital camera. Pre- and post-treatment data regarding clinical resolution and apoptosis were compared in and between both groups. Tissue samples were evaluated macroscopically and placed in a tissue processing system. Tissue samples were incubated in formaldehyde at 37 °C for 2 hours followed by embedding in alcohol solutions with increasing concentrations for 1 hour each. After 4.5 hours of incubation in xylol and 3 hours in paraffin, the samples were taken from the device and paraffin blocks were prepared. The blocks were refrigerated for 30 minutes before the preparation of 5 micrometer-thin sections on microscope slides containing poly-L-lysine adhesive. The sections were incubated for 1 hour in an oven at 60 °C, processed with consequent xylol and alcohol solutions with decreasing concentrations, and finally rinsed with distilled water. Sections were then boiled for 20 minutes in 10% citrate buffer solution. In order to minimize non-specific staining and background noise, all preparations were treated with 3% H_2O_2 for 10 minutes and washed with buffered saline solution for 10 minutes. Ready-to-use antibodies against fas, fas-ligand, bax, Bcl-2, galectin-3 and STAT-3 were used as primary antibodies. Immunohistochemical staining was performed. The slides were treated with increasing concentrations of alcohol solutions, embedded in xylol and closed with a sealing solution. Intestinal tissue, prostatic tissue, Hodgkin lymphoma specimens, tonsillar tissue, thyroid tissue and breast cancer specimens were used as positive controls for fas, fas-ligand, bax, Bcl-2, galectin-3 and STAT-3 expression studies, respectively. Tissue preparations were examined under a light microscope. Immunohistochemically, cytoplasmic staining of keratinocytes and lymphocytes for bax and Bcl-2 was considered positive Unstained cells were deemed negative (Figure 1, 2, 3). For Bcl-2 and bax assessment, all microscopic fields were examined for pre- and post-treatment specimens. A total of 10 positively stained fields were examined under low power magnification and scored according to the average positively stained cell numbers as: score 0% (-), 1-25% (+), 26-50% (++), 51-100% (+++). Staining intensities of lymphocytes

were classified as no staining, weak, moderate and intense. Presence of epidermal lymphocytes before and after treatment was evaluated as no epidermal lymphocyte, few and present.

Statistical Analysis

Chi-square and Mann-Whitney U tests were used to compare age, sex, and disease duration. Fas, fas-ligand, bax, Bcl-2, STAT-3 and galectin-3 staining intensities before and after treatment were compared with Wilcoxon signed-rank test. Mann-Whitney U test was used to compare the staining intensities of narrow-band UVB only and isotretinoin + narrow-band UVB treatment groups. In both treatment groups, intragroup pre- and post-treatment symptom severity and lesion size comparisons were performed using Wilcoxon signed-ranks test. Values of $p<0.05$ were considered statistically significant.

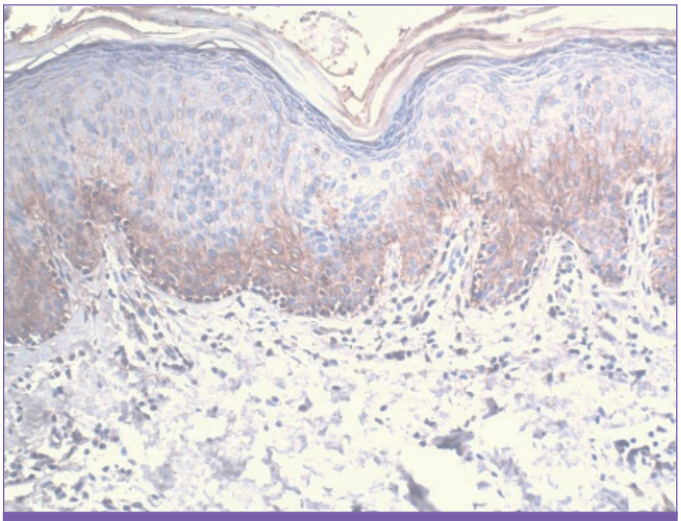

Figure 1. Positive cytoplasmic fas staining (immunoperoxidase x100)

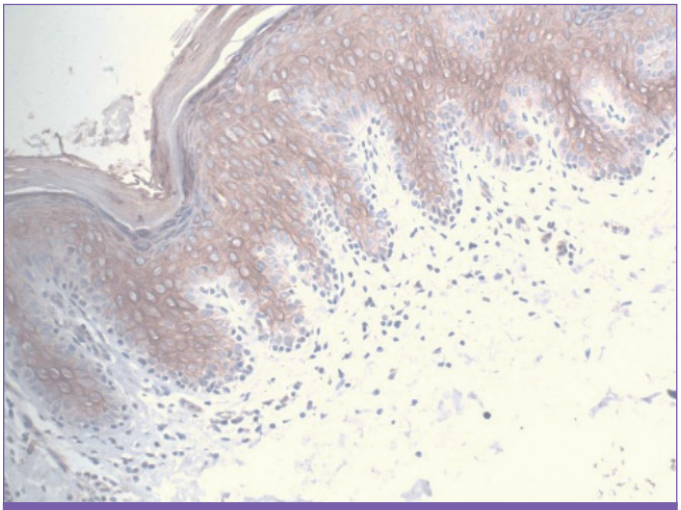

Figure 2. Positive cytoplasmic fas-ligand staining (immunoperoxidase x100)

Results

In our study, 10 patients received narrow-band UVB alone and eleven patients received narrow-band UVB + isotretinoin combination treatment. Nine (42.9%) of the patients were female and 12 (57.1%) were male. Mean age was 48.33±12.39 years in all patients, 50.00±12.15 years in the narrow-band UVB only group, and 46.81±12.99 years in the narrow-band UVB + isotretinoin group. There was no statistically significant difference between the groups in terms of gender and age ($p=0.130$, $p=0.672$, respectively), (Table 1). Mean disease duration was 8.89±7.28 years in the first group and 4.60±3.93 years in the second group ($p=0.216$). Eight of the patients were in stage 1A, 9 in stage 1B, and 4 in stage 2A. Six of the stage IA patients had narrow-band UVB only and 2 of them had narrow-band UVB + isotretinoin, 2 of the stage 1B patients had narrow-band UVB only and 7 had narrow-band UVB + isotretinoin, and 2 of stage 2A patients had narrow-band UVB only and 2 received narrow-band UVB + isotretinoin treatment. Pre and post-treatment symptom severity scores were 12.50±6.16 and 5.40±4.97 in the narrow-band UVB only group and 16.90±4.50 and 5.18±4.42 in the narrow-band UVB + isotretinoin combination group, respectively. In both groups, the differences between pre- and post-treatment symptom severity scores were statistically significant ($p<0.009$ in narrow-band UVB only group and $p<0.003$ in narrow-band UVB + isotretinoin combination group). Overall, pre-treatment symptom severity was high and there was a significant decrease after treatment ($p=0.09$) (Table 2). In the first group, pre- and post-treatment lesion sizes were 10.80±6.01 and 6.70±6.54, while in the second group they were measured to be 14.63±2.54 and 7.90±6.04 (Table 3). The pre-treatment lesions in both groups were large, but there was a significant decrease in lesion sizes after the treatment. No significant difference was detected when pre-treatment lesion

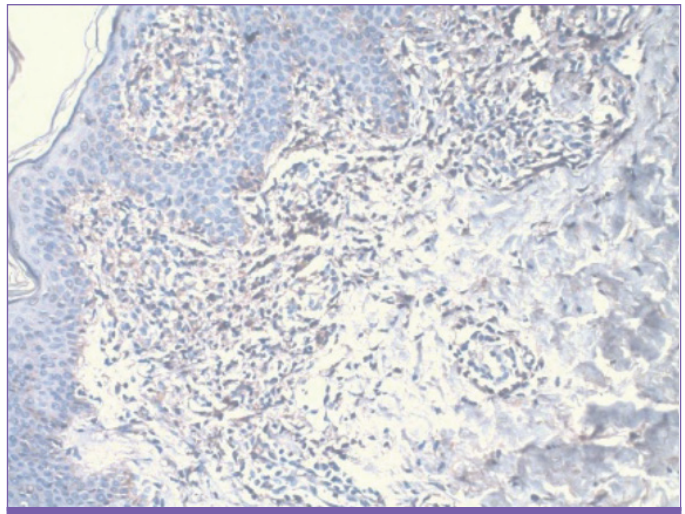

Figure 3. Positive nuclear + cytoplasmic STAT-3 staining (immunoperoxidase x100)

sizes and post-treatment lesion sizes were separately compared between the two treatment groups (p=0.20 for pre-treatment sizes, p=0.43 for post-treatment sizes). Clinical response to treatment was significantly earlier in the narrow-band UVB + isotretinoin combination group than the narrow-band UVB only group, and the results were statistically significant. In the narrow-band UVB only group, the difference between the of Bcl-2 epidermal staining intensities obtained from pre- and post-treatment biopsy samples were statistically significant (p=0.04). However in the same group, pre- and post-treatment samples revealed similar results regarding Bcl-2 epidermal staining diffuseness, epidermal lymphocyte staining intensities and diffuseness and presence of epidermal lymphocytes (p>0.05). In addition, again in the same group, pre-treatment and post-treatment epidermal staining intensities and diffuseness for fas, fas-ligand, bax, STAT-3 and galectin-3, as well as epidermal lymphocyte staining intensities and diffusiveness and presence of epidermal lymphocytes were not significantly different. In the narrow-band UVB + isotretinoin group, on the other hand, the intensity and diffuseness of epidermal staining for fas, fas-ligand, bax, Bcl-2, STAT-3 and galectin-3, the staining intensities and extent of epidermal lymphocytes and the presence of epidermal lymphocytes were not significantly different between the pre-treatment and post-treatment samples. Overall epidermal staining intensities and diffuseness for fas, fas-ligand, Bcl-2, STAT-3 and galectin-3, epidermal lymphocyte staining intensities and diffuseness, and presence of epidermal lymphocytes did not show significant differences between the pre-and post-treatment samples (p>0.05). No positive staining for bax protein was detected (Table 4).

