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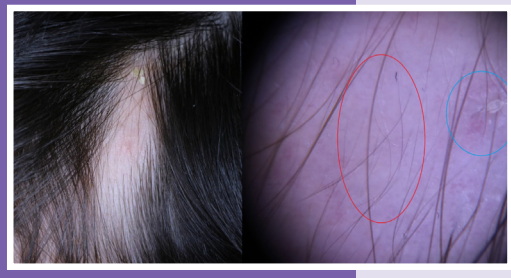

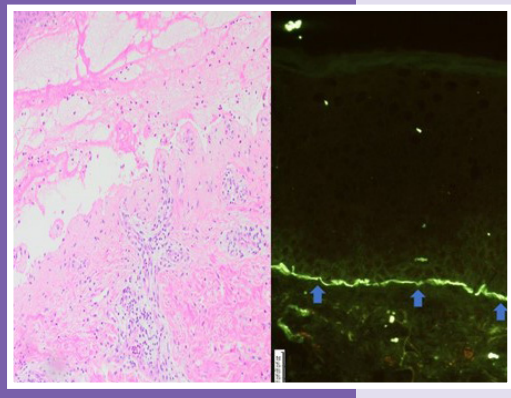

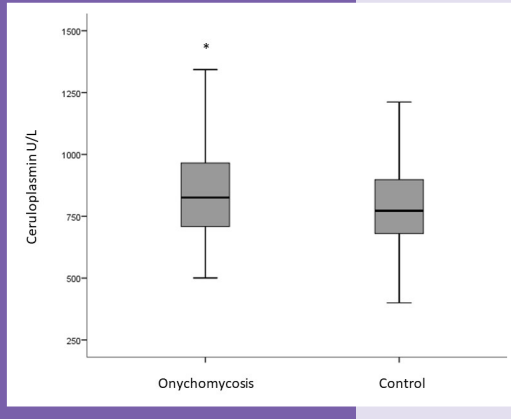

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REVIEW

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Anogenital Lichen Sclerosus: Clinical Considerations and Management

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ABSTRACT

Lichen sclerosus (LS) is a chronic inflammatory disease, which commonly involves anogenital region. It may cause significant functional and cosmetic problems and may show malignant transformation. Treatment modalities change according to the age of the patient, severity and duration of the lesions. In this review, the clinically important aspects of anogential LS and its treatment will be discussed.

Keywords: Balanitis, Dyspareunia, Dysuria, Fissures, Genital, Premalignant, Squamous cell carcinoma, Vulvar disease, Vulvar dermatosis

Introduction

Lichen sclerosus (LS) is a chronic inflammatory disease of unknown etiology that commonly involves anogenital region. It can severely impact quality of life by causing severe functional and cosmetic problems. Anogenital LS may show malignant transformation. Extragenital manifestations may occur, however they do not cause functional impairment most of the time and do not have a risk of malignant transformation. In this review, we will discuss clinical features and treatment options of anogenital LS.

Epidemiology

In general gynecology practice, vulvar LS prevalence of 1.7% was reported [1]. Examination of 96 elderly women who were nursing home residents revealed that 3% of them had genital LS. This high rate may be attributed to age, immobilization and incontinence [2]. An increasing incidence of premenarchal genital LS was observed, with an estimated prevalence of 1 in 900 [3]. Male genital LS is probably an under-recognized and under-reported condition. Studies have shown that one-third of adult male genital LS patients had a delay of at least two years before the definitive diagnosis was established [4,5]. A United States based electronic medical record revealed an incidence of 1.4 male genital LS cases per 100,000 visits [6]. Epidemiology of the disease may vary between countries as the condition has a propensity to occur in uncircumcised men. Males with a history of neonatal circumcision are unequivocally spared from the disease [5].

Etiology

Several factors including genetic factors, autoimmunity, hormonal factors, infections and drugs have been suspected, which are beyond the scope of this review. However, as they are important from clinical point of view, chronic irritation and trauma (Koebnerization) will be briefly discussed. The chronic contact with urine has been implicated in the development of LS [5,7,8]. Cases of vulvar LS have been reported in association with urinary incontinence and, in some cases, lesions resolved following treatment of urinary incontinence [9]. As mentioned above, LS do not occur in neonatally circumcised males and urinary dribbling is a frequent finding in male patients

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with genital LS. Thus, it is likely that the moist and occlusive environment under the prepuce contributes to the pathogenesis of LS. In men, lesions of LS spare almost invariably the perianal region, which does not come into contact with urine [5,8]. No difference was found in urinary constituents of males with and without genital LS [10].

