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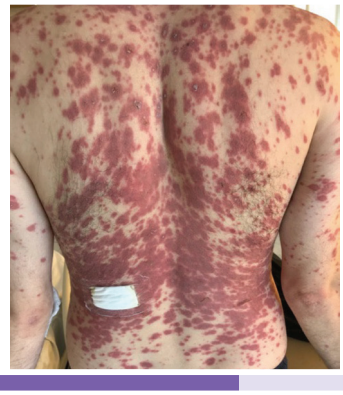

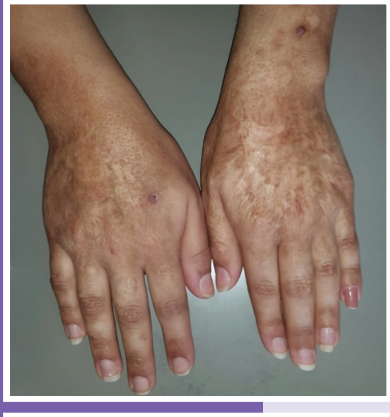

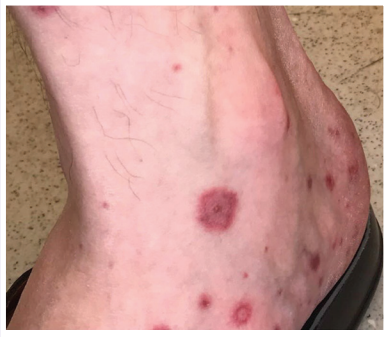

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the appendices

FIGURE LEGENDS

TABLES

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

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

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CONTENTS

REVIEW

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Atypical Variants of Mycosis Fungoides

Dursun Dorukhan Altınışık, Özge Aşkın, Tuğba Kevser Uzunçakmak, Burhan Engin

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

ABSTRACT

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and it is characterised by specific histological features. MF is in a spectrum of disorders which includes Sezary syndrome and other CTCL subtypes. Clinically and histopathologically it can imitate other T-cell mediated dermatosis hence making its diagnosis difficult. Due to different prognosis and difference in treatment strategies other subtypes of CTCL must be differentiated from MF. MF is a clinically indolent low-grade lymphoma which is seen in people aged between 55-60 and it's seen more commonly in men (2:1 ratio). Meanwhile other subtypes of MF like folliculotropic variant may show relatively a more aggressive course and our treatment strategy may differ.

Keywords: Mycosis fungoides, Cutaneous T-cell lymphoma, Phototherapy, PUVA

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and it is characterised by specific histological features [1]. MF is in a spectrum of disorders which includes Sezary syndrome and other CTCL subtypes. Clinically and histopathologically it can imitate other T-cell mediated dermatosis hence making its diagnosis difficult [2]. Due to different prognosis and difference in treatment strategies other subtypes of CTCL must be differentiated from MF. MF is a clinically indolent low-grade lymphoma which is seen in people aged between 55-60 and it's seen more commonly in men (2:1 ratio). Meanwhile other subtypes of MF like folliculotropic variant may show relatively a more aggressive course and our treatment strategy may differ [3,4].

MF Subtypes

Folliculotrophic MF (FMF)

FMF has a broad spectrum of clinical presentations. Varying from patches, infiltrative plaques to tumours, prurigo nodularis or keratosis pilaris like lesions [5]. These lesions tend to contain the follicles frequently causing alopecia and in the paediatric population it tends to accompany hypopigmented patches and plaques. FMF preferentially involves the head and neck region however it can sometimes involve the trunk or the extremities [6]. Patients with FMF have significant pruritus which may be overlapped by *S. aureus* infection [7].

Histologically FMF presents with perifollicular infiltrates around the infundibulum sparing the bulbar region and the epidermis showing folliculotropism instead of epidermotropism. Immunohistochemistry shows in almost all cases a CD4+ phenotype. Clinical presentation of FMF depends upon the clinical presentation hence when located on the scalp it could cause alopecia which could be mistaken as alopecia areata, trichotillomania and cicatricial alopecias. It could present as follicular spiky papules resembling keratosis pilaris, lichen spinulosus, pitriasis rubra pilaris and lichen planopilaris. FMF is known as an aggressive variant of MF based on many series it is corelated with quick disease progression and worse outcome similar to tumour-stage MF. The estimated five-year survival is 94% for early-stage FMF while it's 69% for tumour-stage [8].

Address for Correspondence: Dursun Dorukhan Altınışık MD, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Dermatology, Istanbul, Turkey
Phone: +90 541 919 21 99 E-mail: doruk.altinisik@gmail.com ORCID ID: orcid.org/0000-0001-8674-0779
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Management of FMF is based on it's aggressive behaviour and it is treated as such. Due to the perifollicular infiltrates being harder to target by skin-based therapies alone so it should be emphasized that narrow band UVB phototherapy cannot penetrate and target deep adnexal components of FMF hence psoralen and ultraviolet A (PUVA) is the first choice of treatment of early stages of FMF [9]. However, in later stages it could be combined with systemic retinoids like bexarotene or interferon (IFN). In late stages single agent chemotherapy like gemcitabine or histone deacetylase inhibitors like vorinostat and romidepsin may be used [10].

Pagetoid Reticulosis (PG)

PG or Woringer-Kolopp disease is a localised variant of MF. It is characterised by localised, slow growing patches or plaques located mainly at the distal extremities. These lesions are hyperkeratotic or psoriasiform in appearance. Histopathology shows a verrucous or psoriasiform hyperplasia with intraepidermal (pagetoid) diffusion of highly epidermotropic, abnormal lymphocytes seen in dispersed nests or throughout the epidermis. The neoplastic lymphocytes are $CD3^+$ and express $CD4^{+/-}$ and $CD8^{+/-}$. It is a benign disease which is treated locally with success by excision or radiotherapy [11].

Granulomatous Slack Skin (GSS)

GSS is an uncommon clinicopathological subtype of MF. It is characterised by slow growing of large, infiltrated drooping folds of atrophic skin in the intertriginous areas (axilla and groins).

Histopathology reveals many features resembling MF however the number of multifocal giant cells in GSS is larger displaying 20-30 nuclei per cell which is quite pathognomonic for GSS. Elastophagocytosis, elastic fibre loss and engulfment of lymphocytes are additional findings. Neoplastic lymphocytes mainly express $CD4^+$ and $CD8^+$. Depending on the stage of the disease PUVA, topical mustard, radiotherapy and systemic chemotherapy can be used however patients with GSS need a lifelong observation for secondary lymphoid malignancies the main culprit being Hodgkin's disease [12].

Granulomatous MF (GMF)

Granulomatosis could be detected in many of the MF cases either as initial presentation or in later stages of the disease. The pathogenesis of granulomatosis in MF is unknown although it is known that in other disorders it is mediated by Th1 and Th2 cells. Treatment of CTCL with IFN or bexarotene might also induce granuloma formation. GMF is a histopathologic subtype of MF that may be found in histological sections from patients with classical, poikilodermous, hyperpigmented or FMF. In some instances the clinical characteristics may suggest granulomatous disease as it may mimic granuloma annulare or sarcoidosis. Pathologic criteria for GMF includes granuloma formation or numerous giant cells with histiocyte rich infiltration and loss of elastic fibres. Diagnosis of GMF may be difficult due to granulomatous component obscuring the abnormal lymphocytic infiltrate. Epidermotropism which is a major pathological evidence of MF may not be found in all cases [13].

GMF is associated with rapid disease progression and irresponsiveness to skin directed treatments so systemic treatment is a must. Individuals with GMF are also prone to developing secondary malignancies like Hodgkin's disease so frequent follow ups is a must [14].

Poikilodermatous MF (PMF)

Poikilodermous MF is a clinical variant of patch stage MF characterised by atrophy, telangiectasia and pigmentary changes. It is usually located around the gluteal region, breasts and hips and is frequently associated with classical and other subtypes of MF.

Histopathology reveal features of MF together with poikiloderma like epidermal atrophy, basal hydropic degeneration, pigment incontinence and telangiectasia. Immunophenotyping shows an overexpression of $CD8^+$ cells. PMF is a mild variant of MF usually showing benign behaviour and responds to phototherapy [15].

Hypopigmented MF (HMF)

HMF is a variant of MF affecting people with dark skin and children or adolescents [16]. Hypopigmentation in HMF is due to loss of melanocytes in the lesional skin due to cytotoxic T-cells like in vitiligo. Clinical features of HMF includes irregular round shaped hypopigmented patches and plaques and this may be the only manifestation of MF or seen together with other variants like classical MF. In children the hypopigmented lesions may be accompanied by early folliculotrophic lesions. Histopathology reveals many similarities with classical MF, HMF is highly epidermotrophic composed of atypical lymphocytes, decreased melanin in stratum basale of the epidermis and melanophages. Compared to classical MF HMF is mainly composed of $CD8^+$ lymphocytes [17].

Due to it's slow indolent course and it's lack of signs or symptoms multiple biopsies may be needed for definitive diagnosis. HMF is extremely responsive to phototherapy and resulting in favourable prognosis [16].

Hyperpigmented MF (HPMF)

HPMF is a rare subtype of MF seen mainly in darker individuals [18]. It presents itself with hyperpigmented patches or plaques with ill-defined borders and variable amounts of scaling and skin atrophy. These lesions may be lone or accompanied by different types of MF. Histopathology shows features of classic MF together with vacuolar degeneration of basal keratinocytes and basal hydropic degeneration. Immunohistochemistry shows in most of the HPMF cases a $CD8^+$ phenotype. These cytotoxic T-cells cause vacuolar

degeneration resulting in interphase dermatitis and marked melanin incontinence. HPMF has an indolent clinical course similar to of early-stage MF with good response to phototherapy [19].

MF Palmaris et Plantaris (MFPP)

MFPP is a rare histopathologic variant of MF. Specific involvement of the palms and soles are seen in MFPP, these lesions tend to be bilateral and are characterised by erythematous hyperkeratotic patches and plaques covered in fissures or scales. These lesions may be accompanied by ulcerative lesions and dystrophic nails [20].

Histopathologically usual features of MF are found in MFPP but due to the spongiotic dermatitis seen in MFPP correct diagnosis might be difficult. Immunophenotyping and T-cell clonality must be analysed to confirm the diagnosis. The differential diagnosis of MFPP includes dermatophyte infections, eczema or palmoplantar psoriasis [21].

MFPP is considered as stage 1A MF and is treated as such giving positive clinical response to skin directed therapies like topical steroids, topical bexarotene, radiotherapy and phototherapy [22].

Pigmented Purpuric Dermatosis (PPD)-like MF (PPDMF)

PPDMF is a rare variant of MF characterised by purpuric lesions. This version of MF is reported in both adults and children, it could be seen as a lone manifestation or it could be together with other unusual subtypes of MF. Histopathologically PPDMF shows similar features to that of MF including epidermotropism with atypical lymphocytes together with the presence of siderophages typically seen in PPD [23].

Major characteristic that separates PPDMF from PPD is the distribution of the lesions. While the lesions of PPD are located mainly on the lower extremities the lesions in PPDMF is located throughout the body and may be accompanied by other types of MF lesions or large-plaque parapsoriasis. Also, in PPDMF classic patterns of MF could be seen like larger numbers of atypical lymphocytes and papillary dermal fibrosis easing the diagnosis [24].

Bullous MF (BMF)

BMF is a rare subtype of MF usually appearing a couple of months after the onset of MF or SS. The bullae in BMF tend to be tense or flaccid making it difficult to differentiate from bullous pemphigoid or pemphigus. These bullae may transform to ulcers in time effecting predominantly the trunk or the limbs. Histopathologically the blisters may be subcorneal, intraepithelial or subepidermal accompanied by typical histopathology of MF. This subtype is usually associated with a poor prognosis [25].

Other clinicopathological variations include interstitial MF, syringothrophic MF, papular and pityriasis lichenoides chronica like-MF. MF and it's subtypes could easily be mistaken as other T-cell mediated dermatosis so lesions refractory to long term treatment should be followed up closely and biopsied if lymphoma is suspected [2,4].

Conclusion

Other extremely rare clinicopathological variations of MF include interstitial MF, syringothrophic MF, papular and pityriasis lichenoides chronica like-MF. MF and it's subtypes could easily be mistaken as other T-cell mediated dermatosis so lesions refractory to long term treatment should be followed up closely and frequently biopsied if lymphoma is suspected.

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Authorship Contributions

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References

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, Diaz-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768.
2. Nashan D, Faulhaber D, Ständer S, Luger TA, Stadler R. Mycosis fungoides: a dermatological masquerader. Br J Dermatol 2007;156:1.
3. Ahn CS, ALSayyah A, Sangüeza OP. Mycosis fungoides: an updated review of clinicopathologic variants. Am J Dermatopathol 2014;36:933-48;quiz 949-51.
4. Martínez-Escala ME, González BR, Guitart J. Mycosis Fungoides Variants. Surg Pathol Clin 2014;7:169.
5. van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. Arch Dermatol 2002;138:191.
6. Muniesa C, Estrach T, Pujol RM, Gallardo F, Garcia-Muret P, Climent J, Servitje O. Folliculotropic mycosis fungoides: clinicopathological features and outcome in a series of 20 cases. J Am Acad Dermatol 2010;62:418.
7. Hodak E, Amitay-Laish I, Feinmesser M, Davidovici B, David M, Zvulunov A, Pavlotsky F, Yaniv I, Avrahami G, Ben-Amitai D. Juvenile mycosis fungoides: cutaneous T-cell lymphoma with frequent follicular involvement. J Am Acad Dermatol 2014;70:993.
8. Mantaka P, Helsing P, Gjersvik P, Bassarova A, Clausen OP, Delabie J. Clinical and histopathological features of folliculotropic mycosis fungoides: a Norwegian patient series. Acta Derm Venereol 2013;93:325.
9. Gerami P, Rosen S, Kuzel T, Boone SL, Guitart J. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. Arch Dermatol 2008;144:738.