Discussion

Mycosis fungoides is a cutaneous T-cell lymphoma characterized by varying degrees of atypical lymphocyte infiltration in the papillary dermis. Phototherapy is accepted as an effective treatment approach for mycosis fungoides in that it exerts a suppressive effect against T-lymphocytes and Langerhans cells. Although narrow-band UVB phototherapy is frequently used especially in the treatment of early stage mycosis fungoides, in our study it did not result in significant changes in apoptotic markers. This may be due to the fact that apoptosis is not yet a prominent process in the early stage of the disease. In advanced stages of mycosis fungoides, other systemic treatment alternatives may be combined with phototherapy. There are many alternative drugs such as isotretinoin, bexarotene and vorinostat. Retinoids are vitamin A derivatives that regulate cell proliferation, differentiation and apoptosis. Isotretinoin, one of the first retinoids, was observed to show its clinical effects earlier when combined with narrow-band UVB, rather than being used alone. However, there was no difference between pre-treatment and post-treatment results in our narrow-band UVB only and isotretinoin +

Table 1. Comparison of patient and control groups

	Patient group	Narrow-band UVB	Narrow-band UVB + isotretinoin	p
Number of patients	21	10	11	0.827
Male female	12/9	4/6	8/3	0.130
Age (years)	48.33±12.39	50.00±12.15	46.81±12.99	0.672

UVB: Ultraviolet B

Table 2. Comparison of symptom severity before and after treatment between groups

	Symptom severity Mean±SD		p
	Before treatment	After treatment	
Narrow-band UVB	12.50±6.16	5.40±4.97	0.009
Narrow-band UVB + isotretinoin	16.90±4.50	5.18±4.42	0.003
p	0.09	0.91	

UVB: Ultraviolet B, SD: Standard deviation

Table 3. Comparison of lesion size before and after treatment between groups

	Lesion size Mean±SD		p
	Before treatment	After treatment	
Narrow-band UVB	10.80±6.01	6.70±6.54	0.007
Narrow-band UVB + isotretinoin	14.63±2.54	7.90±6.04	0.012
p	0.20	0.43	

UVB: Ultraviolet B, SD: Standard deviation

Table 4. Before and after treatment; comparison of fas, fas-ligand, Bcl-2, STAT-3, galectin-3

	Narrow-band UVB		p	Isotretinoin + narrow-band UVB		p
	Pre-treatment Med. (min.-max.)	After treatment Med. (min.-max.)		Pre-treatment Med. (min.-max.)	After treatment Med. (min.-max.)	
Fas epidermal severity	2.2 (1-2)	2.2 (1- 3)	0.99	2.0 (1-3)	2.4 (1-3)	0.23
Fas epidermal diffuseness	2.1 (1-3)	2.0 (1-3)	0.74	2.1 (1-3)	2.0 (1-3)	0.58
Fas lymphocyte severity	2.2 (1-3)	2.1 (1-3)	0.76	2.4 (1-3)	2.2 (1-3)	0.52
Fas lymphocyte diffuseness	2.4 (1-3)	2.0 (1-3)	0.34	2.3 (1-3)	1.9 (1-3)	0.09
Fas number of epidermal lymphocytes	1.0 (1-1)	0.9 (0-2)	0.70	1.0 (2-2)	1.0 (0-2)	0.99
Fas ligand epidermal severity	2.7 (3-3)	2.7 (1-3)	0.99	2.6 (2-3)	2.7 (2-3)	0.65
Fas ligand epidermal diffuseness	3.0 (3-3)	3.0 (3-3)	0.99	3.0 (3-3)	3.0 (3-3)	0.99
Fas ligand lymphocyte severity	1.7 (1-3)	1.5 (0-3)	0.48	1.4 (1-2)	1.6 (0-3)	0.41
Fas ligand lymphocyte diffuseness	2.0 (1-3)	1.5 (0-3)	0.09	1.8 (1-3)	1.5 (0-3)	0.58
Fas ligand number of epidermal lymphocytes	0.6 (0-1)	0.2 (0-2)	0.19	0.5 (0-1)	0.3 (0-1)	0.48
Bcl-2 epidermal severity	0.1 (0-1)	0.5 (0-1)	0.04	0.5 (0-2)	0.4 (0-1)	0.56
Bcl-2 epidermal diffuseness	0.2 (0-2)	1.0 (0-3)	0.06	0.9 (0-3)	0.6 (0-2)	0.25
Bcl-2 lymphocyte severity	0.5 (0-2)	0.4 (0-2)	0.70	1.09 (0-2)	0.4 (0-1)	0.08
Bcl-2 lymphocyte diffuseness	0.5 (0-2)	0.6 (0-2)	0.70	1.1 (0-3)	0.5 (0-2)	0.14
Bcl-2 number of epidermal lymphocytes	1 (1-1)	0.8 (0-1)	0.15	1 (1-1)	0.8 (0-2)	0.41
STAT-3 epidermal severity	1.5 (0-3)	1.7 (1-3)	0.48	1.8 (0-3)	1.8 (1-3)	0.99
STAT-3 epidermal diffuseness	1.8 (0-3)	1.9 (1-3)	0.73	2.3 (0-3)	2.0 (1-3)	0.31
STAT-3 lymphocyte severity	1.4 (0-3)	0.8 (0-3)	0.16	1.0 (0-3)	1.2 (0-2)	0.62
STAT-3 lymphocyte diffuseness	1.7 (0-3)	1.1 (0-3)	0.19	1.3 (0-3)	1.3 (0-2)	0.90
STAT-3 number of epidermal lymphocytes	1.0 (1-1)	1.0 (1-1)	0.99	1.0 (0-2)	0.8 (0-2)	0.31
Galectin-3 epidermal severity	1.1 (0-3)	1.6 (0-3)	0.157	1.0 (0-2)	1.7 (0-3)	0.142
Galectin-3 epidermal diffuseness	1.1 (0-3)	1.4 (0-3)	0.180	1.2 (0-3)	1.5 (0-3)	0.417
Galectin-3 lymphocyte severity	0.6 (0-3)	0.1 (0-1)	0.180	0 (0-0)	0 (0-0)	0.99
Galectin-3 lymphocyte diffuseness	0.6 (0-3)	0.1 (0-1)	0.180	0 (0-0)	0 (0-0)	0.99
Galectin-3 number of epidermal lymphocytes	0.8 (0-1)	0.9 (0-1)	0.317	0.9 (0-1)	0.9 (0-1)	0.99

Med.: Median, min.: Minimum, max.: Maximum, UVB: Ultraviolet B

narrow-band UVB groups (p=0.005). Fas is an apoptosis-associated protein of lymphoid cells, and in mycosis fungoides, its expression decreases as the disease stage progresses. Narrow-band UV increases the expression of fas/fas-ligand, which has a strong inducing effect for apoptosis [15]. Fas-directed apoptosis is inhibited by the antiapoptotic Bcl-2 protein. The presence of Bcl-2 expression leads to resistance development to apoptosis and is a negative prognostic factor. Our patients did not show a prominent Bcl-2 expression was observed in patients, and a number of previous studies have shown that Bcl-2 expression is decreased in these patients [16], implying that Bcl-2 function is not pronounced in early-stage patients. Proapoptotic bax protein induces apoptosis by increasing the production of fas and suppressing Bcl-2. Although increased bax expression following ultraviolet exposure and its role in intracellular signaling pathways in the pathogenesis of mycosis fungoides are well-established, bax levels were not found to be significant in our study [17]. STAT-3 activation was observed in malignant cells obtained from the skin and blood of patients with cutaneous T-cell lymphoma. STAT-3 positivity is rarely seen in early-stage mycosis fungoides lesions because most lymphocytes in this stage are inflammatory rather than neoplastic. We found that both cutaneous T-cell lymphoma patients and the control group showed positive keratinocyte staining for STAT-3 in the keratinocytes, revealing no significant difference between the patients and the control group [18].

STAT-3 positivity is an indicator of progression to advanced stages and this protein is one of the potential molecules that can be targeted in novel treatment strategies for patients in this stage.

In our study, STAT-3 expression levels were similar between pre- and post-treatment samples in both groups, and between the two treatments groups. This may be attributable to the fact that STAT-3 expression is mostly observed in advanced stage patients and is not specific for malignant cells since STAT-3 is also present in proliferating keratinocytes. Galectin-3 is a lectin-binding beta-galactosidase and its expression is increased in various neoplastic cell types. It is functionally involved in epithelial cell proliferation, malignant transformation and metastasis. Galectin-3 expressing cells show resistance to apoptosis [19]. In our study, the median post-treatment galectin-3 staining levels were increased when compared to pre-treatment levels in both groups, the differences being statistically insignificant. This was thought to be due to the variations in cell surface glycosylation between individuals.