Genital LS may also occur following trauma, such as surgery, instrumentation and at sites of genital jewelries, and recurs in circumcision scars and grafts [7,8].

Clinical Features

Adult Female Anogenital Lichen Sclerosus

About 60% with women with anogenital LS are symptomatic. However, this ratio reaches 100% in patients who are referred to specialists [11]. Cardinal symptom of the disease is pruritus, which is frequently severe, often aggravates at night and may lead to sleep disturbances [7,11,12]. Erosions and fissures may lead to pain, soreness, dysuria, urinary retention and dyspareunia [7,12,13]. Sexual dysfunctions including dyspareunia, decreased frequency of intercourse, apereunia and difficulty achieving orgasm were reported and may also result from anatomical changes such as stenosis of the introitus [14]. Perianal stenosis may lead to pain during defecation [15]. Comprehensive list of symptoms associated with anogenital LS in women can be found in Table 1.

Early findings of the adult female anogenital LS include a well-demarcated, slightly erythematous plaque and edema at the periclitoral hood [7,16]. Porcelain white papules and plaques are characteristic lesions of the disease, that are often accompanied by ecchymoses [12]. Follicular delling and hyperkeratosis may be seen [7,12]. Fissuring is another important feature, that tends to occur in the area between clitoris and urethra, interlabial sulci and the base of posterior fourchette [7,16]. Ulcerations, erosions and rarely blisters may be seen [15]. Due to chronic scratching, some patients may exhibit accompanying subepithelial hemorrhage and lichen simplex chronicus lesions [7]. Long-lasting disease leads to hypopigmentation, sclerosis and atrophy of the skin, termed as cellophane paper-like appearance [7]. Scarring may eventually result in partial or complete resorption of the labia minora, burring of the clitoris and sealing of the clitoral hood [7,12]. Pseudocyst smegmatis may develop due to adhesions of the clitoral hood [17]. Any persistent ulcerated and/or hyperkeratotic firm lesion on vulva should raise a suspicion of squamous cell carcinoma (SCC) [17]. Basal cell carcinoma and Merkel cell carcinoma have been reported, which were probably co-incidental [13]. Pigmented lesions, most commonly lentigines and melanocytic nevi, may also arise in vulvar LS lesions [17,18]. Genital melanocytic nevi associated with LS display severe histopathological atypia and may mimic melanoma [18]. Vulvar melanoma has rarely been reported [18].

The extent of involvement in female anogenital LS may vary considerably. In some patients the disease may be restricted to a small, focal area; while in others it may cover the entire vulva, perineum and perianal region [7]. Labia minora, interlabial sulci, clitoris, clitoral hood and perineal body are the typical regions affected in adult females with anogenital LS. Perianal involvement has been reported in 30% of the patients (Figure 1). Genital LS affecting vulvar, perineal and anal areas gives rise to "figure-of-eight" shape, also termed as "keyhole" or "hourglass" appearance [19]. In extensive cases, lesions may involve gluteal region and genitocrural folds [12]. In contrast to lichen planus, the vagina and cervix are unlikely to be involved in LS [12]. There are rare cases of LS that have been reported to affect the vagina, most of which had associated pelvic organ prolapse [20,21,22]. Concerning the latter cases, it is hypothesized that the metaplasia of the vaginal epithelium due to chronic irritation might have led to the development of LS on the vaginal mucosa [22].

Table 1. Symptoms of anogenital lichen sclerosus in women

Itching
Pain, soreness, burning sensation
Hemorrhage
Dysuria, urethral discharge, poor urinary stream
Dyspareunia, apareunia, decreased frequency of intercourse, difficulty achieving orgasm
Vaginal discharge
Changing anatomy of the genitalia
Pain during defecation, constipation, stool holding, rectorrhagia
Sleep disturbances