10. van Santen S, van Doorn R, Neelis KJ, Daniëls LA, Horváth B, Bruijn MS, Sanders CJG, van Rossum MM, de Haas ERM, Veraart JCJM, Bekkenk MW, Vermeer MH, Willemze R. Recommendations for treatment in folliculotropic mycosis fungoides: report of the Dutch Cutaneous Lymphoma Group. Br J Dermatol 2017;177:223.

11. Haghighi B, Smoller BR, LeBoit PE, Warnke RA, Sander CA, Kohler S. Pagetoid reticulosis (Woringer-Kolopp disease): an immunophenotypic, molecular, and clinicopathologic study. Mod Pathol 2000;13:502.

12. Kempf W, Ostheeren-Michaelis S, Paulli M, Lucioni M, Wechsler J, Audring H, Assaf C, Rüdiger T, Willemze R, Meijer CJ, Berti E, Cerroni L, Santucci M, Hallermann C, Berneburg M, Chimenti S, Robson A, Marschalko M, Kazakov DV, Petrella T, Fraitag S, Carlotti A, Courville P, Laeng H, Knobler R, Golling P, Dummer R, Burg G; Cutaneous Lymphoma Histopathology Task Force Group of the European Organization for Research and Treatment of Cancer. Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization For Research and Treatment of Cancer (EORTC). Arch Dermatol 2008;144:1609.

13. Li JY, Pulitzer MP, Myskowski PL, Dusza SW, Horwitz S, Moskowitz A, Querfeld C. A case-control study of clinicopathologic features, prognosis, and therapeutic responses in patients with granulomatous mycosis fungoides. J Am Acad Dermatol 2013;69:366.

14. Haruyama S, Sugita K, Kawakami C, Nakamura M, Tokura Y. Development of a prominent granulomatous eruption after interferon-gamma therapy in a patient with mycosis fungoides. Acta Derm Venereol 2010;90:190.

15. Vasconcelos Berg R, Valente NYS, Fanelli C, Wu I, Pereira J, Zatz R, Sanches JA. Poikilodermatous Mycosis Fungoides: Comparative Study of Clinical, Histopathological and Immunohistochemical Features. Dermatology 2020;236:117.

16. Castano E, Glick S, Wolgast L, Naeem R, Sunkara J, Elston D, Jacobson M. Hypopigmented mycosis fungoides in childhood and adolescence: a long-term retrospective study. J Cutan Pathol 2013;40:924.

17. Singh ZN, Tretiakova MS, Shea CR, Petronic-Rosic VM. Decreased CD117 expression in hypopigmented mycosis fungoides correlates with hypomelanosis: lessons learned from vitiligo. Mod Pathol 2006;19:1255.

18. Lee JS, Yun SJ, Lee JB, et al. A case of hyperpigmented mycosis fungoides: a rare variant. J Eur Acad Dermatol Venereol 2007;21:983.

19. Pavlovsky L, Mimouni D, Amitay-Laish I, Feinmesser M, David M, Hodak E. Hyperpigmented mycosis fungoides: an unusual variant of cutaneous T-cell lymphoma with a frequent CD8+ phenotype. J Am Acad Dermatol 2012;67:69.

20. Topf S, Lüftl M, Neisius U, Brabletz T, Simon M, Schuler G, Schultz E. Mycosis fungoides palmaris et plantaris--an unusual variant of cutaneous T-cell lymphoma. Eur J Dermatol 2006;16:84.

21. Spieth K, Grundmann-Kollmann M, Runne U, Staib G, Fellbaum C, Wolter M, Kaufmann R, Gille J. Mycosis-fungoides-type cutaneous T cell lymphoma of the hands and soles: a variant causing delay in diagnosis and adequate treatment of patients with palmoplantar eczema. Dermatology 2002;205:239.

22. Nakai N, Hagura A, Yamazato S, Katoh N. Mycosis fungoides palmaris et plantaris successfully treated with radiotherapy: case report and mini-review of the published work. J Dermatol 2014;41:63.

23. Martínez W, del Pozo J, Vázquez J, Yebra-Pimentel MT, Almagro M, García-Silva J, Fonseca E. Cutaneous T-cell lymphoma presenting as disseminated, pigmented, purpura-like eruption. Int J Dermatol 2001;40:140.

24. Kim DH, Seo SH, Ahn HH, Kye YC, Choi JE. Characteristics and Clinical Manifestations of Pigmented Purpuric Dermatosis. Ann Dermatol 2015;27:404.

25. Sato S, Okamoto O, Kawamoto M, Oishi M, Yada N, Kohno K, Yokoyama,S, Fujiwara S. Bullous mycosis fungoides associated with an extensive ulcer and a severe leukemoid reaction. Dermatol Reports 2011;3:e54.

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Triggering Factors in Patients Diagnosed Urticaria

Özge Aşkın, Rozerin Neval Altunkalem, Tuğba Kevser Uzunçakmak, Server Serdaroğlu

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

ABSTRACT

Background: Urticaria is a skin disease that is common in all societies and characterized by itchy and edematous plaques that appear suddenly and disappear spontaneously within the same day. Urticaria that lasts for less than six weeks is called acute, while urticaria that lasts longer and can last for years is chronic. While antihistamines are preferred in the first place in treatment, other treatment options may be considered according to the treatment response. In addition to diagnosis and treatment, it is essential to identify and eliminate triggering factors. Common triggers include physical triggers, foods, medicines, fatigue, stress, infections, smoking, dust, pollen and the premenstrual period.

Materials and Methods: In our study, the files of 145 patients who applied to the dermatology outpatient clinic between 1 January 2019 and 1 September 2020 were retrospectively scanned.

Results: Ninety-one (62.7%) of the patients were female, 54 (37.2%) were male. Average age was 38.9. While triggering factors are seen in 62 (42.7%) of the patients; dermographism was seen in 37 (25.5%) of the patients. Trigger factors were common in women and between the ages of 20 and 40. Physical triggers were the most common triggers, followed by foods and drugs.

Conclusion: Urticaria is a dermatological emergency affecting the patient's quality of life. Therefore, success in treatment is very important. Finding and removing triggering factors besides pharmacological treatment will significantly improve the patient's quality of life.

Keywords: Urticaria, Triggering factors, Physical triggers

Introduction

Urticaria is a skin disease that is common in all societies and characterized by itchy and edematous plaques that appear suddenly and disappear spontaneously within 24 hours. It occurs for different reasons and different mechanisms and is classified in a heterogeneous way [1].

Apart from the acute forms of the disease that last less than about six weeks, there are chronic forms that last for years, their types with angioedema, and less frequent inducible or syndromic forms. Approximately half of the cases are accompanied by angioedema [2].

Urticaria significantly adversely affects the quality of life of patients, especially in its chronic forms, and can lead to socio-economic problems. Therefore, diagnosis and treatment selection is very important [3].

The choice of treatment is usually tailored to the duration, frequency and response of the attack and is individualized for each patient. In the treatment, second-generation H1 antihistamines, but also H2 antihistamines, hydroxyzine, doxepin, oral glucocorticoids, omalizumab/anti-immunoglobulin (Ig) E therapy, phototherapy, physical desensitization, immunomodulatory agents are used [4,5].

Address for Correspondence: Özge Aşkın MD, Istanbul University-Cerrahpasa, Cerrahpasa Faculty Medicine, Department of Dermatology and Venereology, Istanbul, Turkey
Phone: +90 530 370 70 17 E-mail: ozgee_karakus@hotmail.com ORCID ID: orcid.org/0000-0003-1413-9436
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In addition to pharmacological treatment, it is also important to find and avoid triggering factors. Common triggers include physical triggers (dermographism, cold urticaria, pressure urticaria, solar urticaria, heat urticaria, vibration angioedema, cholinergic urticaria, contact urticaria, aquagenic urticaria), foods (eggs, milk, soy, peanuts in children; fish, shellfish, seafood, nuts in adults), medicines [aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, codeine, penicillin], fatigue, stress, infections, smoking, dust, pollen and the premenstrual period [6,7,8].

In this study, it was aimed to determine the triggering factors in our patients with urticaria.

Materials and Methods

One hundred forty-five patients who applied and treated in the Dermatology Department of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine between 2019-2020 were included in the study. All the patients diagnosed with urticaria the files were examined and their age, gender, and predisposing factors were analyzed retrospectively.

Statistical Analysis

Statistical analyzes were performed using Statistical Package for the Social Sciences version 21 software. The compliance of the variables to normal distribution was examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyzes were given using mean and standard deviation for normally distributed variables, median and interquartile range for non-normally distributed variables, and frequency tables for categorical variables.

Results

Ninety-one (62.7%) of the patients were female, 54 (37.2%) were male. Average age was 38.9. While triggering factors are seen in 62 (42.7%) of the patients; dermographism was seen in 37 (25.5%) of the patients. Trigger factors were common in women and between the ages of 20 and 40. Physical triggers were the most common triggers, followed by foods and drugs (Table 1).

Aquagenic urticaria was the most common physical trigger. Fish and nuts were the most common causes of food-related urticaria. NSAID were held responsible for drug-related urticaria to a large extent. The least common trigger factor was the premenstrual period (Table 2).

Discussion

There are many factors that are held responsible in the etiology of urticaria. Some of these are the primary causes, while others are the factors that trigger the lesions and cause exacerbation. While these triggering factors are seen in 10-20% of patients in many studies, etiology cannot be found in 50% of the patients [9,10,11].

In a study in which triggering factors were investigated only in pediatric population, this rate was found to be 21-55%. In another study, while 75.9% of the patients described the triggering factor, only 36.3% of the tests performed rash after the triggers [12,13].

In our study, triggering factors were seen at a rate of 42.7%.

As in other studies, association with triggering factors was more common in female and young adult patients in our study [14,15].

The most common triggering factor was physical triggers in many studies in the literature, as in our study. It was followed by foods and drugs [14,15,16].

Studies show that foods are responsible for 5.3% of acute urticaria cases. IgE mediated food allergy is rarely observed in urticaria. In IgE-mediated urticaria, if the responsible food is eliminated from the diet, the lesions disappear within 24-48 hours. The most common foods that caused urticaria were eggs and milk in children, while fish and shellfish in adults. There was no pediatric age group in our study. In adults, fish were often found to be the trigger factor, in accordance with the literature [17,18].

In some of the studies, antibiotics are the most frequently held responsible group for drug-induced urticaria, while in others NSAIDs. Urticaria is estimated to occur in 0.1% to 0.3% of the patients who use NSAIDs. NSAID and aspirin use is not recommended, especially in chronic urticaria cases. In our study, it was observed that NSAIDs triggered more urticaria attacks compared to other drugs [19,20]. ACE inhibitors can cause angioedema. Therefore, it is not appropriate to use ACE inhibitors in urticaria cases accompanied by angioedema [21]. In our study, there was no patient group in whom urticaria or angioedema was observed with ACE inhibitors.

In cases of physical and emotional fatigue and stress, both lesions and pruritus may increase, the patient is recommended to stay away from stressful environments that they are aware of and can avoid. Some patients may benefit from psychological support [22].

Table 1. Trigger factors

Trigger factors	Number of cases (%)
Physical triggers	34 (23.4)
Foods	14 (9.6)
Drugs	11 (7.5)
Premenstrual period	3 (2)

Table 2. Physical triggers

Physical triggers	Number of cases (%)
Aquagenic urticaria	11 (7.5)
Cholinergic urticaria (physical exercise, stress, hot shower)	7 (4.8)
Pressure urticaria	5 (3.4)
Cold urticaria	4 (2.7)
Solar urticaria	4 (2.7)
Heat urticaria	2 (1.3)
Contact urticaria	1 (0.6)

More rarely reported triggers/aggravates are cigarette smoke, house dust mites, pollen, mold and spores, and there are cases with premenstrual exacerbation [23]. The patient should be informed about all these potential exacerbations.

Study Limitation

The limitation of the study was the inability to test patients for physical triggers.

Conclusion

According to the results of this study, the most common triggers of urticaria are physical triggers, foods and drugs. In addition to pharmacological treatment, avoiding these triggers will significantly increase the quality of life of patients.

Ethics

Ethics Committee Approval: The study were approved by the Istanbul University Cerrahpasa-Cerrahpasa Faculty Medicine Local Ethics Committee (approval number: 83045809-604.01.02-103775, date: June 2, 2021).

Informed Consent: Retrospective study.