Study Limitations

Difficulty in immunohistochemical detection of the apoptotic markers due to their short half-life, different skin types, inter-person variability in retinoid receptor expressions, functional polymorphisms in retinoid metabolism.

Conclusion

According to our findings, narrow-band UVB + isotretinoin combination has no superiority to narrow-band UVB only treatment in terms of both clinical improvement and induction of apoptosis. However, recovery started earlier in the isotretinoin + narrow-band UVB group. The results we obtained with our study revealed important issues that may establish a ground for further studies.

Ethics

Ethics Committee Approval: The study was Dermatology and Pathology Departments of the Faculty of Medicine and approved by the Scientific Research Project Commission of the University (project no: TT-06-34, Ethics Committee approval no: 01/181).

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Data Collection or Processing: N.T., A.F.K., Analysis or Interpretation: A.F.K., Ö.C., Literature Search: N.T., Writing: N.T.

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

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The Comparison of Blood Lipid Profile in Patients with and Without Androgenetic Alopecia

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ABSTRACT

Background: Androgenetic alopecia (AGA) is the most common cause of hair loss in both sexes. In several studies investigating the relationship between AGA and dyslipidemia, conflicting results have been reported. In this study, we aimed to compare serum triglyceride (TG) and high-density lipoprotein (HDL) cholesterol levels that one of the criteria of metabolic syndrome in male patients with and without AGA.

Materials and Methods: The study group was consisted of 40 patients who had 2 and higher AGA. The control group was consisted of 40 patients aged who had no AGA at the clinical examination or who had stage 1 AGA. Fasting serum TG and HDL cholesterol levels were compared between study and control groups.

Results: The mean serum TG values in the study group were 89.60; the mean serum TG values in the control group were 85.40. There was no statistical difference in serum TG values between the two groups ($p<0.005$). The number of patients with serum TG value ≥150 mg/dL was 5 (12.5%) in the study group and 3 (7.5%) in the control group; however, this difference was not statistically significant too ($p<0.005$). Mean serum HDL cholesterol levels in the study group were 52.67; the mean serum HDL cholesterol values in the control group were 52.62. There was no significant difference in serum HDL cholesterol levels between the two groups ($p<0.005$). The number of patients with serum HDL cholesterol <40 mg/dL was 4 (10%) in the patient group and 1 (2.5%) in the control group; however, this difference was not statistically significant too ($p<0.005$).

Conclusion: There was no significant difference between serum TG and HDL cholesterol levels in male patients with or without AGA.

Keywords: Androgenetic alopecia, Dyslipidemia, Triglyceride, High-density lipoprotein cholesterol

Introduction

As the name suggests, androgenetic alopecia (AGA) is a hair loss with a specific clinical pattern, characterized by follicular miniaturization, which occurs due to systemic androgens and genetic factors. The most common cause of hair loss in both genders is AGA. Prevalence differs according to ethnic groups. It is more common and more severe in white men than in Asian and black men. The incidence increases with age. According to Hamilton's study, the prevalence is 30% in men at the age of 30, and 50% in the age of 50. Generally, the age of onset is the 3rd and 4th decade, but hair loss can begin immediately after puberty and continues progressively. The phenotypes seen in men and women are different. In women, a diffuse dilution is observed while maintaining the frontal hairline. In men, the hairline is drawn backwards from the bitemporal regions and baldness appears in the vertex. Although clinical manifestations are different in both sexes, their pathogenesis is the same [1]. Although environmental factors on the severity of AGA cannot be revealed clearly, there are studies showing that it is more severe in overweight and simultaneous smokers [2]. At the same time, it was shown that both genders had more severe hair loss in

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patients with a family history and the disease started at an earlier age in male patients with a family history [3].

Although AGA is only a cosmetic problem, many studies have found the relationship between AGA and risk factors for cardiovascular disease or cardiovascular disease. In these patients, comorbidities such as hypertension, overweight, abnormal lipids, insulin resistance, carotid atheromatosis, and diabetes have been reported or increased risks of death from heart disease [4]. Metabolic syndrome is a combination of metabolic risk factors that pose a risk for type 2 diabetes and cardiovascular diseases. According to ATP 3 criteria, having at least three of the following 5 features is defined as metabolic syndrome [5]:

1. Abdominal obesity (waist circumference ≥102 cm in men, waist circumference ≥88 cm in women),

2. Serum triglyceride (TG) level ≥150 mg/dL or current drug use due to increased TG,

3. Serum high-density lipoprotein (HDL) cholesterol level <40 mg/dL in men, <50 mg/dL in women,

4. Blood pressure ≥130/85 mmHg or current drug use for hypertension,

5. Fasting blood sugar ≥100 mg/dL.

Various studies have investigated the possible relationship between AGA and metabolic syndrome. However, the relationship between AGA and the components of the metabolic syndrome has not been clearly established, as the results in the studies are contradictory. Many studies have been published examining the relationship between AGA and dyslipidemia, one of the criteria of metabolic syndrome. Some studies found a significant relationship, while others did not. Therefore, the relationship between AGA and dyslipidemia is still controversial. Our aim in this study is to reveal the relationship between AGA and dyslipidemia.

Material and Methods

This prospective study included male individuals between the ages of 18-30 who applied to the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Skin and Venereal Diseases outpatient clinic between December 1, 2017 and June 1, 2018. The study were approved by the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine of Local Ethics Committee (protocol number: A-14, date: 02.01.2018).

Forty patients with stage 2 and higher AGA according to Hamilton-Norwood scale in the clinical examination, as a patient group; 40 patients, without AGA on clinical examination or with the most stage 1 AGA according to the Hamilton-Norwood scale were accepted as the control group. Hamilton-Norwood stages of the patients were determined by clinical examination:

Type 1: There is no hairline retraction or minimal retraction in the frontotemporal region.

Type 2: The frontotemporal region hairline shows symmetrical and triangular retraction, although it is less common in the middle of the frontal region.

Type 3: This stage is the period when the presence of baldness becomes evident. There is symmetrical deep frontotemporal retraction.

Type 4: There is severe frontal and frontotemporal hair loss. Significant dilution is seen in the vertex. These two areas are separated along the hill with a thick headband.

Type 5: It is seen that the headband specified in type 4 becomes thinner. The hairless areas in the vertex and frontotemporal have increased.

Type 6: Regions expressed as hair bands have also been shed and the two regions merge.

Type 7: It is the most severe form. Only a narrow band of hair in a horseshoe shape remains on the sides and back of the scalp. This hair is usually not dense and may be quite fine.

Pull test was evaluated in patients with hair loss. For the pull test, approximately 50-100 hairs were held between the thumb and forefinger and gently pulled from the proximal to the distal. Easy removal of more than 6 hairs during this pull process has been interpreted as positive. In addition, body mass indexes (BMI), concomitant diseases of all patients, whether there is male-type shedding in the first degree relative are recorded in the files. Verbal and written consent was obtained from all participants by informing all patients about the purpose and method of the study. Fasting serum TG and HDL cholesterol values were studied in the blood taken from the patients participating in the study. The reference values are 150 mg/dL for TG and 40 mg/dL for HDL cholesterol. TG and HDL values were compared between these two groups and according to reference intervals.

Exclusion criteria from the study:

- Patient group outside the 18-30 age range,
- Patients with a different hair disease other than AGA,
- Those with systemic disease,
- Patients receiving medical treatment for dyslipidemia,
- Those with familiar lipid disease in the family,
- Patients who use drugs that can affect their blood fat,
- Patients with a BMI of 30 and above (obese).

Statistical Analysis

Descriptive statistical evaluations of all variables in the study were made by calculating the mean and standard deviation values.

Mann-Whitney U test was used to compare two independent groups, McNemar test was used to compare dependent groups, and Pearson chi-square analysis was used to analyze categorical data. All statistical analyzes were done with Statistical Package for the Social Science 21st edition (SPSS-21) program. In statistical decisions, $p<0.05$ level was accepted as an indicator of significant difference.

Results

The study included 40 patients in the patient group and 40 patients in the control group. The average age of the patient group is 23.12 and the average age of the control group is 21.95. There is no statistical difference between the two groups in terms of age distribution ($p<0.005$).

According to the Hamilton-Norwood classification, 33 patients (82.5%) were in stage 2, 5 patients (12.5%) in stage 3, 1 patient (2.5%) in stage 4, 1 patient (2.5%) in stage 6. 'dr. While 28 patients (70%) did not have AGA in the control group, the number of patients with stage 1 was 12 (30%).

Fourteen people (35%) in the patient group and 12 people (30%) in the control group reported having AGA in their first degree relatives. There was no statistical difference between the two groups in terms of family history ($p<0.005$).

While 24 (60%) patients in the patient group did not have any additional dermatological diseases other than hair loss, acne vulgaris in 7 patients (17.5%), seborrhea in 2 patients (5%), seborrheic eczema in 5 patients (12.5%), milium in 1 patient (12.5%) and folliculitis in 1 patient (12.5%). While 18 (45%) patients in the control group did not have any additional dermatological diseases, 12 patients (30%) had acne vulgaris, 6 patients (15%) had seborrheic eczema, 2 patients (%5) had tinea pedis, 1 patient (2.5%) had folliculitis and 1 patient (2.5%) had tinea versicolor. The most common comorbidity in both groups is acne vulgaris.