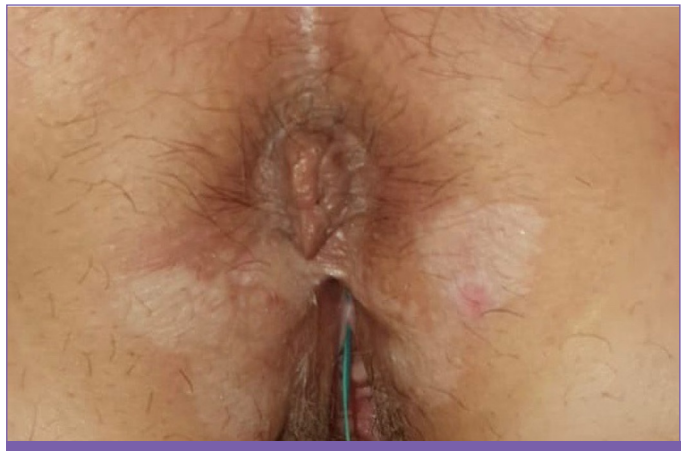

Figure 1. Genital lichen sclerosus in a postmenopausal woman. Porcelain white plaques involving perianal region can be seen. Authors declare patient consent was obtained for clinical photographs

Child Female Anogenital Lichen Sclerosus

The symptoms and clinical features of child female anogenital LS are generally similar to those observed in adult females (Figure 2,3) [12].

However, there are several differences that are worth mentioning. Behavioral problems, urinary symptoms and constipation are more frequently observed in children [23]. Clinically, the ecchymoses and purpura may be very prominent in children, and may be confused with sexual abuse [7]. In addition, infantile perineal protrusion (IPP) is a finding that occurs almost always in prepubertal girls. Formerly termed as "infantile perianal pyramidal protrusion", IPP a soft tissue protrusion most commonly located anterior to anus. The condition may occur concomitantly with LS or may precede the latter [24]. Cases of labial fusion, defined as partial or complete adherence of labia minora in the midline, have been reported in association with LS [25].

Similar to adults, vulvar melanocytic nevi may be superimposed on LS lesions in children [18,26,27]. Rare cases of vulvar melanoma have been reported in children in association with LS [28,29,30]. However, it is postulated that some of the latter cases may possibly represent melanocytic nevi misdiagnosed as melanoma [26].

Clinical features of female anogenital LS are summarized in Table 2.

Adult Male Genital Lichen Sclerosus

Most common symptoms of male genital LS include dyspareunia and urological symptoms such as impaired urinary flow. Burning and itching sensation may occur [5,31]. A comprehensive list of symptoms associated with male genital LS can be found in Table 3.

Male genital LS is mostly a clinical diagnosis [5]. Typical sites of involvement are the foreskin and glans penis [5,31]. Loss of coronal sulcus anatomy, hypopigmented patches and plaques, bullae, ulcerations and erosions can be observed [5]. Sclerotic plaques and bands lead to the tightening of the prepuce, termed as constrictive sclerotic posthitis, which may result in the development of paraphimosis and phimosis [5,12]. Ring-like constriction, also termed as pseudo-ainhum, has been reported at the penile shaft [32]. Meatal and urethral disease, varying from isolated meatal to panurethral involvement may occur [12,31]. High rates of urethral involvement, affecting 20% of the patients, were reported in urological literature [33]. Scarring of the meatal area may lead to stenosis and obstruction [12]. Unlike female genital LS, perianal LS is very unusual in men [5]. New-onset indurations arising on LS lesions should be biopsied to rule out SCC [34]. Benign pigmented lesions, namely postinflammatory hyperpigmentation, lentigines and melanocytic nevi, may co-exist with LS on glans and prepuce [27,35,36]. Penile melanoma, an extremely rare entity, was reported to develop on LS lesions in three adult males [37].

Child Male Genital Lichen Sclerosis

Phimosis is the most common presentation of child male genital LS, followed by balanitis and buried penis [38]. Of note, LS is the most frequent cause of acquired phimosis in boys [17]. Perianal involvement is very rare, as in adult men [7,12].

Clinical features of male genital LS are summarized in Table 4.

Differential Diagnosis

Differential diagnosis of genital LS in adults include lichenoid disorders such as lichen planus, lichen simplex chronicus, and contact dermatitis. In children with genital LS, vitiligo is the major differential diagnosis. Wood's lamp examination may be helpful in