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Authorship Contributions

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

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References

1. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, Church MK, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Abdul Latiff AH, Mathelier-Fusade P, Metz M, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Simons FE, Staubach P, Sussman G, Toubi E, Vena GA, Wedi B, Zhu XJ, Nast A, Maurer M; Dermatology Section of the European Academy of Allergy and Clinical Immunology; Golbal Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. Methods report on the development of the 2013 revision and update of the EAACI/GA2 LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2014;69:1-29.
2. Yuan Y, Xiao Y, Chen X, Li J, Shen M. A Systematic Review and Meta-Analysis of Health Utility Estimates in Chronic Spontaneous Urticaria. Front Med (Lausanne) 2020;7:543290.
3. Weldon DR. Quality of life in patients with urticaria. Allergy Asthma Proc 2006;27:96-99.
4. Pozderac I, Lugović-Mihić L, Artuković M, Stipić-Marković A, Kuna M, Ferček I. Chronic inducible urticaria: classification and prominent features of physical and non-physical types. Acta Dermatovenerol Alp Pannonica Adriat 2020;29:141-148.
5. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, Pföhler C, Staubach P, Treudler R, Wedi B, Magerl M. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. J Allergy Clin Immunol 2018;141:638-649.
6. Maurer M, Fluhr JW, Khan DA. How to Approach Chronic Inducible Urticaria. J Allergy Clin Immunol Pract 2018;6:1119-1130.
7. Abajian M, Schoepke N, Altrichter S, Zuberbier T, Maurer M. Physical urticarias and cholinergic urticaria. Immunol Allergy Clin North Am 2014;34:73-88.
8. Maurer M, Ortonne JP, Zuberbier T. Chronic urticaria: a patient survey on quality-of-life, treatment usage and doctor-patient relation. Allergy 2009;64:581-588.
9. Folci M, Ramponi G, Brunetta E. A Comprehensive Approach to Urticaria: From Clinical Presentation to Modern Biological Treatments Through Pathogenesis. Adv Exp Med Biol 2021 Jan 1.
10. Weller K, Giménez-Arnau A, Grattan C, Asero R, Mathelier-Fusade P, Bizjak M, Hanna M, Maurer M; CURE Investigators. The Chronic Urticaria Registry: rationale, methods and initial implementation. J Eur Acad Dermatol Venereol 2020 Sep 18.
11. Curto-Barredo L, Pujol RM, Roura-Vives G, Gimenez-Arnau AM. Chronic urticaria phenotypes: clinical differences regarding triggers, activity, prognosis and therapeutic response. Eur J Dermatol 2019;29:627-635.
12. Caffarelli C, Duse M, Martelli A, Calvani M, Cardinale F, Chiappini E, Marseglia GL, Miraglia Del Giudice M, Tosca MA, Castagnoli R, Brambilla I, Santoro A, Procaccianti M, Giannetti A, Ricci G, Minasi D. Urticaria in childhood. Acta Biomed 2020;91:2020013.
13. Ataseven A, Durmaz K, Ozer I, Dursun R. Gallstones at chronic spontaneous urticaria patients: A retrospective clinical study. Dermatol Ther 2020;33:13212.
14. Hon KL, Leung AKC, Ng WGG, Loo SK. Chronic Urticaria: An Overview of Treatment and Recent Patents. Recent Pat Inflamm Allergy Drug Discov 2019;13:27-37.
15. Schaefer P. Acute and Chronic Urticaria: Evaluation and Treatment. Am Fam Physician 2017;95:717-724.
16. Sánchez J, Amaya E, Acevedo A, Celis A, Caraballo D, Cardona R. Prevalence of Inducible Urticaria in Patients with Chronic Spontaneous Urticaria: Associated Risk Factors. J Allergy Clin Immunol Pract 2017;5:464-470.
17. Skrie VC, Orellana JC. Reacción adversa por aditivos alimentarios en un paciente pediátrico [Adverse reaction to food additives in a pediatric patient]. Rev Alerg Mex 2018;65:187-191.
18. Jaros J, Shi VY, Katta R. Diet and Chronic Urticaria: Dietary Modification as a Treatment Strategy. Dermatol Pract Concept 2019;10:2020004.
19. Rauscher C, Petrov AA, Fajt ML. Factors Associated with Self-Reported Drug Allergies in a Large Chronic Spontaneous Urticaria Cohort. Curr Drug Saf 2020 Oct 2.
20. Kowalski ML, Woessner K, Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema. J Allergy Clin Immunol 2015;136:245-251.
21. Rasmussen ER, Mey K, Bygum A. Angiotensin-converting enzyme inhibitor-induced angioedema--a dangerous new epidemic. Acta Derm Venereol 2014;94:260-264.
22. Varghese R, Rajappa M, Chandrashekar L, Kattimani S, Archana M, Munisamy M, Revathy G, Thappa DM. Association among stress, hypocortisolism, systemic inflammation, and disease severity in chronic urticaria. Ann Allergy Asthma Immunol 2016;116:344-348.
23. Chow SK. Management of chronic urticaria in Asia: 2010 AADV consensus guidelines. Asia Pac Allergy 2012;2:149-160.

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Medical Therapy of Burn Scar Before Any Plastic Surgery by Using Topical Corticosteroid Combined with Oral Zinc Sulfate

Khalifa E. Sharquie[1], Raed I. Jabbar[2]

[1]University of Baghdad, College of Medicine, Medical City Teaching Hospital, Department of Dermatology, Baghdad, Iraq
[2]Al-Anbar Health Directorate, Fallujah Teaching Hospital, Department of Dermatology, Anbar, Iraq

ABSTRACT

Background: Burn scar is one of the commonest medical problems that need intervention as initially treat burn infection, then preventing the scar, followed by treatment of scar.Plastic surgery interference should be considered as a last resort.

Materials and Methods: This is case series descriptive and therapeutic interventional study where a total of 170 patients with burn scar were managed and evaluated. Their ages ranged from 1-40 years with a mean 25 year, 120 (70.58%) males and 50 (29.41%) females. All had history of burn and the age of scar was ranged from 0.5-3 years. All cases were treated with topical diluted clobetasol ointment combined with oral zinc sulfate with duration of 2-4 months. Scoring system of reduction of burn scar was introduced and applied and three parameters of response were considered: scar size reduction, improvement of itching and pigmentation whether hyper or hypopigmentation. The reduction in scoring was estimated as mild, moderate and marked reduction.

Results: The results of this study showed 50% reduction rate while scoring system demonstrated statistically significant reduction with p value ≤0.001 at two months of therapy. While at four months, there was 75% reduction rate and with highly statistically significant reduction of scoring system p value ≤0.0001. The reduction of scar scoring was mild in 20% of cases and moderate in 30% while marked in 50% of patients at the end of four months of therapy.

Conclusion: Medical therapeutic intervention should be started as early as possible to minimize scar formation, to reduce the scar size and treat pigmentary problems. This therapeutic trial will minimize plastic surgery need. Also newly invented scoring system was introduced to evaluate the response to treatment.

Keywords: Burn scar, Corticosteroid, Zinc sulfate, Plastic surgery

Introduction

Although there is great improvement in acute burn management still there is considerable unmet problem in burn recovery and skin scarring and the prevalence of hypertrophic scarring following burn is about 70% [1].

After skin burn injury, there is linear deposition of collagen that develops a scar that lacks the pliability of normal skin. This collagen deposition happens in excess resulting in the appearance of a pathological scar that is thick and hard [2]. Furthermore, the scar is painful and pruritic which worsens the patient outcome and quality of life [3]. There are two types of scarring that originate from burn trauma-keloid or hypertrophic scar. Keloids, develop months to years after initial injury and spread beyond the margin of the original defect. It continues to evolve over time, without a quiescent or regressive phase and do infiltrate the surrounding tissue [4]. Hypertrophic scars on the other hand, happen within the

Address for Correspondence: Prof Khalifa E Sharquie, MD, PhD, FRCP, University of Baghdad, College of Medicine, Medical City Teaching Hospital, Department of Dermatology, Baghdad, Iraq
Phone: +009647901468515 E-mail: ksharquie@ymail.com ORCID ID: orcid.org/0000-0002-0265-2040
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borderlines of the original defect, are raised, red to pink in color, and appear within 4-8 weeks after initial trauma or injury [5]. This scar will mature and gradually regress to a flatter scar over a period of two years. Like keloid, hypertrophic scars are raised and erythematous. In both keloids and hypertrophic scarring there is increased collagen deposition that is oriented in thick bundles, however, the arrangement of collagen fibers differs. Keloids are primarily composed of disorganized bundles of type 1 and type 3 collagen arranged haphazardly to the epithelium surface [6]. In contrast, in hypertrophic scarring, histology reveals a profusion of collagen type 3 fibers oriented parallel to the surface of the epithelium [6].

The formation of pathological scars is regarded as a result of dysregulation in the process of wound healing which characterizes by an inflammatory phase, a proliferative phase, and a remodeling phase [5,7]. The inflammation is critical to the removal of dead tissue and the prevention of infection by neutrophils and macrophages through the secretion of cytokines and proteases and the actions of phagocytosis [8]. The proliferation phase was finished by the migration and proliferation of different cells. Activated by the cytokines and growth factors, such as platelet-derived growth factor and transforming growth factor-beta (TGF-β) released mainly from macrophages, fibroblasts are stimulated to produce extracellular matrix and collagen. Angiogenesis is initiated by the action of endothelial cells in response to the up regulation of vascular endothelial growth factor [9]. Keratinocytes from the border of the wound and adnexal structures migrate and proliferate to make the wound healed by re-epithelialization. While the remodeling phase can take up to a year or longer to complete, which is characterized by the replacement of collagen 3 by collagen 1, rearrangement of granulation tissue, and the contracture of the scar through the action of myofibroblasts. During the remodeling phase, a variety of extracellular matrix and their corresponding enzyme system act to obtain the aim of restoring normal histological structure [10]. Even after remodeling for many years, the wounded tissue never regains the characteristics of normal skin. The dysregulation of apoptosis and proliferation of fibroblasts, a disproportion between synthesis and degradation collagen in the extracellular matrix, and abnormal structure of epithelium are responsible for scarring [11]. The early stage scars have extreme abnormally arranged collagen fibers and diffuse capillaries in histology, which manifest as a red hypertrophic scars, whereas the late stage of scars has excessive fiber deposition and blocked vessels, which manifest as normal color or reduced color scars with elevation, flat, or atrophy in morphology [11].

Treatment of Burn Scar

Non-invasive options: Which include use of compression treatment (such as pressure garments with or without gel sheeting); static and dynamic splints; acrylic casts; masks and clips; application of a variety of creams, oils and lotions, silicon sheeting, with or without adhesive and hydrotherapy [1,12,13,14].

Invasive treatments: Include surgical excision and resuture [7]. Intralesional steroid injection [15] is commonly used but is prone to complications like dermal thinning, fat atrophy and pigment changes. Other therapy that have been recommended with variable outcomes include injections of 5-fluorouracil [16] and bleomycin [17], laser therapy [18], radiotherapy [19], cryosurgery [20] and debulking with intralesional injection of methotrexate [21].

Corticosteroids were proved to induce scar regression through many different actions. First, they repress inflammation by inhibiting monocyte and leukocyte migration and phagocytosis [22], second, they have an antimitotic effect that impedes fibroblasts and keratinocytes, slowing reepithelialization and new collagen formation. Third, they are powerful vasoconstrictors, thus reducing the conveyance of oxygen and nutrients to the wound bed [22].

Zinc, is an essential micronutrient for humans and its importance can be gauged from the fact that it is an essential component of more than 300 metalloenzymes and over 2000 transcription factors that are needed for regulation of lipid, protein and nucleic acid metabolism and gene transcription [23]. Sharquie introduced oral zinc sulfate widely in treatment different and diverse skin diseases such as cutaneous leishmaniasis [24], basal cell carcinoma [25], plane warts [26], xeroderma pigmentosum [27] and others [28,29,30,31].

Also he used zinc sulfate in treatment of many skin sclerosing conditions like morphea, lichen sclerosus et atrophicans and different types of scars including hypertrophic and keloid [32].

From extensive reviewing literature, we found that there is no marked limiting factor between hypertrophic scar and keloid. Hence we prefer to use the term burn scar to include both hypertrophic scar and keloid.

So, the aim of this present study to record all cases of burn scar that followed burn as early as possible and treat them by medical therapy before any plastic intervention.

Materials and Methods

This case series descriptive and therapeutic interventional study that was carried out during the period from April 2014 to July 2020 where a total of 170 patients with burn scar were managed and evaluated. Their ages ranged from 1-40 years with a mean 25 year, 120 (70.58%) males and 50 (29.41%) females. All had a history of burn and the age of the scar was ranged from 0.5-three years. Most patients mentioned that the scar appeared few weeks after healing

of burn. The number of scars was often multiple and variable in size. The sites were face and neck in 68 (40%) cases, limbs in 144 (84.7%), while trunk in 64 (37.64%) of patients.

All cases enrolled in the present study had no history of therapy with topical or systemic remedies for at least two months before starting the current work.

A full history was taken with emphasis on age, sex, duration of scar, associated symptoms, previous scar treatment and past medical and surgical history. A careful physical examination was carried out to identify the site, size, type, and color of the scars.

Formal written consent was taken for each patient before starting the therapy, after a full explanation about the nature of the disease, course, the method of treatment, complications, follow, prognosis, and the need for photographs before treatment and each visit during the following.

All patients were treated with topical diluted clobetasol propionate ointment (clobetasol ointment 0.05% 50 gm + vaseline ointment 25 gm + salicylic acid 1.5 gm) twice a day under occlusion in some suitable sites combined with oral zinc sulfate (5-10 mg/kg/day in two divided doses) with a duration of 2-4 months. The clobetasol propionate 0.05% w/w ointment (Promax®) is manufactured by Jamjoom Pharma.

A scoring system of reduction of burn scar was newly introduced and applied and three parameters of response were considered: scar size reduction, improvement of itching and pigmentation whether hyper or hypopigmentation. The reduction in scoring was estimated as mild (1-3), moderate (4-7) and marked reduction (8-11). Also percentage of reduction was assessed (Table 1).

This scoring is semi- parametric assessment and it was carried out before therapy, at two months and at four months of therapy.

Two dermatologists compared the photos of patients before and during follow-up besides the clinical evaluation using scoring system in Table 1.

Patient's satisfaction to response to the treatment was assessed as follow:

1) Full satisfaction.

2) Partial satisfaction.

3) No satisfaction.

Statistical Analysis

All statistical calculations were performed using a Statistical Package for the Social Science version 22. Data were statistically described in terms of range, mean, median, frequencies (no. of cases), percentage (%), scar duration and male to female ratio. The p value of ≤0.05 was considered statistically significant.

So the total scores will be 11 and this could be divided into: Mild reduction (1-3); moderate reduction; (4-7) marked reduction (8-11). So scoring should be carried out before therapy, at two months and at four months of therapy.

Results

The results of this study showed 50% reduction in scar size at two months therapy and this was statistically significant reduction with p value ≤0.001. While at four months, there was 75% reduction rate in scar size and with a highly statistically significant reduction p value ≤0.0001. There was marked rapid reduction and clearance of hyperpigmentation during therapy while leukoderma showed slow response. While the total reduction of scar scoring was mild in 34 (20%) of cases and moderate in 51 (30%) and marked in 85 (50%) of patients at the end of four months of therapy and these results were also highly statistically significant p value ≤0.0001.

Itching was the main symptom and was found in 118 (69.41%) of patients.

There were no untoward effects from topical therapy such as allergy,dermal thinning or fat atrophy noticed during the course of the study.