The average BMI of the patient group was 23.78. The average BMI of the control group is 23.60. There is no statistical difference between the two groups in terms of BMI ($p<0.005$).

The mean of serum TG values in the patient group was 89.60. The mean of serum triglyceride values in the control group is 85.40. There was no statistical difference between the two groups in terms of serum TG values ($p<0.005$). The number of people with serum TG value ≥150 mg/dL is 5 (12.5%) in the patient group and 3 (7.5%) in the control group; however, this difference was not statistically significant ($p<0.005$).

The average of serum HDL cholesterol values in the patient group was 52.67; the average of serum HDL cholesterol values in the control group is 52.62. There was no significant difference between serum HDL cholesterol values between both groups ($p<0.005$). The number of people with serum HDL cholesterol value <40 mg/dL is 4 (10%) in the patient group and 1 (2.5%) in the control group; however, this difference was not statistically significant ($p<0.005$).

Since the number of patients with different AGA severity was not sufficient for each stage according to the Hamilton-Norwood classification in the patient group, the relationship between AGA severity and TG and HDL cholesterol values could not be evaluated.

In the patient group, the number of patients with positive pull test was 16 (40%) and the number of patients with negative pull test was 24 (60%). TG and HDL cholesterol values were compared between positive and negative patients with pull test, but no relation was found ($p<0.005$) (Table 1).

Discussion

The pathophysiology of the relationship between AGA and dyslipidemia has not been clearly established. One of the most likely mechanisms to explain this relationship is altered peripheral sensitivity to androgens. Testosterone is converted to dihydrotestesterone with 5 alpha reductase enzymes in peripheral tissues and DHT has 5 times more affinity than androgen receptors. Five alpha reductase enzymes and androgen receptors are found in the arterial wall, blood vessels and adipose tissue. It has been suggested that increased sensitivity to androgens will be responsible for symptoms of AGA and metabolic syndrome. However, more research is needed on this subject. The second factor to explain the link between AGA and dyslipidemia is chronic microinflammation. Perifollicular inflammatory infiltration observed in the course of AGA may be a local reflection of systemic inflammation leading to the development of metabolic syndrome. Proinflammatory cytokines make serum lipid disorders by making changes in cholesterol transport and apolipoproteins [6].

In the metaanalysis published by Kim et al. [4] by analyzing 19 studies related to AGA and dyslipidemia, they stated that serum total cholesterol, TG and low-density lipoprotein (LDL) cholesterol levels were higher in AGA groups compared to control groups, and HDL cholesterol values were lower in AGA groups compared to control groups. These results indicate that AGA patients have a more atherogenic lipid profile and may partially explain the increased cardiovascular disease risk relationship in AGA patients. When subgroup analysis was performed by sex, higher total cholesterol, TG and LDL cholesterol levels were found in male patients and lower HDL levels were found in female patients compared to the control groups. However, the number of studies with women is very low and more studies are needed to evaluate the difference between genders.

The increased sensitivity of the scalp to androgens is part of the pathophysiology of AGA. Androgens affect the risk factors (hyperinsulinemia, glucose intolerance, high TG and low HDL

Table 1. Demographic, clinical and laboratory data of patients

	Patients (40)		Control (40)	
AGA severity according to Hamilton-Norwood classification	Stage 2	33 (82.5%)	Stage 1	12 (30%)
	Stage 3	5 (12.5%)	No AGA	28 (70%)
	Stage 4	1 (2.5%)		
	Stage 6	1 (2.5%)		
Age (years) (average)	23.12		21.95	
BMI (kg/m^2) (average)	23.78		23.60	
Family story	14 (35%)		12 (30%)	
Concomitant dermatological diseases	7 (17.5%)	Acne vulgaris	12 (30%)	Acne vulgaris
	2 (5%)	Seborrhea	6 (15%)	Seborrheic eczema
	5 (12.5%)	Seborrheic eczema	2 (5%)	Tinea pedis
	1 (2.5%)	Milium	1 (2.5%)	Folliculitis
	1 (2.5%)	Folliculitis	1 (2.5%)	Tinea versicolor
	24 (60%)	No additional diseases	18 (45%)	No additional diseases
TG value mg/dL (average)	89.60		85.40	
Number of patients with TG value ≥150 mg/dL	5 (12.5%)		3 (7.5%)	
HDL cholesterol value mg/dL (mean)	52.67		52.62	
Number of patients with HDL value <40 mg/dL	4 (10%)		1 (2.5%)	

AGA: Androgenetic alopecia, BMI: Body mass index, TG: Triglyceride, HDL: High-density lipoprotein

cholesterol values, hypertension and obesity) determined for coronary heart disease. The epidemiological relationship between AGA and coronary heart diseases is assumed to be based on these risks. While some studies support this relationship, some studies do not. Giltay et al. [7] followed 81 transsexual patients who switched from female to male, using testosterone esters in this process. In 38.3%, AGA developed, but they did not notice a difference in their blood fat or weight. In our study, to support this study, no difference was found between the patient and control groups between TG and HDL cholesterol values and BMI.

Epidemiological studies show that male patients with AGA have higher insulin resistance and coronary heart disease. Insulin resistance has an additional pathogenetic role in hair follicle maturation. Vasoactive substances released due to endothelial dysfunction in insulin resistance cause perifollicular vasoconstriction and proliferation in smooth muscle cells in the vascular wall. As a result, microvascular circulation is impaired, local tissue hypoxia occurs, and a progressive miniaturization is observed in the hair follicles.

Mumcuoglu et al. [8] conducted a study evaluating the insulin resistance and presence of metabolic syndrome in male patients with early-onset AGA (at least stage 3 according to the Hamilton-Norwood scale) compared to the control group. According to the results of this study, no difference was observed in fasting glucose, insulin, TG, HDL cholesterol and oral glucose tolerance tests between the two groups. However, HOMA and FIRI indices showing insulin resistance in AGA group are higher than control group. In addition, diastolic blood pressure and total cholesterol levels were higher in the AGA group. Considering the metabolic syndrome criteria, there is no difference between the two groups. In our study, we compared TG and HDL levels, one of the criteria of metabolic syndrome, between patients with and without AGA. As in this study, we did not include obese patients (patients with a BMI above 30) in our study to eliminate the weight factor, which can affect blood fat. In addition, the age ranges of the patient and control groups are the same with this study. In our study, the difference between the blood fats between the two groups supports this study. However, in our study, 33 patients (82.5%) were stage 2, 5 patients (12.5%) were stage 3, 1 patient (2.5%) was stage 4, 1 patient (2.5%) was stage 6. In other words, the number of patients included in the early-onset AGA classification is only 7 (17.5%). Since the number of patients with different AGA severity in the patient group was not sufficient for each stage, we could not evaluate the relationship between AGA severity and TG and HDL cholesterol values.

In a study by Gopinath and Upadya [9], 85 patients diagnosed with early-onset AGA between the ages of 18-55 and 85 male patients without hair loss were compared in terms of metabolic syndrome criteria. Metabolic syndrome was 22.4% in the AGA group and 9.4% in the control group. The frequency of abdominal obesity, hypertension is significantly higher and HDL cholesterol values are lower in patients with AGA compared to the control group. Based

on this study data, researchers stated that screening would be beneficial especially in patients with early-onset AGA in terms of metabolic syndrome.

In another study examining the relationship between metabolic syndrome and AGA, 740 men aged 40-91 years in a community were evaluated for the presence of AGA and metabolic syndrome criteria. There was a significant relationship between the presence of AGA and metabolic syndrome. In addition, those who meet the metabolic syndrome criteria more frequently have a higher risk of AGA. Among the metabolic syndrome criteria, the most important factor associated with AGA was low HDL cholesterol. No relationship was found between other lipid levels and AGA. Considering the relationship between AGA severity and metabolic syndrome, patients with severe AGA (N-H stage 5 and above) are 2.6 times more likely to experience metabolic syndrome than moderate AGA patients (N-H stage 3-4). People with metabolic syndrome have a higher risk of having stage 4 and above AGA than those without metabolic syndrome. An inverse relationship was detected between HDL values and AGA severity. In the light of all these results, it has been said that individuals with moderate and severe AGA (N-H stage 3 and above) have a higher risk of dyslipidemia and metabolic syndrome and screening can be done in this direction [10].

In a study by Chakrabarty et al. [11], it was stated that metabolic syndrome is seen more in those with AGA. However, in this study, no relation was found between AGA severity and metabolic syndrome. This result may indicate that there is no relation, or it may be due to insufficient sample size to define this relation precisely. In the study of Chakrabarty et al. [11], it was reported that those with AGA also had higher TG values, higher blood pressure and lower HDL cholesterol levels. The results in our study do not support this study. However, the number of patients in the patient and control group in our study is very low compared to this study. At the same time, our study was conducted only among individuals applying to the hospital. Therefore, it is possible that our sample set does not represent the whole society.

Although the pathogenetic mechanism of atherosclerosis is well known, the relationship between alopecia and atherosclerosis is not clear. High cholesterol and TG levels are involved in the process, along with other mechanisms that initiate atheromatosis. On the other hand, HDL cholesterol protects the vascular wall from aggressive factors (endothelial adhesion, migration of monocytes, etc.) and provides reverse transport of cholesterol. The relationship between lipid disorders and coronary heart disease in patients with male and female AGA is explained through these mechanisms [12]. In one study, blood lipid levels of 150 patients (80 men and 70 women) aged 35-60 with early onset AGA and 150 control patients (80 men and 70 women) who presented for other skin diseases were compared. In patients with AGA, significantly higher TG values, total cholesterol values, LDL values and lower HDL values were found compared to the control group. In men with AGA, significantly higher TG values, total cholesterol values and LDL values were observed compared to the control group. However, there was no significant difference in HDL values in male patients compared to the control group. The frequency of dyslipidemia was found to be higher in women and men with AGA. No significant relationship was observed between lipid parameters and AGA severity in male and female patients [12].

In a study by Sadighha and Zahed [13], in patients with and without AGA, a significantly higher TG and total cholesterol/HDL-cholesterol ratio was found in men with AGA and HDL values were found to be significantly lower.

According to the Hamilton-Norwood scale, patients with stage 3 vertex or more severe hair loss before age 35 are classified as early-onset AGA. Some authors have suggested that early-onset AGA is genetically different from late-onset. Matilainen et al. [14] conducted a community-based case-control study to assess whether early-onset AGA is a risk factor for early-onset and severe coronary artery disease requiring surgical intervention. In this study, 85 male patients who had undergone coronary surgery in a region with a population of 7200 were included and an age-matched control group was established for each case. Patients were compared in terms of BMI, blood pressures, serum total cholesterol, TG, HDL-cholesterol, glucose levels. It was observed that the rates of dyslipidemia in patients with AGA were higher than the control groups. Patients with early and late-onset AGA were evaluated for having early or late coronary revascularization surgery. Male patients with early-onset AGA were found to have a higher rate of undergoing coronary surgery under the age of 60 than those with late-onset AGA or normal hair. This study supports the hypothesis that early-onset AGA may be an indicator of impaired endothelial function, the main pathogenetic mechanism of atherosclerosis.

Sharma et al. [15] examined the relationships between AGA and coronary heart disease risks, with 100 male patients aged 25-40 years old with Hamilton-Norwood stage 2 and above were compared with the control group. In the group with AGA, significantly higher TG, total cholesterol, LDL cholesterol, VLDL cholesterol and lower HDL cholesterol values were found compared to the control group, and these values were observed to increase with increasing AGA severity (HDL decreased with increasing AGA severity). Similar to this study, we compared male patients with Hamilton-Norwood stage 2 and above with the control group. However, in our study, the age range included younger patients than this study. In our study, we found TG and HDL cholesterol

levels similar between patient and control groups. This may be because patients and controls are at a younger age compared to this study. In our study, we could not evaluate the relationship between AGA severity and TG and HDL cholesterol values since the number of patients with different AGA severity was not sufficient for each stage.

As well as the pathophysiological mechanisms responsible for the relationship between AGA and dyslipidemia, the effect of this relationship on treatment is a matter of curiosity. Statins are drugs that reduce the level of serum cholesterol that acts by inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) enzyme. Statins also have immune regulatory effects by inhibiting major histocompatibility complex class 2 mediated antigen presentation, preventing mast cell activation, stimulating regulatory T cells, and regulating the Th1/Th2 balance. In addition, statins have pleiotropic effects such as improving endothelial function, reducing oxidative stress, inflammation and thrombogenic response [16].

Finasteride, used in the treatment of AGA at a dose of 1 mg/day, is a 5 alpha reductase (type 2) enzyme inhibitor. In a study that examined whether finasteride therapy in AGA reduced dihydrotestesterone levels and improved some metabolic syndrome criteria that may be associated with this condition, 12 early-onset AGA patients who received finasteride therapy for 12 months were followed. As expected in this process, serum dihydrotestesteron levels decreased, serum testosterone, androstenedione levels increased and free testosterone index increased. An increase in serum total cholesterol, HDL and LDL cholesterol was observed initially and these levels remained constant during treatment. There was a significant decrease in HbA1c levels, and a decrease in the limit of insulin resistance, which was evaluated using the constant for plasma glucose disappearance-KITT, was detected [17].

Conclusion

There are many studies in the literature examining the relationship between AGA and dyslipidemia, one of the criteria of metabolic syndrome. While most studies have found a significant relationship, data in some studies do not support this. Therefore, the relationship between AGA and dyslipidemia is still controversial. It is suggested that due to this relationship between AGA and metabolic syndrome, patients have a higher risk of coronary heart disease and type 2 diabetes, and screening for these patients will be beneficial. In our study, unlike most studies in the literature, no relationship was found between the presence of AGA and dyslipidemia. However, more studies with randomized controlled, larger patient series are needed to resolve the debate on this issue.

Ethics

Ethics Committee Approval: The study were approved by the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine of Local Ethics Committee (protocol number: A-14, date: 02.01.2018).

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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Cerrahpasa Experience in Topical Immunotherapy Treatment in Patients with Alopecia Areata, Totalis and Universalis

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ABSTRACT

Background: Alopecia areata is a common hair problem and affects patients psychologically. Although the disease has a wide range of treatments, the responses are variable.

Materials and Methods: We retrospectively analyzed the data of 213 patients who received topical immunotherapy treatment in our clinic between 2014 and 2019.

Results: There was no significant difference in response rates in the two treatment types in women (p=0.120). The total response rate of the patients treated with squaric acid dibutyl ester (SADBE) was 42.9% (30/70) and the total response rate of the patients treated with diphenylcyclopropenone (DPCP) was significantly higher than 19.2% (10/52) (p=0.023). The mean age (9.73 years) of those who received full response from SADBE treatment was significantly lower than the mean age (12.65 year) of those who received full response from DPCP treatment (p=0.003). In all response cases, there was no significant difference between both treatment types and disease duration. Considering all the data, 1 month increase in the disease duration caused 1% worse response to the treatment (Wald=8.97, p=0.003). Considering all the data, 1 month increase in the treatment period caused 1.04% better response to the treatment (Wald=9.79, p=0.002). Those with a pre-treatment loss of less than 25% were found to be 7.5 times better than those with a pre-treatment loss of 100% (Wald=19.37 p<0.001). Considering all the data, the patients who received SADBE treatment received 2 times better response to treatment than those who received DPCP treatment (Wald=8.875, p=0.003).

Conclusion: In conclusion, we think that topical immunotherapy is an important form of treatment in alopecia areata and more studies are needed.

Keywords: Alopecia areata, Alopecia totalis, Alopecia universalis, Immunotherapy

Introduction

Alopecia areata is characterized by acute-onset, sharply limited alopecic plaques [1]. In severely affected individuals, alopecia areata can progress to include all scalp hair (alopecia totalis) or all scalp and body hair (alopecia universalis) [2]. Alopecia areata affects approximately 2% of the population [3]. Among the US population, the cumulative lifetime incidence of alopecia areata is estimated at 2% [4]. The pathomechanism remains unknown [5]. The management of alopecia areata involves both addressing the psychologic needs of the patient and offering treatment to patients who desire intervention. A variety of topical, intralesional, and systemic agents, as well as devices, have been used for alopecia areata, but the response to treatment varies widely. Topical immunotherapy is probably the most effective treatment for patients with extensive or recurrent scalp

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involvement [6,7]. A potent contact allergen is applied weekly to the scalp to precipitate hair regrowth [8,9]. The reason for this response remains unknown, but an immunomodulatory effect on the inflammatory infiltrate surrounding affected hair follicles is thought to play a role. Theories for the mechanism of action have focused on the inhibition of the pathologic immune response via antigenic competition [10] the induction of lymphocyte apoptosis [11], or an effect on the type or function of lymphocytes in the inflammatory infiltrate [12,13,14].

Materials and Methods

In our study, we aimed to investigate the effectiveness of topical immunotherapy agents used in the treatment of patients with alopecia areata, totalis, and universalis, or the factors affecting the response received with these treatment methods. We analyzed the data of patients with alopecia areata, totalis and universalis who received topical immunotherapy between 2014-2019 retrospectively. We examined the data of a total of 213 patients. All patients' age, gender, disease duration, duration of treatment, percentage of hair loss before and after treatment, presence of nail involvement, and type of treatment findings were recorded.

Statistical Analysis

Statistical analysis part was done using SPSS version 21. Normalities of continuous variables were evaluated with Kolmogorov-Smirnov and Q-Q plots. Binary comparisons were made by using the chi-square in categorical variables and Fisher's exact test according to the location, and the t-test in independent groups and the Mann-Whitney U test according to their normalities in continuous variables. Relationship in multi-eyed categorical variables was examined using Cramer's V test. During the examination of the treatment response with univariate analyzes, the chi-square test was used. Spearman correlation test was used to determine the variables that were correlated in continuous variables. In the multivariate analysis, independent predictors in predicting the outcome of the treatment using possible factors identified in previous analyzes were examined using ordinal regression analysis. Necessary tests were examined for model fit. P value under 0.05 was considered significant.