Mild adverse effects were recorded due to oral zinc sulfate therapy, these adverse effects were mild and did not necessitate to stoppage of therapy. These were nausea in 55 (32.35%) and mild epigastric pain in 25 (14.70%) patients.

Photos of patients before and during follow up period were showed in Figures 1, 2, 3.

Full satisfaction was in 111 (65.29%) patients while 59 (34.7%) patients had partial satisfaction.

Discussion

Cutaneous burn scarring is a persistent medical problem and characteristically underlies post-burn physical and psychosocial

Table 1. Scoring system to assess burn scar response to medical therapy

Parameter		Score			
		1	2	3	4
1	Scar size reduction	1-25%	>25-50%	>50-75%	>75-100%
2	Pigmentations reduction	1-25%	>25-50%	>50-75%	>75-100%
3	Itching reduction	Mild	Moderate	Marked	-

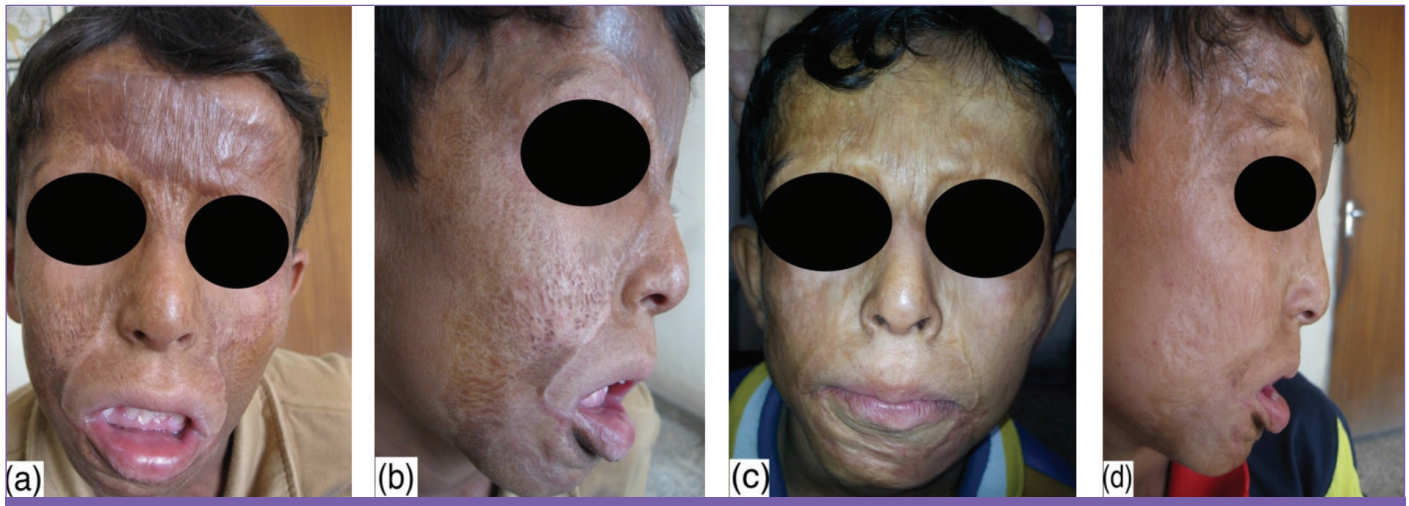

Figure 1. Twenty-three years old male with post burn scar of the face. Before treatment (a and b) and four months after treatment (c and d)

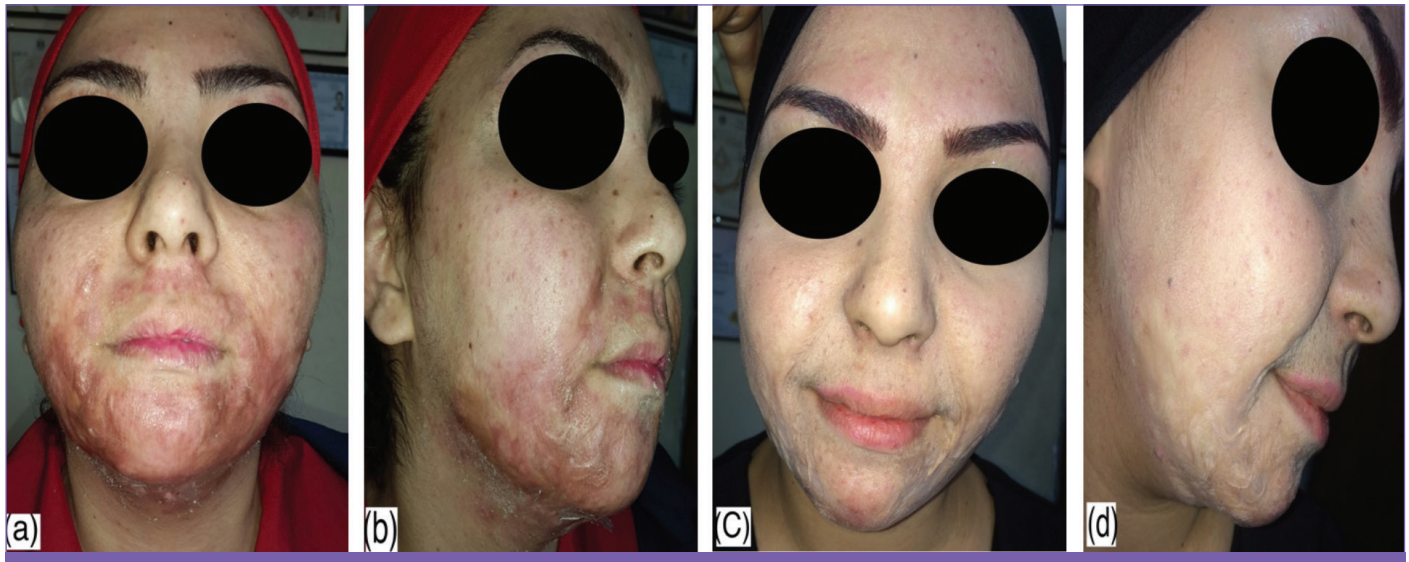

Figure 2. Thirty-seven years old female with post burn scar of the face. Before treatment (a and b) and four months after treatment (c and d)

morbidity [1]. The treatment of scars is challenging and needs multimodal management [33].

To our knowledge, the efficacy of topical diluted clobetasol ointment (clobetasol + vaseline + salicylic acid) has never been investigated in the treatment of scar but only one study by Atiyeh [34] demonstrated some efficacy of topical steroid in treatment of keloid, while another study recorded no effect [35].

Furthermore many previous studies pertaining to intralesional steroid alone or in combination with other therapy showed variable results with many side effects like high recurrence rate especially in keloid and many side effects such as pain at the site of injection, dermal thinning, fat atrophy and pigment changes [15].

The benefits of steroid in therapy of scars are by decreasing collagen/glycosaminoglycan synthesis, inhibit leukocyte and monocyte activity, decrease in fibroblast activity via antimitotic activity, induce hypoxia via a vasoconstriction effect, increase in beta fibroblast growth factor and decrease in TGF-β1 [22,36].

While topical salicylic acid causes desquamation of corneocytes as it dissolves the intercellular cement and reduces the pH of the stratum corneum, thereby increasing softening and hydration of epidermis [37]. Furthermore, it has antipruritic and anti-inflammatory actions and these actions may be explained by its inhibitory effects on prostanoids and cyclooxygenase. Also because of its keratolytic effects, salicylic acid increases the penetration of topical steroids [38,39].

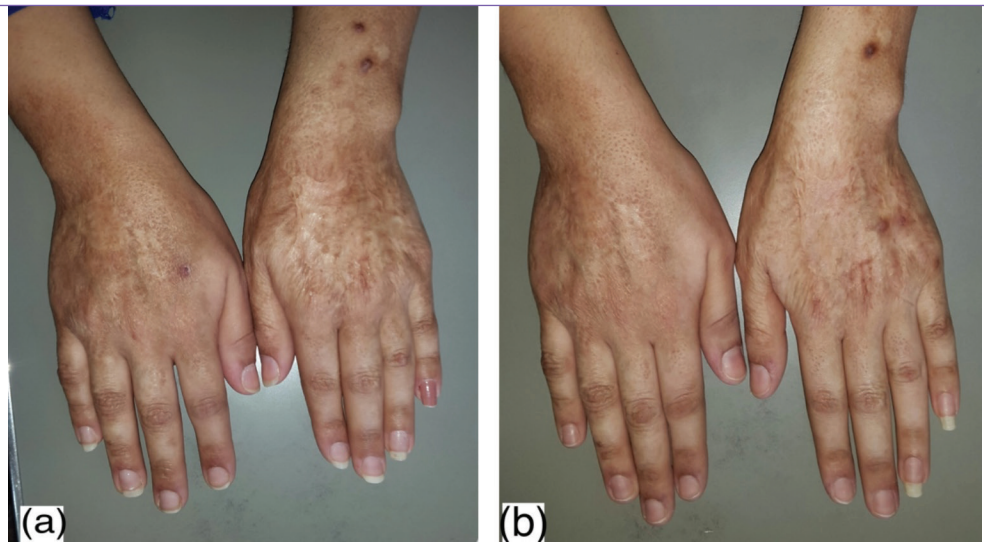

Figure 3. Twenty-one years old female with post burn scare of both hands. Before treatment (a) and after two months (b)

Petroleum jelly ointment (vaseline) when applied daily for 1-3 weeks are excellent alternatives to maintain wound bed moisture [40]. It enhances hydration of stratum corneum by reducing transepidermal water loss. Also, it has another benefit by decreasing scar erythema [41].

Sharquie introduced oral zinc sulfate in the treatment of morphea,lichen sclerosus et atrophicans and different types of scars since 1985 [32] and this work had encouraged us to conduct the present work by using oral zinc sulfate in addition to diluted topical and clobetasol ointment. The beneficial effect of topical zinc in the management of scar has been attributed to its capability to enhance collagenase and prevent lysyl oxidase that leads to increased degradation and decreased production of collagen. Moshref [42] recorded a complete clearance of keloids with a very low rate of recurrence in 34% cases with the application of a zinc tape. Similarly, Söderberg et al. [43] recorded a clinical improvement in 23 of the 41 cases with keloids after six months of application of a zinc tape.

From these different mechanisms of the different medications mentioned above in addition to our experience with the oral zinc sulfate in the treatment of different skin disorders, we encouraged to conduct the current study by using these combinations to get a synergistic effect, short duration of treatment, low recurrence rate, with minimal or no side effects.

Also, occlusive therapy enhances percutaneous absorption of clobetasol ointment and shows more potent action [44]. Besides, occlusion prevents transepidermal water loss and promote hydration of stratum corneum. Finally, pressure effects of the occlusion cause vasoconstriction which leads to hypoxia and this hypoxia decreases the scar size and prevents it from growing more or increase in size [45,46,47].

Surgical treatment of scar is costly, associated with risk of infection, needs good experience in the treatment of scar, high recurrence rate especially with keloid or when it is used alone. In addition, the scar may develop at the donor site when grafting is indicated and sometimes need general anesthesia [48]. The results of this surgical maneuver is in contrast to results of current work using combination therapies as they are non-costly, easy to use, no risk of infection, 75% reduction rate in scar size with 50% reduction in scar scoring after four months of therapy. And with marked clearance of pigmentation and itching, these reductions were statistically significant. Also 64.7% of patients showed full satisfaction with no or mild side effects.

We believe that this innovative treatment regimen is a useful alternative to surgical intervention for post burn scar especially in early cases.

So the message from this present study is to encourage using non-surgical approaches as early as possible including the combination of therapy as applied in this study. And to postpone surgical intervention (unless it is urgent) and give time for these medical treatments to exert their effects on burn scar, as medical treatments may show good therapeutic outcome.

Study Limitation

In our study, biopsy was not performed as it was refused by all patients.

Conclusion

Diluted clobetasol propionate ointment under occlusion combined with oral zinc sulfate is an effective mode of therapy for burn scar with mild or no side effects.

Medical therapeutic intervention should be started as early as possible to minimize scar formation, to reduce the scar size and treat pigmentary problems. The present therapeutic protocol gave satisfactory responses in all patients and will minimize plastic surgery need. Also the present work introduced new scoring system that used to assess the response to therapy.

Ethics

Ethics Committee Approval: The study followed the Declaration of Helsinki Principles and it was approved by the Ethics Committee of Fallujah Teaching Hospital (approval number: 425, date:10/11/2020).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.E.S., R.I.J., Concept: K.E.S., R.I.J., Design: K.E.S., R.I.J., Data Collection or Processing: K.E.S., R.I.J., Analysis or Interpretation: K.E.S., R.I.J., Literature Search: K.E.S., R.I.J., Writing: K.E.S., R.I.J.