Results

We examined the data of a total of 213 patients. Of these 213 patients, 91 were male and 122 were female. The median age of the patients was 10.9 years. The mean disease duration of the patients was 3.6 years. The mean treatment period of the patients was 1.38 years. We detected the loss of pre-treatment (40.8% of the patients) as the 100% hair loss. Of 213 patients, 117 (54.9%) had nail changes prior to treatment. Out of 213 patients, 125 were treated with squaric acid dibutyl ester (SADBE) and 88 were treated with diphenylcyclopropenone (DPCP). There was no significant difference in response rates in the two treatment types in women (p=0.120). The total response rate of the patients treated with SADBE was 42.9% (30/70) and the total response rate of the patients treated with DPCP was significantly higher than 19.2% (10/52) (p=0.023). The mean age (9.73 years) of those who received full response from SADBE treatment was significantly lower than the mean age (12.65 year) of those who received full response from DPCP treatment (p=0.003). In all response cases, there was no significant difference between both treatment types and disease duration. Considering all the data, 1 month increase in the disease duration caused 1% worse response to the treatment (Wald=8.97, p=0.003). Considering all the data, 1 month increase in the treatment period caused 1.04% better response to the treatment (Wald=9.79, p=0.002). Those with a pre-treatment loss of less than 25% were found to be 7.5 times better than those with a pre-treatment loss of 100% (Wald=19.37, p<0.001). Considering all the data, the patients who received SADBE treatment received 2 times better response to treatment than those who received DPCP treatment (Wald=8.875, p=0.003) (Figure 1, 2, 3, and 4).

Discussion

The purpose of treatment in alopecia areata involves both addressing the psychological needs of the patient and offering treatment to patients seeking intervention. In our clinic, we apply

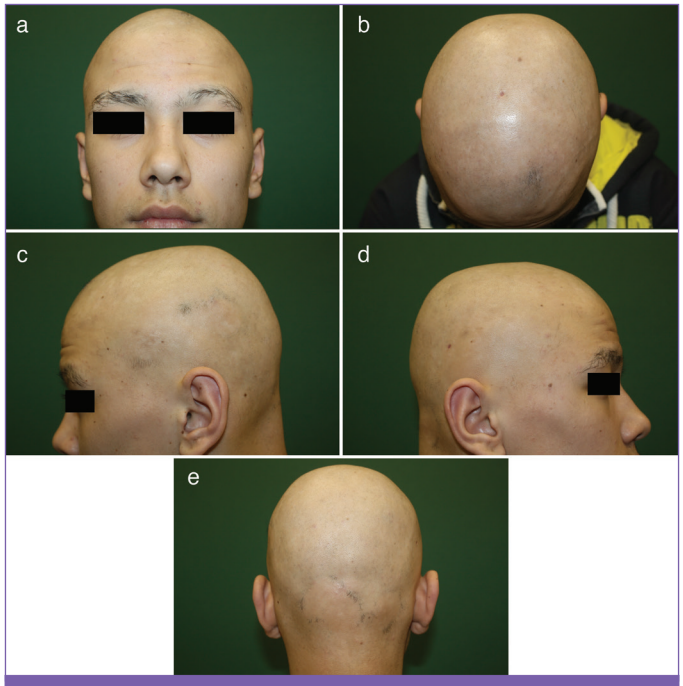

Figure 1. Before the squaric acid dibutyl ester treatment

topical immunotherapy for patients who need treatment and who have extensive or recurrent scalp involvement.

Randomized trials evaluating topical immunotherapy are lacking, and uncontrolled studies have found variable rates of response. A systematic review and meta-analysis of studies evaluating contact immunotherapy with DPCP or SADBE for patchy alopecia areata, alopecia totalis, and/or alopecia universalis found an overall rate of complete (90 to 100 percent) hair regrowth of 32.3 percent [95% confidence interval (CI): 25.3-40.2]. Patients with patchy alopecia areata had better response rates than patients with either alopecia totalis or universalis (25 versus 43 percent for complete regrowth). Factors associated with poorer hair regrowth outcomes included a Severity of Alopecia Tool score ≥50 [odds ratio (OR): 3.05, 95% CI: 2.26-4.11], atopic disease (OR: 1.61, 95% CI: 1.03-2.50), and nail involvement (OR: 2.06, 95% CI: 1.26-3.36). Although longer disease duration is often considered a negative prognostic factor, disease duration ≥1 year was not a statistically significant prognostic factor in this study (OR: 1.56, 95% CI: 0.95-2.55). Relapse after treatment was common. Analysis of studies reporting treatment status at the time of relapse revealed recurrence rates among patients not receiving and receiving maintenance treatment of 38 and 49 percent, respectively [15].

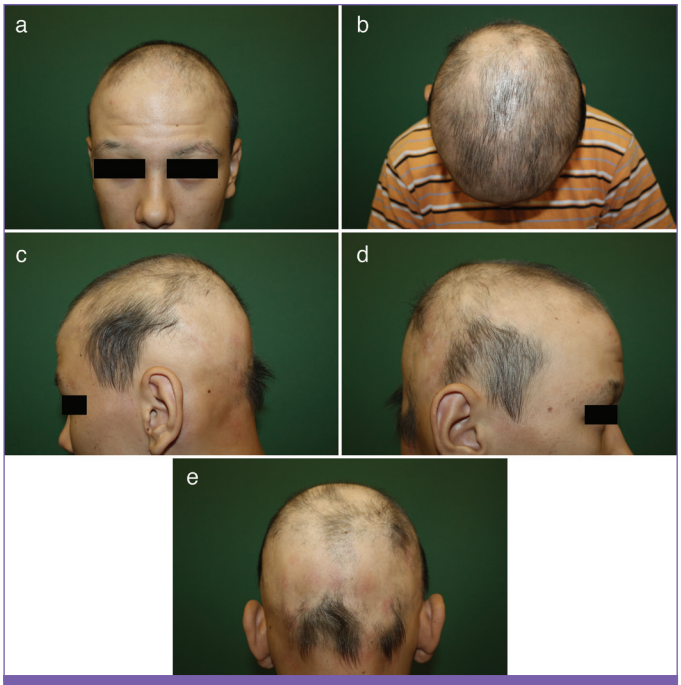

Figure 2. Fifth month in the squaric acid dibutyl ester treatment

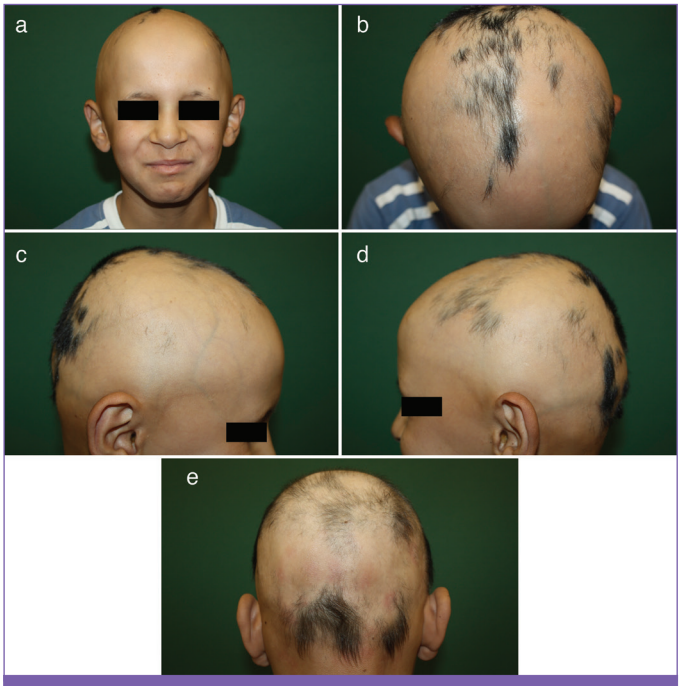

Figure 3. Before the diphenylcyclopropenone treatment

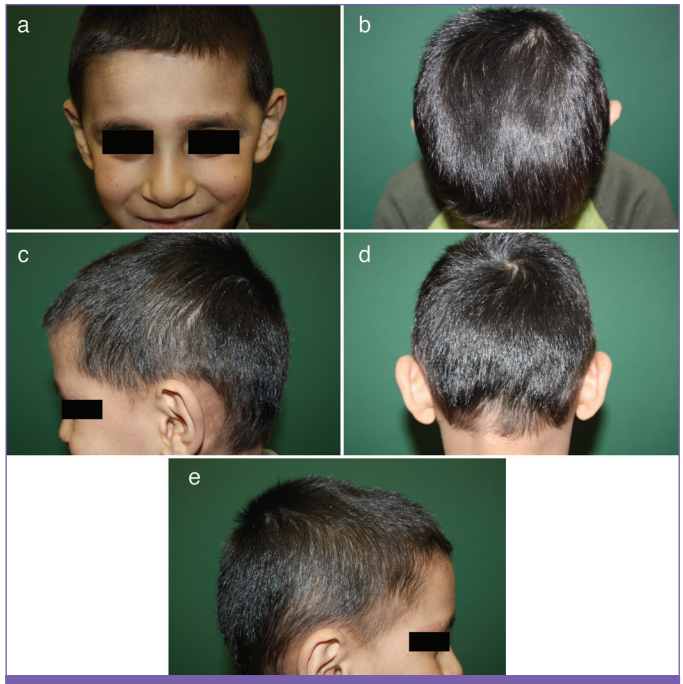

Figure 4. Sixth month in the diphenylcyclopropenone treatment

Conclusion

In our study, we found that those who had a pre-treatment loss of less than 25% received a better response from treatment were 7.5 times better than those with a pre-treatment loss of 100%. This data was compatible with the above mentioned metaanalysis. In contrast to the above metaanalysis, considering all the data in our study, 1-month increase in disease duration caused 1% worse response to treatment (Wald=8.97, p=0.003).

There are few studies comparing two topical immunotherapy in the literature. Our study contributes to the literature in this respect and reflects the Cerrahpasa experience. Further studies are needed in this treatment arm.

Ethics

Ethics Committee Approval: Ethics committee approval was not received.

Informed Consent: Not received.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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

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Vulvovaginal-gingival Syndrome: As a Rare Variant of Erosive Lichen Planus

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ABSTRACT

Observation: The Vulvovaginal-Gingival syndrome is an uncommon variant of erosive mucosal lichen planus (LP) which is characterized by erosions and desquamation of the vulva, vagina, and gingiva that may lead to mucocutaneous scarring and vaginal stricture formation in long time. Due to its progression the early diagnosis and treatment through a multidisciplinary approach is essential. Treatment is usually difficult and unforunately there are no evidence based studies in the treatment. Herein we want to present a 63-year-old female with a 10 year history of erosions over oral and genital region which was consistent with erosive LP histologically. Topical clobetasole propionate cream and systemic acitretin 25 mg/d were administered for her initial therapy but on the sixth month of this therapy minimal regression was detected and we have changed this therapy with systemic corticosteroids. Clinical symptoms were regressed almost 50% on 2nd month of this therapy. We want to present this case to remind this unusual and treatment resistant form of LP in differential diagnoses of erosive lesions of mucosal surfaces.

Keywords: Acitretin, Lichen planus, Vulvovaginal-Gingival syndrome

Introduction

Lichen planus (LP) is a chronic immune mediated inflammatory disorder with unknown etiology, effecting both skin and mucosal surfaces [1]. Mucosal involvement is usually characterized by oral mucosal lesions and involvement of other mucosal surfaces such of vulvovaginal region is rare and may also be challenging in differential diagnoses. The prescence of erosive LP of the vulva and vagina with desquamative gingivitis has been described as Vulvovaginal-Gingival syndrome or Hewitt-Pelisse syndrome and there are only a few case reports regarding this rare and severe syndrome in the literature [2,3].

Case Report

A 63-year-old female presented to our outpatient clinic with a 10 year history of erosions over oral and genital mucosa. Dermatological examination revealed widespread hyperemia and erosions on gingival surfaces, buccal mucosa and marked atrophy and erythema on bilateral labium minus (Figure 1, 2). We performed two punch biopsies and a direct immunflourescence investigation from genital mucosa with initial diagnoses of LP, lichen sclerosus and pemfigus vulgaris. Histopathological examination revealed widespread band like lichenoid infiltration (Figure 3) and direct immunflorescence was negative. She was diagnosed as Vulvovaginal-Gingival syndrome and topical clobetasole propionate cream and systemic acitretin 25

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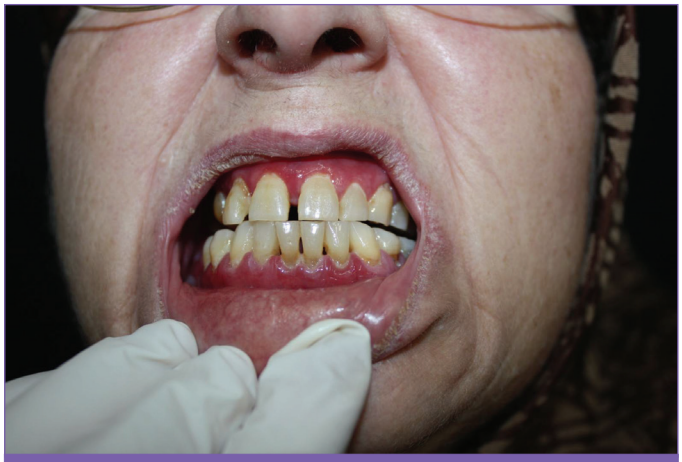

Figure 1. Widespread hyperemia and erosions on gingival surfaces

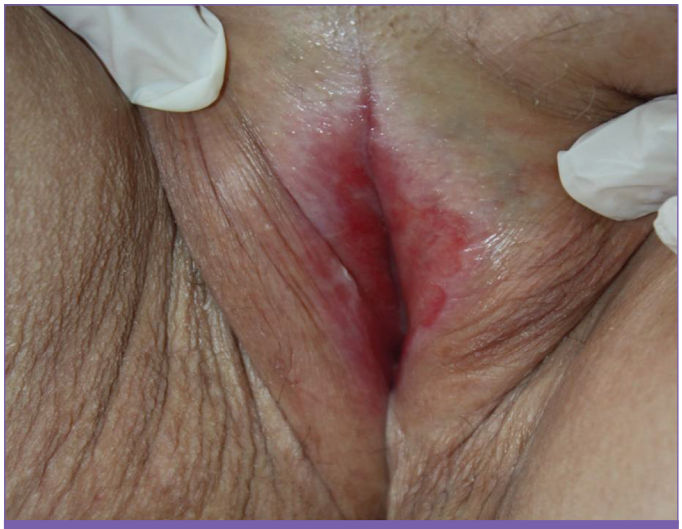

Figure 2. Marked atrophy and erythema on bilateral labium minus

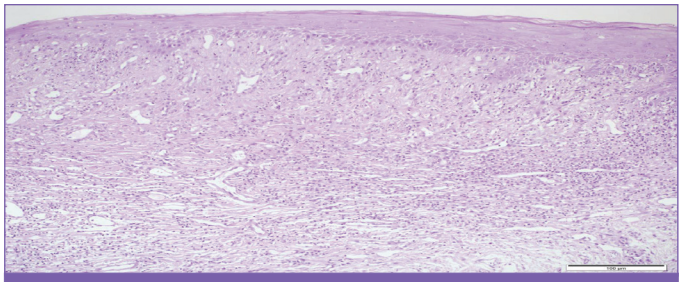

Figure 3. Microscopically, hyperkeratosis, achantosis and focal basal vacuoler changes in epidermis, vascular proliferation, band-like infiltration of lymphocytes in dermis were seen. This findings are compatible to late period of lichen planus

mg/d were administered. On sixth month of this therapy minimal regression was detected and she was still suffering from itching and pain on genital region so we have changed this therapy with systemic corticosteroids. Systemic methylprednisolone 60 mg/d was administered and was given with 20% of tapering doses biweekly. Clinical symptoms were regressed almost 50% on 2nd month of this therapy. After cession of the prednisolone on 6th month her lesions reactivated and systemic cyclosporine 200 mg/d was initiated, marked remission was detected on her genital lesions. She is still under follow up with systemic cyclosporine and topical clobetasol propionate cream.

Discussion

LP is an idiopathic, inflammatory, immune mediated disorder which may affect both mucosal surfaces, such as the oral, genital mucosa, and the skin including the scalp and nails [4]. Ocular, esophageal, bladder, nasal, laryngeal, otic, gastric, and anal involvement have been also reported in the literature but the most common mucosal involvement is seeen in oral mucosa [4]. Oral mucosal lesions are generally characterized by whitish-gray reticular or annular patches or strings that may be present mostly (80%) in the buccal mucosa, followed by tongue, lips, in floor of mouth and palate [5]. Vesicle and bullae formation may be also seen [5]. In recent studies the role of overexpression of tumor necrosis factor-alpha in the cytoplasm of basal epithelial keratinocytes was shown in etiopathogenesis of erosive LP which may be target in the treatment [6].

Different than classical cutaneous involvement of LP, mucosal lesions may progress to sequelae formation leading to mucosal stenosis which really impacts on regional functions such as opening of the mouth, dysurea, dysparonia, postcoital bleeding and increased risk of malignant change in long time duration.

Vulvovaginal-Gingival syndrome was first described in 1982 by Pelisse et al. as a special form of erosive mucosal LP and up to date there are very few case reports about this syndrome in the literature. It is challenging if this variant of LP is likely to be underreported or really a rare disorder. Most of the patients have been usually treated as vaginal yeast infections or other diagnosis such as idiopathic desquamative vaginitis, idiopathic erosive vulvitis and vulvar lichen sclerosus [7]. We performed histological examination and direct immunflorescence with these differential diagnoses and it was consistent with erosive LP. Recognition of Vulvovaginal-Gingival syndrome may avoid unnecessary medical and surgical procedures and also may prevent patients from malignant progression.

Early diagnosis and treatment is very important to prevent the patients from genital sequelae formation. Topical corticosteroids are usually the first step of treatment and they are also the most commonly used drugs. Topical tacrolimus may also be topical treatment option. Systemic agents include corticosteroids, azathioprine, acitretin, metronidazole, mycophenolate mofetil and adalimumab [8]. In our patient we initiated systemic acitretin

because of her age and her diabetes history but in 6th month of there were no satisfactory results and we offered systemic corticosteroids for faster recovery with close monitorization of blood sugar. Almost 50% remission was detected on second month of this therapy without any recurrence but six months after the treatment cession her lesions reactivated. We couldn't start systemic corticosteroids because of her disregulated blood sugar and age. We have initiated systemic cyclosporine for her lesions and again achieved a marked remission in her lesions.

We want to present this case to remind this unusual form of mucosal LP in differential diagnoses of erosive lesions of mucosal surfaces especially anogenital region and gingival surfaces. We also want to lay emphasis on examination of all mucosal surfaces in patients who presented with oral mucosal erosions.