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References

1. Bombaro KM, Engrav LH, Carrougher GJ, Wiechman SA, Faucher L, Costa BA, Heimbach DM, Rivara FP, Honari S. What is the prevalence of hypertrophic scarring following burns? Burns 2003;29:299-302.
2. Tredget EE, Levi B, Donelan MB. Biology and principles of scar management and burn reconstruction. Surg Clin North Am 2014;94:793-815.
3. Trace AP, Enos CW, Mantel A, Harvey VM. Keloids and Hypertrophic Scars: A Spectrum of Clinical Challenges. Am J Clin Dermatol 2016;17:201-223.
4. Finnerty CC, Jeschke MG, Branski LK, Barret JP, Dziewulski P, Herndon DN. Hypertrophic scarring: the greatest unmet challenge after burn injury. Lancet 2016;388:1427-1436.
5. Profyris C, Tziotzios C, Do Vale I. Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics Part I. The molecular basis of scar formation. J Am Acad Dermatol 2012;66:1-10;quiz 11-2.
6. Martin P, Nunan R. Cellular and molecular mechanisms of repair in acute and chronic wound healing. Br J Dermatol 2015;173:370-378.
7. Berman B, Maderal A, Raphael B. Keloids and Hypertrophic Scars: Pathophysiology, Classification, and Treatment. Dermatol Surg 2017;43:3-18.
8. Wang J, Hori K, Ding J, Huang Y, Kwan P, Ladak A, Tredget EE. Toll-like receptors expressed by dermal fibroblasts contribute to hypertrophic scarring. J Cell Physiol 2011;226:1265-1273.
9. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev 2003;83:835-870.
10. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature 2008;453:314-321.
11. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med 2011;17:113-125.
12. Kim S, Choi TH, Liu W, Ogawa R, Suh JS, Mustoe TA. Update on scar management: guidelines for treating Asian patients. Plast Reconstr Surg 2013;132:1580-1589.
13. Anzarut A, Olson J, Singh P, Rowe BH, Tredget EE. The effectiveness of pressure garment therapy for the prevention of abnormal scarring after burn injury: a meta-analysis. J Plast Reconstr Aesthet Surg 2009;62:77-84.
14. Stavrou D, Weissman O, Winkler E, Yankelson L, Millet E, Mushin OP, Liran A, Haik J. Silicone-based scar therapy: a review of the literature. Aesthetic Plast Surg 2010;34:646-651.
15. Boutli-Kasapidou F, Tsakiri A, Anagnostou E, Mourellou O. Hypertrophic and keloidal scars: an approach to polytherapy. Int J Dermatol 2005;44:324-327.
16. Fitzpatrick RE. Treatment of inflamed hypertrophic scars using intralesional 5-FU. Dermatol Surg 1999;25:224-232.
17. Reddy R, Harinatha S, Raghunath N. The role of Bleomycin in management of hypertrophic scars and keloids–A clinical trial. Our Dermatol Online 2015;6:404-406.
18. Ouyang HW, Li GF, Lei Y, Gold MH, Tan J. Comparison of the effectiveness of pulsed dye laser vs pulsed dye laser combined with ultrapulse fractional CO2 laser in the treatment of immature red hypertrophic scars. J Cosmet Dermatol 2018;17:54-60.
19. van Leeuwen MC, Stokmans SC, Bulstra AE, Meijer OW, Heymans MW, Ket JC, Ritt MJ, van Leeuwen PA, Niessen FB. Surgical Excision with Adjuvant Irradiation for Treatment of Keloid Scars: A Systematic Review. Plast Reconstr Surg Glob Open 2015;3:e440.
20. Har-Shai Y, Amar M, Sabo E. Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. Plast Reconstr Surg 2003;111:1841-1852.
21. Sharquie KE, Noaimi AA, Al-Karhi MR. Debulking of keloid combined with intralesional injection of methotrexate and triamcinolone versus intralesional injection of methotrexate and triamcinolone. J Clin Dermatol Ther 2014;1:003.
22. Roques C, Téot L. The use of corticosteroids to treat keloids: a review. Int J Low Extrem Wounds 2008;7:137-145.
23. Bibi Nitzan Y, Cohen AD. Zinc in skin pathology and care. J Dermatolog Treat 2006;17:205-210.
24. Sharquie KE, Al-Azzawi K. Intralesional therapy of cutaneous leishmaniasis with 2% zinc sulphate solution. J Pan Arab League Dermatol 1996;7:41-46.
25. Sharquie KE, Al-Nuaimy AA, Al-Shimary FA. New intralesional therapy for basal cell carcinoma by 2% zinc sulphate solution. Saudi Med J 2005;26:359-361.
26. Sharquie KE, Khorsheed AA, Al-Nuaimy AA. Topical zinc sulphate solution for treatment of viral warts. Saudi Med J 2007;28:1418-1421.
27. Sharquie KE, Noaimi AA, Kadir NO. Topical Therapy of Xeroderma Pigmentosa with 20% Zinc Sulfate Solution. The Iraqi Postgraduate Medical Journal 2008;7:231-236.
28. Sharquie KE, Al-Mashhadani SA, Salman HA. Topical 10% zinc sulphate solution for treatment of melasma. Dermatol Surg 2008;34:1346-1349.
29. Sharquie KE, Hayani RK, Al-Dori WS, Sharquie IK, Noaimi AA. Treatment of pityriasis versicolor with topical 15% zinc sulfate solution. In 15th Congress of EADV, 2006; Abstract no. 950962.
30. Sharquie KE, Noaimi AA, Al-Salih MM. Topical therapy of acne vulgaris using 2% tea lotion in comparison with 5% zinc sulphate solution. Saudi Med J 2008;29:1757-1761.
31. Sharquie KE, Al-Mashhadani SA, Noaimi AA, Hasan AA. Topical zinc sulphate (25%) solution: a new therapy for actinic keratosis. J Cutan Aesthet Surg 2012;5:53-56.

32. Sharquie KE. Iraqi society of dermatology and venereology activities. IMCAS 2017. Available from: http://www.imcas.com

33. Waibel JS, Wulkan AJ, Shumaker PR. Treatment of hypertrophic scars using laser and laser assisted corticosteroid delivery. Lasers Surg Med 2013;45:135-140.

34. Atiyeh BS. Nonsurgical management of hypertrophic scars: evidence-based therapies, standard practices, and emerging methods. Aesthetic Plast Surg 2007;31:468-492.

35. Riaz Y, Cook HT, Wangoo A, Glenville B, Shaw RJ. Type 1 procollagen as a marker of severity of scarring after sternotomy: effects of topical corticosteroids. J Clin Pathol 1994;47:892-899.

36. Niessen FB, Spauwen PH, Schalkwijk J, Kon M. On the nature of hypertrophic scars and keloids: a review. Plast Reconstr Surg 1999;104:1435-1458.

37. Lebwohl M. The role of salicylic acid in the treatment of psoriasis. Int J Dermatol 1999;38:16-24.

38. Yosipovitch G, Sugeng MW, Chan YH, Goon A, Ngim S, Goh CL. The effect of topically applied aspirin on localized circumscribed neurodermatitis. J Am Acad Dermatol 2001;45:910-913.

39. Tiplica GS, Salavastru CM. Mometasone furoate 0.1% and salicylic acid 5% vs. mometasone furoate 0.1% as sequential local therapy in psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009;23:905-912.

40. Trookman NS, Rizer RL, Weber T. Treatment of minor wounds from dermatologic procedures: a comparison of three topical wound care ointments using a laser wound model. J Am Acad Dermatol 2011;64:8-15.

41. Commander SJ, Chamata E, Cox J, Dickey RM, Lee EI. Update on Postsurgical Scar Management. Semin Plast Surg 2016;30:122-128.

42. Moshref S. Topical zinc oxide adhesive tape for keloid management. The Egyptian Journal of Surgery 2006;25:169-177.

43. Söderberg T, Hallmans G, Bartholdson L. Treatment of keloids and hypertrophic scars with adhesive zinc tape. Scand J Plast Reconstr Surg 1982;16:261-266.

44. Riley K. Flurandrenolone (Cordran) tape as occlusive therapy. J S C Med Assoc 1969;65:171-172.

45. Niessen FB, Spauwen PH, Robinson PH, Fidler V, Kon M. The use of silicone occlusive sheeting (Sil-K) and silicone occlusive gel (Epiderm) in the prevention of hypertrophic scar formation. Plast Reconstr Surg 1998;102:1962-1972.

46. Marks R, Sawyer M. Glucocorticoid-induced vasoconstriction in human skin. An inhibitory role on phospholipase A2 activity. Arch Dermatol 1986;122:881-883.

47. Engrav LH, Heimbach DM, Rivara FP, Moore ML, Wang J, Carrougher GJ, Costa B, Numhom S, Calderon J, Gibran NS. 12-Year within-wound study of the effectiveness of custom pressure garment therapy. Burns 2010;36:975-983.

48. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids. Plast Reconstr Surg 2010;125:557-568.

ORIGINAL ARTICLE

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The Frequency of Comorbidities and Their Effects on Disease Severity in Hidradenitis Suppurativa

Tuğba Kevser Uzunçakmak, Elif Cansel Özçakır, Özge Aşkın, Burhan Engin

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

ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic, inflammatory disease of the apocrine glands which may progress with remissions and attacks. Clinically lesions are frequently located in the axillary, perianal, and inguinal regions which may present with painful nodules, abscesses, sinuses, or scars. Metabolic syndrome, cardiovascular diseases, rheumatological diseases can be associated with HS and may cause impaired life quality and mortality risk. In this study, we aimed to determine the demographic data and accompanying comorbidities of patients diagnosed with HS, as well as to investigate whether is there any effect of comorbidities on disease severity.

Materials and Methods: Clinical findings of 120 patients, who were diagnosed as HS in our clinic or consulted to our clinic between 2017 and 2020 were evaluated retrospectively. Demographic and clinical data of the patients including age, gender, Hurley stage at presentation, smoking status, and comorbidities of the patients were obtained from medical records. The statistical analysis was performed with the Statistical Package for the Social Sciences 21.

Results: According to our study results, 49 (40.8%) patients were women and 71 (59.2%) were men. The average age of the patients was 35.23±10.25 (17-59), the average age of our female patients was in female patients was 32.5±9.47, and the average age of our male patients was 37.1±10.4. The mean age of disease onset was 25.44±9.03 (10-52). Thirteen patients were in Hurley stage 1, 80 patients were in Hurley 2 and 27 patients were in Hurley 3. Ninety-eight patients (81.7%) had a smoking history. Of 121 patients, 59 (49.2%) of our patients had comorbidity. Metabolic syndrome was the most common comorbid disease. The presence of comorbidity only makes a significant difference in terms of being in the first stage of the disease.

Conclusion: HS may be associated with various comorbidities, especially metabolic syndrome. Although we found no significant difference between having a comorbidity and disease stage systemic evaluation of the patients may be useful both in the early diagnosis and treatment of comorbidities and increasing the life quality of these patients.

Keywords: Apocrine glands, Dermatology, Inflammation, Hidradenitis suppurativa, Comorbidities, Metabolic syndrome

Introduction

Hidradenitis suppurativa (HS) is a chronic auto-inflammatory disease with exacerbation episodes observed in areas of skin rich in apocrine glands. The disease is characterized by painful nodules, abscesses, and scars [1]. It is more common in the postpubertal period and women are more affected than men. Its prevalence is between 0.05% and 4% [2,3]. Its etiology is not clear but it is considered a component of the follicular occlusion triad which is thought to begin with hair follicle hyperkeratinization and follicle occlusion [4,5]. Studies have shown that the incidence is higher in smokers [6]. It has been stated that cigarette content, especially nicotine, can increase follicle occlusion, inflammatory cell chemotaxis, and

Address for Correspondence: Tuğba Kevser Uzunçakmak MD, Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine, Department of Dermatology, Istanbul, Turkey
Phone: +90 530 664 02 26 E-mail: drtugbakevser@gmail.com ORCID ID: orcid.org/0000-0002-0328-4171
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tumor necrosis factor-α release, which play a role in pathogenesis [4,5]. The diagnosis of the disease is made by clinical symptoms and signs. The typical appearance of the lesions, their distribution, and their progressive and chronic features with recurrences are important in diagnosis [7]. Histopathological evaluation can be used in cases where the differential diagnosis cannot be made [8]. Hurley staging is used in the severity evaluation of HS [9]. Physical and psychosocial problems are also commonly seen in patients with HS, and the disease may be accompanied by metabolic syndrome, cardiovascular diseases, psychiatric diseases, dermatological diseases, and other inflammatory diseases [10].

Materials and Methods

In this retrospective study, 120 patients who applied to Istanbul University Cerrahpasa-Cerrahpasa Faculty Medicine Dermatology and Venereal Diseases Department between January 2017 and August 2020 and were diagnosed with HS were evaluated. We conducted our research according to the World Medical Association Declaration of Helsinki and obtained the approval of the Istanbul University Cerrahpasa-Cerrahpasa Faculty Medicine Local Ethics Committee (ethical approval: 17.12.2020/164438). The age, gender, Hurley stage at presentation, smoking status, and comorbidities of the patients were retrospectively reviewed and noted.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 21. Descriptive analyzes mean and standard deviation, median, 25-75 by data type. It is given as quartiles and percentages. The distribution of continuous data was evaluated with the Shapiro-Wilk and Kolmogorov-Smirnov test. Comparisons between groups were made with Fisher's Exact test (Fisher's exact test) when the chi-square test and chi-square test conditions were not met in categorical variables. The Kruskal-Wallis test was used for multiple comparison procedures for continuous data that did not meet the normality conditions. A p value below 0.05 was considered significant.

Results

According to our study results, 49 (40.8%) of our patients were women and 71 (59.2%) were men. The mean age of the patients was 35.23±10.25 (minimum-maximum: 17-59), 32.5±9.47 (minimum-maximum: 17-58) in females, and 37.1±10.4 (minimum-maximum: 18-59) in males. The mean age at disease onset age was 25.44±9.03 (19-30.75). The median age distribution according to the stage of the patients is given in Table 1. No significant correlation was found between the age of onset and the Hurley stage (p=0.136). According to the Hurley classification, 13 patients were in stage 1 (10.8%), 80 were in stage 2 (66.6%), and 27 were in stage 3 (22.5%) (Table 2). Ninety-eight (81.7%) patients had a smoking history, but no significant relationship was found between smoking and disease stage (Fisher's Exact test, p=0.441) (Table 3). Among the smokers, 9 (9.2%) were in stage 1, 66 (67.3%) were in stage 2 and 23 (23.5%) were in stage 3, and among the non-smokers, 4 (18.2%) patients were in stage 1, 14 (63.6%) patients were in stage 2 and 4 (18.2%) patients were in stage 3. While 59 (49.2%) of our patients had comorbidity, 61 (50.8%) had no accompanying disease. The distribution of comorbidities is shown in Table 4. In 3.4% (n=2) of the patients with comorbidity, the disease is in the first stage, and in 18% (n=11) of the patients without comorbidity, the disease is in the first stage. The presence of comorbidity makes a significant difference in terms of being in the first stage of the disease (Pearson's chi-square test, p=0.03). There was no difference in the presence of comorbidity in patients in stages 2 and 3 (Table 5).