Ethics

Informed Consent: Patient consent was taken before therapy and photographs.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.K.U., A.S.K., E.I.Z., Concept: T.K.U., E.Ö., Design: T.K.U., A.S.K., E.Ö., Data Collection or Processing: T.K.U., E.Ö., E.I.Z., Analysis or Interpretation: T.K.U., A.S.K., N.A., E.I.Z., Literature Search: T.K.U., N.A., Writing: T.K.U.

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

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

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CASE REPORT

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Generalised Mottled Pigmentation in Chediak-Higashi Syndrome in a Child–An Uncommon Manifestation

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ABSTRACT

Observation: Chediak-Higashi syndrome is an extremely rare autosomal recessive disorder characterized by partial oculo-cutaneous albinism, recurrent bacterial infection and abnormally large granules in leukocytes and other cells. Here we report a case who had presented with generalised mottled pigmentation.

Keywords: Chediak-Higashi syndrome, Autosomal recessive disorder, Albinism, Photophobia

Introduction

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by partial oculo-cutaneous albinism, recurrent bacterial infection, bleeding diathesis, nystagmus, photophobia. There are abnormally large granules in leukocytes [1]. It presents usually in childhood and patient may develop severe anemia, bleeding manifestation, organomegaly, overwhelming bacterial infection leading to death [2]. Here we report a case who presented with diffuse hypopigmentation. This case is reported due to its extreme rarity. Less than 500 cases have been reported worldwide [3].

Case Report

A 10-year-old boy presented in the paediatrics outpatient department (OPD) with recurrent cough, respiratory distress and fever from one year of age and was referred to Dermatology OPD for abnormal pigmentation of skin. His younger brother had similar disorder and had died at an age of 6 years. There is history of consanguineous marriage between his parents.

Examination revealed anthropometrically normal for age male. He was pale and febrile. On cutaneous examination there was diffuse mottled hypo and hyper pigmentation over anterior trunk, neck, upper and lower extremities (Figure 1) and over posterior trunk, neck, upper and lower extremities (Figure 2) and dark gray sparse hair with mottled hypo and hyper pigmentation over face (Figure 3). In eyes there was no nystagmus, no photophobia and no albinism. Examination of the abdomen revealed soft abdomen with liver 4 cm below right costal margin, spleen 3 cm below left costal margin. First and second heart sound were normal. Bilateral vesicular breath sounds with no added sounds were present. History of decortications, done on left side for empyema thoracis was reported by mother of the child. The findings of the laboratory investigations were as follows: hemoglobin (Hb): 10.2 gm/dL, total leukocyte count (TLC): 6200/mm^3 (neutrophils 15%, lymphocytes 75%, eosinophils 2%, monocytes 8%), platelets: 1.82 lakhs (done on 05.11.18). Repeat test was performed on 06.11.18 and it showed Hb: 11.6 gm/L, TLC: 6200/mm^3 (neutrophils 25%, lymphocytes 65%, eosinophils 2%, monocytes 8%), platelets 2 lakhs, leukocytes (neutrophils and monocytes) showed giant granules on peripheral blood smear

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stained with hematoxylin and eosin stain at 100x (Figure 4). IgG: 447 mg/dL, IgM: 18.7 mg/dL, IgA: 62 mg/dL. T lymphocytes numbered 1846 cells/microlt, $CD4^+$ T cells: 969 cells/microlt, $CD8^+$ T cells: 771 cells/microlt, CD4/CD8 1026, $CD19^+$ cells, $CD20^+$ cells 14.37% of the lymphocytes. His parents did not give consent for skin biopsy. Based on these findings a diagnosis of CHS was made.

Discussion

CHS was first described by Bequez Cesar in 1934. Further reported by Chediak in 1952 and Higashi in 1954 the hematological features were emphasized [4].

It is a rare autosomal recessive disorder with mutation in a single gene *LYST* localized to 1q42-43 [5]. The basic pathology is defective phagolysosome fusion [6], defects in T cell cytotoxicity, in natural killer cell activity as well as in chemotaxis all leading to increased susceptibility to infection. The giant granules are present in neutrophils, monocytes, lymphocytes, platelets and melanocytes [7]. In melanocytes there are giant melanosomes which prevent even distribution of melanin. Hypopigmentation occurs because the melanosomes within keratinocytes are found within a relatively few large lysosomes rather than dispersed throughout the cell cytoplasm leading to diffuse hypopigmentation. Sparse gray hair occurs associated with pigment clumping [8]. Light microscopic features of skin sections show normal findings. Fontana-Masson stain shows sparse melanin granules, some of which are grouped and others of which are larger than normal.

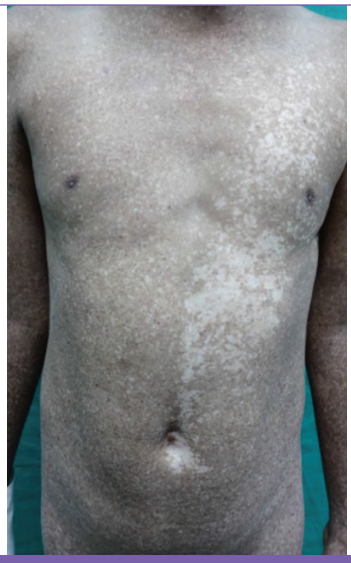

Figure 1. Diffuse mottled hypo and hyper pigmentation over anterior trunk, neck, upper and lower extremities

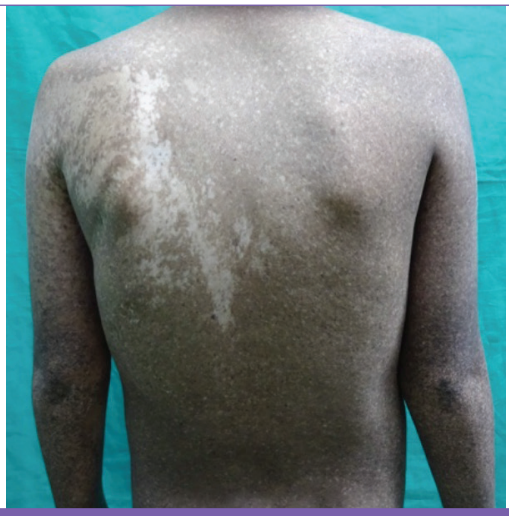

Figure 2. Diffuse mottled hypo and hyper pigmentation over posterior trunk, neck, upper and lower extremities

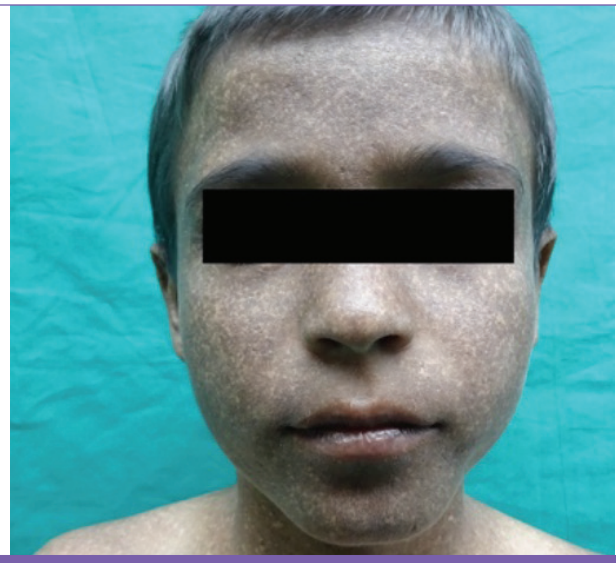

Figure 3. Dark gray sparse hair with mottled hypo and hyper pigmentation over face

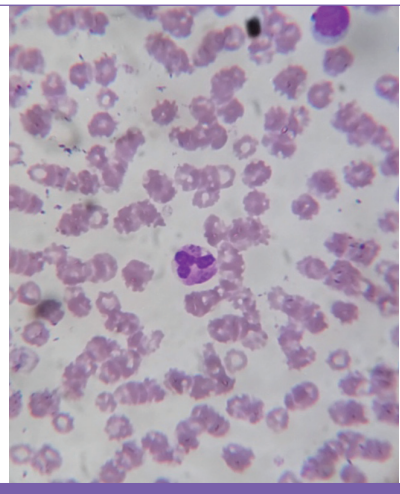

Figure 4. Peripheral blood smear stained with hematoxylin and eosin stain showing giant granules in leukocyte at 100x (oil immersion)

Similar large, irregularly shaped melanin granules are scattered in the upper dermis within melanophages [9]. 50-70% of patients with CHS develop an accelerated phase characterized by fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathy, neurological abnormalities and diffuse mononuclear cell infiltrates into the organs. The accelerated phase may occur shortly after birth or several years later which may be fatal if untreated.

Differential diagnosis of CHS includes Griscelli syndrome and Hermansky Pudlak syndrome; both these lacks giant granules in neutrophils. There is also an entity called pseudo CHS syndrome where abnormal granules are seen only in granulocytes in some cases of acute myeloid leukemia [10].

Our case is important because the child had only diffuse mottled hypo and hyper pigmentation and giant granules in peripheral blood smear with a positive family history which can be a variant of CHS. Any child presenting with recurrent pyogenic infection with features of partial oculocutaneous albinism should thoroughly be screened to rule out CHS as it is progressively fatal, rare disease and patient may enter into the accelerated phase.

Ethics

Informed Consent: Patient's parents had given consent for not disclosing the name of the child.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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