Discussion

Although the prevalence of HS is not fully known, it is estimated that it occurs in approximately one in 300 adults. The usual onset is in the second or third decade of life and rarely occurs before puberty and after the age of 40 [11]. In our study, HS was more common in young adults. It was reported that women are more likely to develop HS than men in United States-based studies [12].

Table 1. Demographic characteristics of the patients

Clinical findings of the patients			
Characteristics	**Female**	**Male**	**Total**
Mean age	32.51±9.47	37.11±10.41	35.23±10.25
Disease onset	23.53±7.98	26.76±9.52	25.44±9.03
Smoking	37	61	98
Metabolic syndrome	14	18	32
Rheumatologic diseases	2	1	3
Psychiatric disorder	4	2	6
Coronary artery disease	2	4	6
Dermatologic diseases	4	2	6
Inflammatory bowel disease	1	1	2
Respiratory tract disease	2	2	4

Table 2. The median age distribution according to the stage of the patients

Hurley	Median (IQR)
Stage 1 (13 patients)	20 (15.5-24.5)
Stage 2 (80 patients)	25 (19.25-30)
Stage 3 (27 patients)	24 (18-35)

IQR: Interquartile range

Table 3. Correlation between smoking and disease severity

			Stage 1	Stage 2	Stage 3	Total
Smoking	No smoking	No	4	14	4	22
		% within smoking	18.2%	63.6%	18.2%	100.0%
	Smoking	No	9	66	23	98
		% within smoking	9.2%	67.3%	23.5%	100.0%
Total		No	13	80	27	120
% within smoking		10.8%	66.7%	22.5%	100.0%	
Fisher's Exact test p=0.441						

Table 4. Distribution of comorbidities

Comorbidity		Frequency	Percent
No comorbidity	Stage 1	11	18.0
	Stage 2	36	59.0
	Stage 3	14	23.0
	Total	61	100.0
Metabolic syndrome	Stage 2	25	78.1
	Stage 3	7	21.9
	Total	32	100.0
Rheumatologic disorder	Stage 1	1	33.3
	Stage 2	2	66.7
	Total	3	100.0
Psychiatric disorder	Stage 2	4	66.7
	Stage 3	2	33.3
	Total	6	100.0
Coronary artery disease	Stage 2	6	100.0
Dermatologic diseases	Stage 2	5	83.3
	Stage 3	1	16.7
	Total	6	100.0
Inflammatory bowel disease	Stage 2	1	50.0
	Stage 3	1	50.0
	Total	2	100.0
Respiratory tract disorder	Stage 1	1	25.0
	Stage 2	1	25.0
	Stage 3	2	50.0
	Total	4	100.0

Table 5. Distribtuion of comorbidities according to stage

	Frequency	Percent	Valid percent
No	61	50.8	50.8
Metabolic syndrome	32	26.7	26.7
Rheumatologic diseases	3	2.5	2.5
Psychiatric disorder	6	5.0	5.0
Coronary artery disease	6	5.0	5.0
Dermatologic diseases	6	5.0	5.0
Inflammatory bowel disease	2	1.7	1.7
Respiratory tract disease	4	3.3	3.3
Total	120	100.0	100.0

In another study which was conducted in Korea HS was found more be more frequent in men [13]. In two studies published in Turkey, HS was reported to be more common in men [14,15]. In our study, male patients were also in the majority. Gender differences in HS in studies conducted in Europe and Asia may be related to hormonal factors, smoking habits, genetic background, geographical and ethnic differences [16].

Mechanical stresses on the skin, obesity, genetic susceptibility, smoking, diet, and hormonal factors are cited as factors that may be associated with the development or exacerbation of HS [17]. There is a strong relationship between smoking and HS [18]. The nicotine released with sweat is thought to induce epithelial hyperplasia in surrounding cells, causing occlusion and hyperkeratosis in the follicle [19]. In a French case-control study of 302 clinically assessed patients with HS and 906 controls, 76% of the patients with HS versus 25% of the controls were current smokers [20]. In another study which was conducted by Kromann et al. [21], tobacco smoking was reported in 92.2% of the patients with HS. In our study, 81.7% of our patients were smoking. Our study results support the high smoking rate in patients with HS. In the Scandinavian study, disease severity was found to be higher in smoking patients [22]. Another study reported that smoking was correlated with disease severity [18]. However, there are also studies reporting that there is no relationship between smoking and disease severity [23]. In our study, the majority of our patients also had smoked, but no significant relationship was found between smoking and disease stage. The results of studies investigating the relationship between smoking and disease severity in HS are contradictory.

In recent years the comorbid diseases accompanying HS have been investigated in several studies. Both inflammatory disorders and autoimmune disorders may be associated with HS. Metabolic syndrome and cardiac diseases were reported as the most common comorbidities in patients with HS [24]. In our study 32 (26.7%) patients had accompanying comorbidity and half of the patients

who have an accompanying disease had metabolic syndrome. Egeberg et al. [25] reported that Crohn's disease and ulcerative colitis may be associated with HS. There are some studies about the relationship between rheumatological diseases, especially axial spondyloarthritis, and HS [26,27]. HS can also cause serious psychosocial problems due to its clinical findings [28]. Therefore, patients with HS should be evaluated and supported in terms of quality of life and psychiatry. In our study, 10% of the comorbidities were psychiatric disorders.

There are few studies in the literature regarding the effect of comorbidities on disease severity in patients with HS [29,30]. In a recent study published by Liakou et al. [29], thyroid disease and active smoking were found to be associated with more severe HS. Özkur et al. [15] also reported that presence of comorbidity and having a delayed diagnosis were associated with disease severity. In our study, we found no significant correlation between disease severity and having comorbidity.

Study Limitation

The main limitation of our study is being a retrospective study that was conducted from a single center with a limited patient number.

Conclusion

In conclusion, HS may be associated with various comorbidities, especially metabolic syndrome. Although we found no significant difference between comorbidities and HS severity, the most common disorders should be questioned and consulted with appropriate clinics. Further investigation of HS disease in larger prospective studies is needed to clarify its clinical-epidemiological characteristics and to better understand its etiology and management.

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Ethics

Ethics Committee Approval: We conducted our research according to the World Medical Association Declaration of Helsinki and obtained the approval of the Istanbul University Cerrahpasa-Cerrahpasa Faculty Medicine Local Ethics Committee (ethical approval: 17.12.2020/164438).

Informed Consent: Retrospective study.

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Authorship Contributions

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

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References

1. Alikhan A, Sayed C, Alavi A, Alhusayen R, Brassard A, Burkhart C, Crowell K, Eisen DB, Gottlieb AB, Hamzavi I, Hazen PG, Jaleel T, Kimball AB, Kirby J, Lowes MA, Micheletti R, Miller A, Naik HB, Orgill D, Poulin Y. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part I: Diagnosis, evaluation, and the use of complementary and procedural management. J Am Acad Dermatol 2019;81:76-90.
2. Cosmatos I, Matcho A, Weinstein R, Montgomery MO, Stang P. Analysis of patient claims data to determine the prevalence of hidradenitis suppurativa in the United States. J Am Acad Dermatol 2013;69:819.
3. Ingram JR, Jenkins-Jones S, Knipe DW, Morgan CLI, Cannings-John R, Piguet V. Population-based Clinical Practice Research Datalink study using algorithm modelling to identify the true burden of hidradenitis suppurativa. Br J Dermatol 2018;178:917-924.
4. van der Zee HH, Laman JD, Boer J, Prens EP. Hidradenitis suppurativa: viewpoint on clinical phenotyping, pathogenesis and novel treatments. Exp Dermatol 2012;21:735-739.
5. Mortaz E, Adcock IM, Ito K, Kraneveld AD, Nijkamp FP, Folkerts G. Cigarette smoke induces CXCL8 production by human neutrophils via activation of TLR9 receptor. Eur Respir J 2010;36:1143-1154.
6. Garg A, Papagermanos V, Midura M, Strunk A. Incidence of hidradenitis suppurativa among tobacco smokers: a population-based retrospective analysis in the USA Br J Dermatol 2018;178:709-714.
7. Jemec GB. Clinical practice. Hidradenitis suppurativa. N Engl J Med 2012;366:158-164.
8. Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. J Am Acad Dermatol 2009;60:539-561.
9. Canoui-Poitrine F, Revuz JE, Wolkenstein P, Viallette C, Gabison G, Pouget F, Poli F, Faye O, Bastuji-Garin S. Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. J Am Acad Dermatol 2009;61:51-57.
10. Dauden E, Lazaro P, Aguilar MD, Blasco AJ, Suarez C, Marin I, Queiro R, Bassas-Vila J, Martorell A, García-Campayo J. Recommendations for the management of comorbidity in hidradenitis suppurativa. J Eur Acad Dermatol Venereol 2018;32:129-144.
11. Slade DE, Powell BW, Mortimer PS. Hidradenitis suppurativa: pathogenesis and management. Br J Plast Surg 2003;56:451-461.
12. Garg A, Lavian J, Lin G, Strunk A, Alloo A. Incidence of hidradenitis suppurativa in the United States: A sex- and age-adjusted population analysis. J Am Acad Dermatol 2017;77:118-122.
13. Yang JH, Moon J, Kye YC, Kim KJ, Kim MN, Ro YS, Park MY, Ahn HH, Lee MW, Lee WJ, Lee JH, Lee JB, Jang MS, Choi YS, Choi YW, Suh DH; Korean Society for Acne Research. Demographic and clinical features of hidradenitis suppurativa in Korea. J Dermatol 2018;45:1389-1395.
14. Yüksel M, Basım P. Demographic and Clinical Features of Hidradenitis Suppurativa in Turkey. J Cutan Med Surg 2020;24:55-59.
15. Özkur E, Karadağ AS, Üstüner P, Aksoy B, Eşme P, Çalışkan E, Akoğlu G, Kalkan G, Demirseren DD, Polat M, Ozden MG, Kılınç F, Yalçınkaya İyidal A, Kıvanç Altunay İ, Türkmen M, Uğurer E, Baysak S, Fettahlıoğlu Karaman B, Mammadlı K, Baykal Selçuk L, Türkoğlu Z, Atcı T, Didar Balcı D, Adışen E,

Temel B, Aktan Ş, Kaçar N, Gündüz K, Türel Ermertcan A, Özdemir M, Ünal Çakıter A, Çölgeçen E, Uçmak D, Kelekçi H, Ataseven A, Durmaz K, Kaya Özden H, Engin B, Yazıcı S, Alpsoy E. Clinical and demographic features of hidradenitis suppurativa: a multicentre study of 1221 patients with an analysis of risk factors associated with disease severity. Clin Exp Dermatol 2021;46:532-540.

16. Happle R. Korean gender differences in hidradenitis suppuratva: nature or nurture? J Eur Acad Dermatol Venereol 2019;33:e256.
17. Seyed Jafari SM, Hunger RE, Schlapbach C. Hidradenitis Suppurativa: Current Understanding of Pathogenic Mechanisms and Suggestion for Treatment Algorithm. Front Med (Lausanne) 2020;7:68.
18. Sartorius K, Emtestam L, Jemec GB, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. Br J Dermatol 2009;161:831-839.
19. Kurzen H, Kurokawa I, Jemec GB, Emtestam L, Sellheyer K, Giamarellos-Bourboulis EJ, Nagy I, Bechara FG, Sartorius K, Lapins J, Krahl D, Altmeyer P, Revuz J, Zouboulis CC. What causes hidradenitis suppurativa? Exp Dermatol 2008;17:455-6; discussion 457-72.
20. Revuz JE, Canoui-Poitrine F, Wolkenstein P, Viallette C, Gabison G, Pouget F, Poli F, Faye O, Roujeau JC, Bonnelye G, Grob JJ, Bastuji-Garin S. Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. J Am Acad Dermatol 2008;59:596-601.
21. Kromann CB, Deckers IE, Esmann S, Boer J, Prens EP, Jemec GB. Risk factors, clinical course and long-term prognosis in hidradenitis suppurativa: a cross-sectional study. Br J Dermatol 2014;171:819-824.
22. Garg A, Besen J, Legler A, Lam CS. Factors Associated With Point-of-Care Treatment Decisions for Hidradenitis Suppurativa. JAMA Dermatol 2016;152:553-557.
23. Matusiak L, Bieniek A, Szepietowski JC. Hidradenitis suppurativa and associated factors: still unsolved problems. J Am Acad Dermatol 2009;61:362-365.
24. Kohorst JJ, Kimball AB, Davis MD. Systemic associations of hidradenitis suppurativa. J Am Acad Dermatol 2015;73:27-35.
25. Egeberg A, Jemec GBE, Kimball AB, Bachelez H, Gislason GH, Thyssen JP, Mallbris L. Prevalence and Risk of Inflammatory Bowel Disease in Patients with Hidradenitis Suppurativa. J Invest Dermatol 2017;137:1060-1064.
26. Rondags A, Arends S, Wink FR, Horváth B, Spoorenberg A. High prevalence of hidradenitis suppurativa symptoms in axial spondyloarthritis patients: A possible new extra-articular manifestation. Semin Arthritis Rheum 2019;48:611-617.
27. Ben David C, Bragazzi NL, Watad A, Sharif K, Whitby A, Amital H, Adawi M. Hidradenitis suppurativa associated with systemic lupus erythematosus: A case report. Medicine (Baltimore) 2018;97:e0186.
28. Alavi A, Farzanfar D, Rogalska T, Lowes MA, Chavoshi S. Quality of life and sexual health in patients with hidradenitis suppurativa. Int J Womens Dermatol 2018;4:74-79.
29. Liakou AI, Kontochristopoulos G, Marnelakis I, Tsantes AG, Papadakis M, Alevizou A, Rotsiamis N, Rigopoulos D. Thyroid Disease and Active Smoking May Be Associated with More Severe Hidradenitis Suppurativa: Data from a Prospective Cross Sectional Single-Center Study. Dermatology 2021;237:125-130.
30. Preda-Naumescu A, Ahmed HN, Mayo TT, Yusuf N. Hidradenitis suppurativa: pathogenesis, clinical presentation, epidemiology, and comorbid associations. Int J Dermatol 2021:22.

CASE REPORT

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Rituximab and IVIG for the Treatment of Bullous Pemphigoid: Critical Analysis of the Current Literature

Melis Gönülal, Didem Didar Balcı

University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital, Clinic of Dermatology, Izmir, Turkey

ABSTRACT

Bullous pemphigoid (BP) is the most common subepidermal autoimmune blistering disease. We want to present a case with resistant BP accompained by telling both clinical features and treatments. A 67 year-old female with diabetes mellitus (DM) applied to dermatology outpatient clinic because of pruritus. Our patient didn't receive complete clinical response with the treatments of methylprednisolone aceponate lotion, bilastine tablet, omalizumab, oral steroid, azathioprine and tetracycline. In addition, she became insulin dependent DM because of oral steroid and azathioprine raised the levels of her liver enzymes. We had to stop these treatments. Now our patient is in remission with the treatments of rituximab and intravenous immunoglobulin (IVIG). We used rituximab and IVIG which are combined last step treatment regimens for our case and achieved to treat her. We think that our case report will contribute to literature because such difficult, rare cases may appear to clinicians at any time and our case may be a guide for clinicians.

Keywords: Bullous pemphigoid, Rituximab, Intravenous immunglobulin

Introduction

Bullous pemphigoid (BP) is the most common subepidermal autoimmune blistering disease. Clinically, it is characterized by tense blisters with widespread erythema. Histology reveals subepidermal bullae with eosinophil infiltration and linear deposition of immunoglobulin (Ig) G and/or C3 along the basement membrane zone. Dementia, Parkinson's disease, psychiatric disorders, and blood disorders may associate with BP. Clinicans diagnose BP with clinical features, histology of lesions taken by skin biopsies, direct immunofluorescence and serum indirect immunofluorescence, (enzyme-linked immunosorbent assay) [1]. The non-collagenous 16A (NC16A) domain of BP180 and C-terminal domain of BP230 are the major epitopes of BP [2]. IgG against the NC16A domain of BP180 can be found in >90% of BP patients and autoantibodies against BP230 can be found in only 60% of BP patients [3]. Most of patients respond to first step treatments but rarely patients unresponsive to treatments can exist. We want to present a case with resistant BP accompained by telling both clinical features and treatments. We have received the informed consent form from the patient.

Case Report

A 67 year-old female with diabetes mellitus (DM) applied to dermatology outpatient clinic of Izmir Tepecik Training and Research Hospital because of pruritus that had been going on for two months. The patient said that sometimes urticaria like papules occured on her body and extremites. She was 80 kg and 154 cm tall. She had been used oral metformin hydrocloride 1000 mg/day because of DM. The physical examination revealed xerosis cutis and excoriations. In laboratory findings, we determined mild anemia because hemoglobin (Hgb) was 11 g/dL, hematocrite was 34.3%, mean cell Hgb (MCH) was 26.6 pg. Creatinine was 1 mg/dL, this value

Address for Correspondence: Melis Gönülal MD, University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital, Clinic of Dermatology, Izmir, Turkey
Phone: +90 506 888 95 69 E-mail: drmelis@gmail.com ORCID ID: orcid.org/0000-0002-6042-656X
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was slightly above normal. All hepatitis makers were negative. Total IgE, sedimentation, vitamine B12, thyroid stimulating hormone and urine test were normal. Methylprednisolone aceponate lotion and bilastine tablet were recommended twice a day. The patient was examined again after three months and we observed urticaria like papules-plaques on her body. Omalizumab treatment was beginned to patient 300 mg once a month and antihistamine medication was continued. Mometasone furoate cream prescribed instead of methylprednisolone aceponate lotion. After one month, cyclosporine was beginned to patient 200 mg a day because pruritus continued severe, but the values of urea, creatinine, total cholesterol, low density lipoprotein, triglyceride, blood potassium increased to 52.8 mg/dL, 1.12 mg/dL, 283 mg/dL, 166 mg/dL, 171 mg/dL, 5.45 mmol/L respectively and value of magnesium decreased to 1.5 mg/dL Therefore cyclosporine treatment was stopped. Omalizumab treatment at 300 mg a month continued for three months after that due to unresponsiveness omalizumab injections were started at 300 mg every two weeks and clinical response was received. But then pruritus of the patient relapsed, totally after 11 doses, omalizumab was stopped. On physical examination, we noticed small vesicules on her body and took a biopsy from the patient (Figure 1). The result of the biopsy was determined as BP. In the biopsy report, linear accumulation of C3 and intermittent accumulation of IgG was determined at dermoepidermal junction. Accumulation of IgM, C1q, IgA and fibrinogen wasn't observed. The patient was referred to the internal medicine outpatient clinic to exclude malignancy. As a result of examinations, no malignancy was detected in the case. As medication, oral methylprednisolone at a dose of 48 mg/day, azathioprine at a dose of 150 mg/day, levocetirizine at a dose of 10 mg/day and topical steroid cream were begun for her, but methylprednisolone was stopped after 15 days because the patient developed insulin dependent DM, accordingly azathioprine was stopped because of high liver enzyme levels. Tetracycline tablet 500 mg dialy was started but after one month the patient complained of severe nausea and we had to stop tetracycline treatment, too. Extensive vesicles and bullaes became on her body (Figure 2). We didn't think BP due to drugs, because when metformin had been stopped and switched to insulin, BP of the case continued. Intravenous Ig (IVIG) treatment was started for the patient whose laboratory findings were normal except Hgb level of 10.6 gr/dL. After 6 doses of IVIG, the patient healed completely, there were no pruritus and no skin findings but after two months pruritus, vesicles and bullaes came back. Rituximab at a dose of 500 mg was given to the patient two weeks apart but clinical response wasn't received. Tetracycline tablet 500 mg daily and nicotinamide ampul 12 mg weekly were started in addition to the current treatment of the patient and nausea didn't occured. Now our patient is in the second month of tetracycline and nicotinamide treatment and she is in remission (Figure 3). Accordingly she took 10 doses of IVIG but

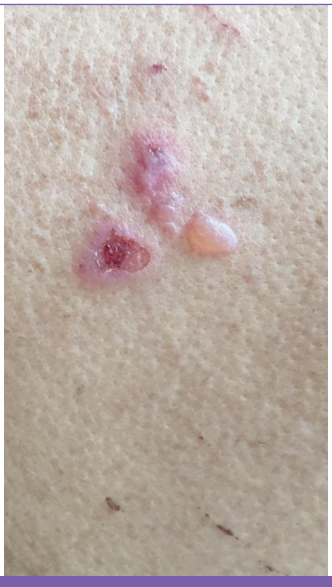

Figure 1. Intact bullae

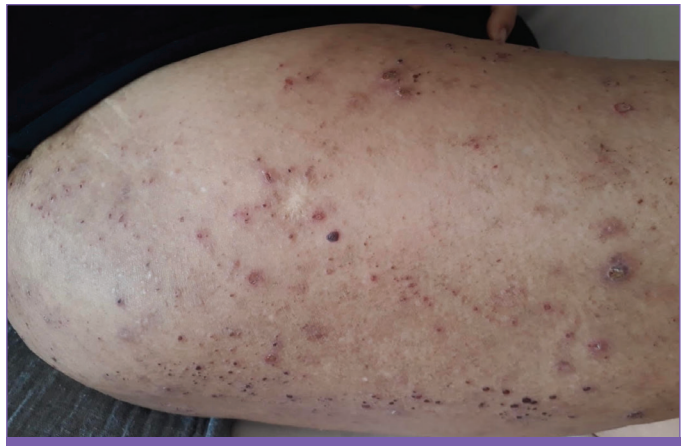

Figure 2. Excoriations, erosions, crusts

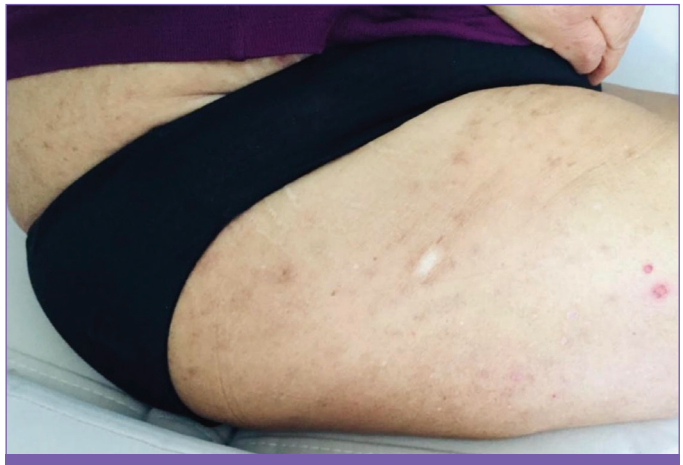

Figure 3. Healed lesions

because of Coronavirus disease-19 pandemic we couldn't continue IVIG treatment. We learned in our phone call that she was well and there was minimal pruritus. We continue now for her the treatments of tetracycline and nicotinamide.

Discussion

There are different treatment models for BP. According to BP diagnostic treatment guide, there are oral corticosteroids on first step for generalise form of disease. Azathioprine, mycophenolate mofetil, tetracycline and nicotinamide, methotrexate, chlorambucil take part on second step of treatment. For resistant cases, rituximab, omalizumab, IVIG, immunoadsorption, plasma exchange, cyclophosphamide are recommended on third step as alternative treatment or initial treatment [4].

Initially, our patient had complaints like urticaria and over time on physical examinations we saw urticaria like papules and plaques on her body. Therefore we recommended oral antihistamines and omalizumab treatment to our patient. Omalizumab took part in the treatment of BP and elevated IgE levels and/or eosinophilia are the important factors to recommend this antibody in BP. When we evaluate the mechanism of IgE in BP, IgE connect the free ectodomain of collagen XVII, which include the NC16A domain, to IgE autoantibodies bound to FceRI expressed on mast cells and eosinophils. This binding stimulate degranulation and started an inflammatory process. In addition, IgE binds to the ectodomain NC16A located in the basal aspect of basal keratinocytes. Omalizumab obstructs the binding of IgE to these receptors [5,6]. Maybe omalizumab could be effective and vesicles,bullaes couldn't appear in time. If it was like this, we could follow her as an urticaria patient and couldn't diagnose BP.

In time, because we observed vesicles on examination, we took biopsy and could diagnose BP. We applied the first step treatment for our patient but then stopped oral corticosteroid because she developed insulin resistant DM. When the patient didn't response to second step of treatment, we switched to tertiary care.

IVIG is an other alternative, safe and effective treatment model for BP. IVIG consists mainly of IgG1 and IgG2. Numerous mechanisms have been reported to explain the immunomodulatory effects of IVIG. To summarize, these proposed modes of action include saturation of the IgG protective neonatal FcR receptor (FcRn), neutralization of autoantibodies by anti-idiotypic antibodies, neutralization of cytokines or modulation of cytokine production, attenuation of complement-mediated tissue damage, modulation of functions of Fc receptors, and modulation of effector functions of T, B, and dendritic cells [7]. In literature, there are patients healed with IVIG but sometimes patients can be resistant to IVIG treatment as in our patient.

Rituximab is a chimeric anti-CD20 monoclonal antibody and an alternative treatment for recalcitrant BP. In Polansky et al.'s [8] study 15 of 20 patients with BP treated with rituximab (75%) achieved durable remission, with 5 patients requiring adjuvant therapy, 7 receiving minimal therapies, and 3 no longer taking any medications. Additionally, 9 patients were no longer taking prednisone at their last visit, suggesting a steroid-sparing benefit to rituximab therapy. Our case was resistant to rituximab.

Dupilumab, targeting interleukin-4 receptor alpha (IL4Rα), is a novel treatment for refractory BP. In recent reports, dupilumab has been successfully used off-label to treat a variety of pruritic disorders, including chronic spontaneous urticaria, anal and genital itch, allergic contact dermatitis, and prurigo nodularis [9]. Dupilumab isn't available in Turkey. If the disease of our case relapses, we can think to plan dupilumab for her with the approval of Turkish ministery of health.

BP can be confused with chronic idiopatic urticaria or other skin diseases like atopic dermatitis. Definitive diagnosis is made by pathology. Rarely, this disease can be refractory. There are different treatment models for resistant type of BP. We used combined last step treatment regimens for our case and achieved to treat her. We think that our case report will contribute to literature because such difficult, rare cases may appear to clinicians at any time and our case may be a guide for clinicians.

Ethics

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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References

1. Liu Y, Wang Y, Chen X, Jin H, Li L. Factors associated with the activity and severity of bullous pemphigoid: a review. Ann Med 2020;52:55-62.
2. Bağcı IS, Horváth ON, Ruzicka T, Sárdy M. Bullous pemphigoid. Autoimmun Rev 2017;16:445-455.
3. Zhao CY, Murrell DF. Outcome measures for autoimmune blistering diseases. J Dermatol 2015;42:31-36.
4. Feliciani C, Joly P, Jonkman MF, Zambruno G, Zillikens D, Ioannides D, Kowalewski C, Jedlickova H, Kárpáti S, Marinovic B, Mimouni D, Uzun S, Yayli S, Hertl M, Borradori L. Management of bullous pemphigoid: the European

Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. Br J Dermatol 2015;172:867-877.

5. Vico-Alonso C, Calleja-Algarra A, Aragón-Miguel R, Sánchez-Velázquez A, Velasco-Tamariz V, Ortiz-Romero PL, Monsálvez-Honrubia V. Omalizumab as an alternative therapeutic tool in the treatment of bullous pemphigoid: A case report. Dermatol Ther 2019;32:12829.
6. Ujiie H. IgE autoantibodies in bullous pemphigoid: supporting role, or leading player? J Dermatol Sci 2015;78:5-10.
7. Li N, Culton D, Diaz LA, Liu Z. Modes of Action of Intravenous Immunoglobulin in Bullous Pemphigoid. J Invest Dermatol 2018;138:1249-1251.
8. Polansky M, Eisenstadt R, DeGrazia T, Zhao X, Liu Y, Feldman R. Rituximab therapy in patients with bullous pemphigoid: A retrospective study of 20 patients. J Am Acad Dermatol 2019;81:179-186.
9. Seidman JS, Eichenfield DZ, Orme CM. Dupilumab for bullous pemphigoid with intractable pruritus. Dermatol Online J 2019;25:13030/qt25q9w6r9.

CASE REPORT

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Hemolytic Anemia: A Rare Side Effect Related with IVIG Therapy in Stevens-Johnson Syndrome

Cüneyt Kara[1], Sevim Baysak[2], Zuhal Erçin[2], Tuğba Falay Gür[2], Sevil Savaş Erdoğan[2], Bilal Doğan[2]

[1]Batman Regional State Hospital, Clinic of Dermatology, Batman, Turkey
[2]Istanbul Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Dermatology, Istanbul, Turkey

ABSTRACT

Intravenous immunoglobulin (IVIG) is commonly used as replacement therapy in immunodeficiency disorders and in higher doses for certain autoimmune and inflammatory conditions. Dermatomyositis, Kawasaki disease, pyoderma gangrenosum, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, pemphigus group and bullous pemhigoid are the most common indications for IVIG treatment. Common side effects of IVIG include headache, flu-like symptoms, nausea, chills, rash, backache, and hypotension. Rare serious adverse events, including anaphylaxis, acute renal failure, aseptic meningitis, transfusion-related acute lung injury, and thrombo-embolic events may also ocur. Only a few cases of hemolytic anemia associated with IVIG therapy have been reported to date. We present a case of hemolytic anemia after IVIG therapy in a patient with SJS.

Keywords: Stevens-Johnson syndrome, Intravenous immunoglobulin, Hemolytic anemia

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and serious cutaneous adverse reactions, associated with high mortality [1]. SJS/TEN can be defined as fissuration of the necrotic epidermis and erosion of mucous membranes of varying severity [2]. SJS/TEN are usually caused by an allergic reaction based on drugs including antibiotics, non-steroidal anti-inflammatory agents, anti-convulsants and allopurinol [3,4]. Infections, including mycoplasma infection, are also known as possible causes of SJS in yong patients [4,5,6]. Many therapeutic methods are used in its treatmet including systemic steroids, plasmapheresis and immunosuppressant drugs [4,7,8]. Its thought that fas blocking antibodies occuring naturally duration of intravenous immunoglobulin (IVIG) inhibit fas mediated keratinocyte apoptosis [9] and therefore they are used in treatment [10]. We present a case with SJS developed hemolytic anemia during IVIG treatment.

Case Report

A 35-year-old man was admitted to our hospital with flu-like symptoms and a widespread rash that was worsening during one week period. One day before the rash the patient had taken dexketoprofen for his backache. Additionally he had been taking lamotrigine, trifluoperazine and buspirone for four months for somatoform disorder which are prescribed by his psychiatrist. His family history was unremarkable. The patient was a non-smoker and had denied alcohol and illicit drug use.

On general examination the patient had malaise and low-grade fever. Dermatological examination showed target lesions and erythematous plaques on his trunk, upper and lower extremities. Some plaques had pustule formation in the center of the lesions (Figures 1, 2). In addition, Nikolsky's sign was positive both on the lesional and healthy skin. Histopathological examination of the lesional skin revealed keratinocyte apoptosis/necrosis

Address for Correspondence: Sevim Baysak MD, Istanbul Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Dermatology, Istanbul, Turkey
Phone: +90 505 817 76 24 E-mail: drsevimharman@hotmail.com ORCID ID: orcid.org/0000-0001-9666-5821
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and dermoepidermal junction detachment. All of the infectious etiologies have been ruled out with negative blood cultures and appropriate tests. According to the clinical findings and biopsy results, we diagnosed the patient as SJS.

As soon as we diagnosed the patient as SJS, we cessated all of his drugs upon permission of psychiatry department. We started combination therapy with systemic corticosteroid and IVIG. The patient was 70 kg and was treated with four consecutive doses of IVIG 0.75 g/kg/day and methylprednisolone 60 mg/day for four days. After four days, erytematous plaques have resolved and Nikolsky's sign had become negative. The patient's temperature also returned to normal. Upon this, we stopped the combination treatment and followed the patient without any intervention. Before starting therapy, the patient's hemoglobin level was 14.93 g/dL and total bilirubin level was 1.1 mg/dL (indirect bilirubin 0.8 mg/dL). The hemoglobin level started to decrease (12.52 g/dL) after the first dose of IVIG therapy. During the following days, on which the patient was taking combination therapy of IVIG and systemic corticosteroid, we observed almost similar hemoglobin levels such as 12.62 g/dL, 12.00 g/dL and 12.40 g/dL. But on hospital day 11, which was six days after ending the combination treatment upon clinical cure of SJS, we observed that the patient had scleral icterus. Laboratory results showed decreased hemoglobin level of 10.7 g/dL and increased total bilirubin level of 1.9 mg/dL (indirect bilirubin level 1.28 mg/dL). We consulted the patient to the hematology department by which some additional laboratory investigation has been undertaken. Haptoglobin level was found <8 mg/dL, direct Coombs test was positive, reticulocyte count was elevated 6% and the other laboratory values including lactate dehydrogenase (LDH), total iron binding capacity, platelet count, vitamin B12, folic acid, prothrombin time, partial thromboplastin time and international normalized ratio were in the normal range. Besides scleral icterus the patient didn't show any other clinical finding. Hematology department diagnosed the patient as hemolytic anemia and recommended observing the patient in the hospital without any intervention. At follow up, five days later, on hospital day 16, we noticed that laboratory values were returning to normal such as hemoglobin level being 11.2 g/dL, total bilirubin level 1.1 mg/dL (indirect bilirubin 0.85 mg/dL), haptoglobin level 18 mg/dL and direct Coombs test has become negative. Hemoglobin levels started to increase dramatically and reached 13.2 g/dL and 14.6 g/dL, two and three weeks after the diagnosis of hemolytic anemia, respectively.

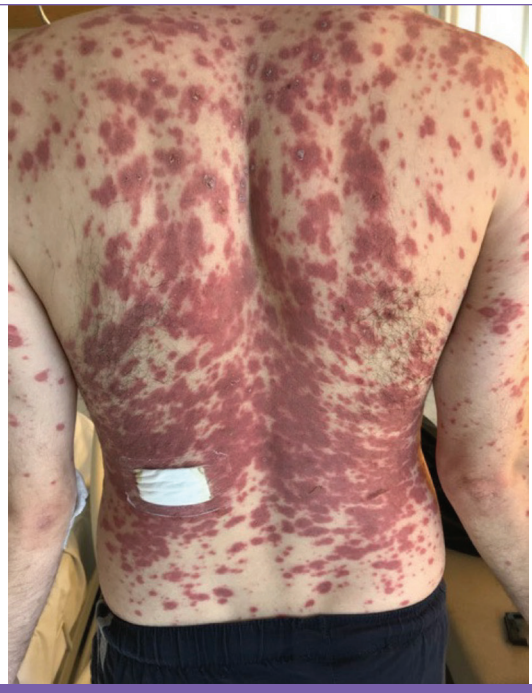

Figure 1. Erythematous papules plaques and detachment on his trunk and upper extremity

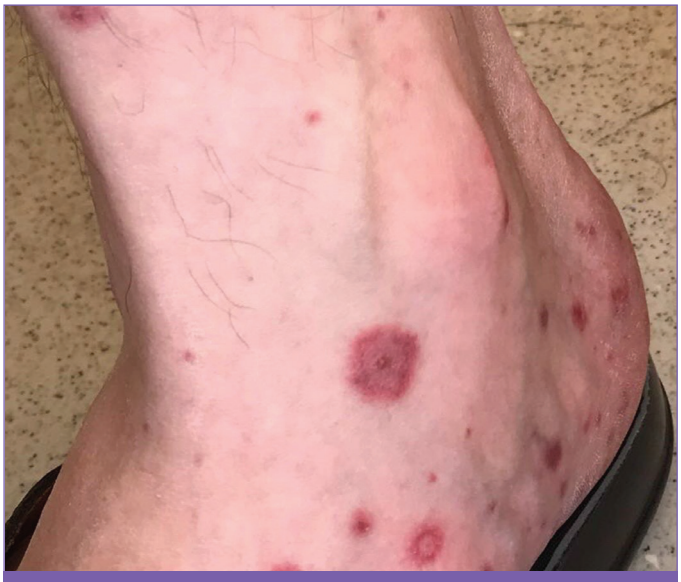

Figure 2. Atypical target lesion on his foot

Discussion

SJS is a rarely encountered disease but has a high mortality. After the diagnosis of SJS or TEN, the culprit drug must be cessated immediately. Supportive care and specific medical treatment is also essential. Systemic corticosteroid, IVIG and cyclosporine are some of the mostly recommended pharmacological agents for the medical treatment. IVIG contains natural anti-Fas antibodies and other immunomodulators that may prevent apoptosis [11]. In our case we applied combined IVIG and systemic corticosteroid treatment.

Rare serious adverse events, including anaphylaxis, acute renal failure, aseptic meningitis, transfusion-related acute lung injury, and thrombo-embolic events may ocur during IVIG therapy [12].

Hemolysis is a rare side effect of IVIG therapy and only a few cases of hemolytic anemia associated with IVIG therapy have been reported to date [13,14]. In a case series of 16 patients; some severe cases required blood transfusion whereas most of the mild cases recovered spontaneously without any intervention [15]. Although not clear, the underlying mechanism of hemolytic anemia is thought to be related to autoimmunity.

We established the diagnosis according to the proposed criteria for the standardized case definition of hemolysis associated with the use of IVIG as developed by the Canadian IVIG Hemolysis Pharmacovigilance Group. These criteria include the onset of hemolysis within 10 days of IVIG administration with a decrease in hemoglobin of greater than or equal to 10 g/L (1.0 g/dL); a positive direct antiglobulin test (DAT) result; and at least 2 of the following: increased reticulocyte count; increased LDH level; low haptoglobin level; unconjugated hyperbilirubinemia; hemoglobinuria; and the presence of significant spherocytosis in the absence of history or examination findings of an alternate cause of blood loss or a negative DAT result [16]. Our patient's hemoglobin level was normal at the time of admission to our hospital (14.93 g/dL). After first dose of IVIG therapy, the hemoglobin level started to decrease gradually until 10.7 g/dL with the clinical finding of scleral icterus and laboratory findings of decrease in hemoglobin level greater than 1 g/dL (4.23 g/dL); positive direct Coombs test, unconjugated hyperbilirubinemia and low haptoglobin level.

Before establishing this diagnosis, it is suggested to exclude other hematological disorders including immune thrombocytopenia, heparin-induced thrombocytopenia, disseminated intravascular coagulation and iron deficiency anemia.

Identified risk factors for IVIG related hemolytic anemia include female gender, non-O blood type and administration of IVIG with high titers of anti-A/B IgG antibodies. The patient had AB blood type and had received 3 g/kg IVIG totally and these factors might have contributed to the development of hemolysis after IVIG therapy in our case [17].

In summary, we have described a patient with acute hemolysis after infusion of IVIG 0.75 g/kg/day for SJS. Hemolytic anemia in our case was mild and has improved without any intervention. Combined systemic corticosteroid therapy may have weakened the hemolytic reaction. IVIG treatment is used for a wide variety of indications in dermatology. Therefore, dermatologists should be cautious about hemolytic anemia after IVIG therapy particularly in the early follow up period.

Ethics

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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References

1. Paulmann M, Mockenhaupt M. Severe drug-induced skin reactions: clinical features, diagnosis, etiology, and therapy. J Dtsch Dermatol Ges 2015;13:625-645.
2. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129:92-96.
3. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272-1285.
4. Yamane Y, Aihara M, Ikezawa Z. Analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan from 2000 to 2006. Allergol Int 2007;56:419-425.
5. Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens-Johnson syndrome during an 8-year period at Mayo Clinic. Mayo Clin Proc 2010;85:131-138.
6. Kunimi Y, Hirata Y, Aihara M, Yamane Y, Ikezawa Z. Statistical analysis of Stevens-Johnson syndrome caused by Mycoplasma pneumonia infection in Japan. Allergol Int 2011;60:525-532.
7. Kirchhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. J Am Acad Dermatol 2014;71:941-947.
8. Egan CA, Grant WJ, Morris SE, Saffle JR, Zone JJ. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. J Am Acad Dermatol 1999;40:458-461.
9. Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, Hunziker T, Saurat JH, Tschopp J, French LE. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 1998;282:490-493.
10. Feldmeyer L, Kerdel FA, French LE. Use of intravenous immunoglobulin in toxic epidermal necrolysis. Arch Dermatol 2011;147:1440-1441.
11. Khalili B, Bahna SL. Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. Ann Allergy Asthma Immunol 2006;97:272-280.
12. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP Jr, Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C; Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4 Suppl):525-553.
13. Morgan S, Sorensen P, Vercellotti G, Zantek ND. Haemolysis after treatment with intravenous immunoglobulin due to anti-A. Transfus Med 2011;21:267-270.

14. Dalakas MC. Mechanism of action of intravenous immunoglobulin and therapeutic considerations in the treatment of autoimmune neurologic diseases. Neurology 1998;51(6 Suppl 5):2-8.

15. Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, Desjardins D, Olberg B, Tinmouth A, Giulivi A. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis. Transfusion 2008;48:1598-1601.

16. Taylor E. Intravenous immune globulin (IVIG): hemolytic reactions. Can Adverse React Newsl 2013;19:1-3.

17. Ririe MR, Blaylock RC, Morris SE, Jung JY. Intravenous immune globulin therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis complicated by hemolysis leading to pigment nephropathy and hemodialysis. J Am Acad Dermatol 2013;69:221-225.