Table 2. Clinical features of female anogenital lichen sclerosus

Well-demarcated erythematous plaques (early finding)
Edema, especially of the periclitoral hood (early finding)
Porcelain white papules and plaques (typical)
Purpura and ecchymoses (more prominent in children)
Follicular delling
Hyperkeratosis
Fissures (between clitoris and urethra, at interlabial sulci, at the base of posterior fourchette)
Ulcerations, erosions
Blisters (rare)
Sclerosis and hypopigmentation
Atrophy of the skin (also termed as cellophane paper-like appearance) (late finding)
Resorption of the labia minora (late finding)
Burring of the clitoris and sealing of the clitoral hood (late finding)
Stenosis of introitus and perianal region (late finding)
Pseudocyst smegmatis (late finding)
Vulvar squamous cell carcinoma, rarely basal cell carcinoma and Merkel cell carcinoma (only in adults)
Vulvar pigmented lesions (lentigines, melanocytic nevi, very rarely melanoma)
Infantile perineal protrusion (only in children)
Labial fusion (only in children)

Table 3. Symptoms of adult male genital lichen sclerosus

Dyspareunia due to painful erection, fissuring during and after sexual intercourse
Dysuria, poor urinary stream with decreased flow and diameter
Dribbling
Difficulty retracting foreskin
Soreness, burning
Itching
Change in the appearance of genitalia
Brusing, bleeding
Erosions, ulcers, blisters

this picture. Another important differential diagnosis that should be kept in mind in child age group is child abuse. Patients should be carefully inspected in this respect. In cases with hyperplastic changes in histopathology, malignancies should be ruled out.

Treatment

The treatment of LS is consituted of many alternatives and has many perspectives. The contact of irritants should be minimized, urinary contact should be avoided and soaps should be substituted with sydnets. Any possible infection should be treated with effective antibiotherapy and the use of emollients should be made routine. Ultrapotent or potent topical corticosteroids are first line for the treatment of the lesions. In steroid-resistant cases, calcineurin inhibitors, topical retinoids, systemic retinoids, systemic immunosuppression phototherapy, photodynamic therapy are the alternatives. The patients should be under surveillance for squamous intraepithelial neoplasia or cancer; and biopsy should be performed in case of suspicion. The three broad categories of general measures, treatment and surveillance are summarized in Table 5 [7,39].

Table 4. Clinical features of male genital lichen sclerosus

Constrictive sclerotic posthitis
Balanitis
Sclerosis of the glans
Loss of coronal sulcus
Pseudo-ainhum of the penis
Meatal stenosis
Hypopigmented patches
Purpura, telangiectasias, petechiae
Bullae, erosions, ulcerations
Penile squamous cell carcinoma, erythroplasia of Queyrat, verrucous carcinoma
Penile pigmented lesions (lentigines, melanocytic nevi, very rarely melanoma)

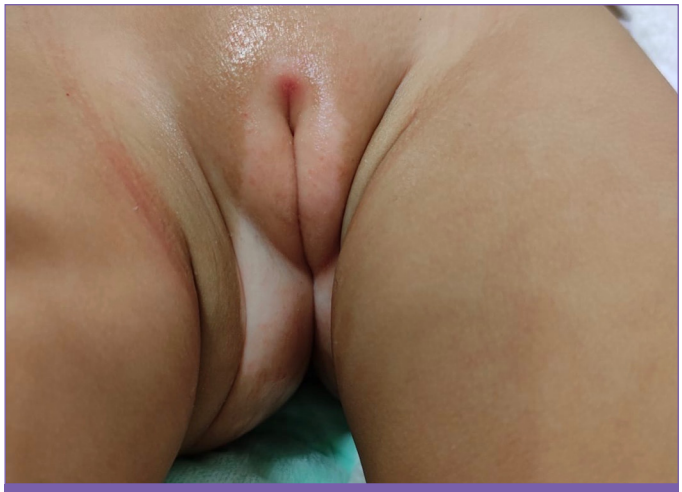

Figure 2. Genital lichen sclerosus in a prepubertal girl. Note the sclerotic white plaques and erosion. Authors declare patient consent was obtained for clinical photographs

Treatment Strategies According to Gender

Ultrapotent and potent topical corticosteroids are the first line treatment for females with genital LS; with greater efficacy than the other treatment alternatives. Complete cure should not be aimed rather the relief of the symptoms is achieved in 75 to 95% of the cases. In male patients with genital LS circumcision is the most effective treatment modality. However, the use of ultrapotent and potent topical corticosteroids should be offered initially for three months. Table 6 summarizes previously reported effective treatment modalities in the literature according to gender [40].

Topical Steroids

Potent topical steroids (eg. Clobetasol propionate 0.05%) are the first line in the treatment of genital LS both in female and male patients [7,40,41]. The use of topical steroids should be combined

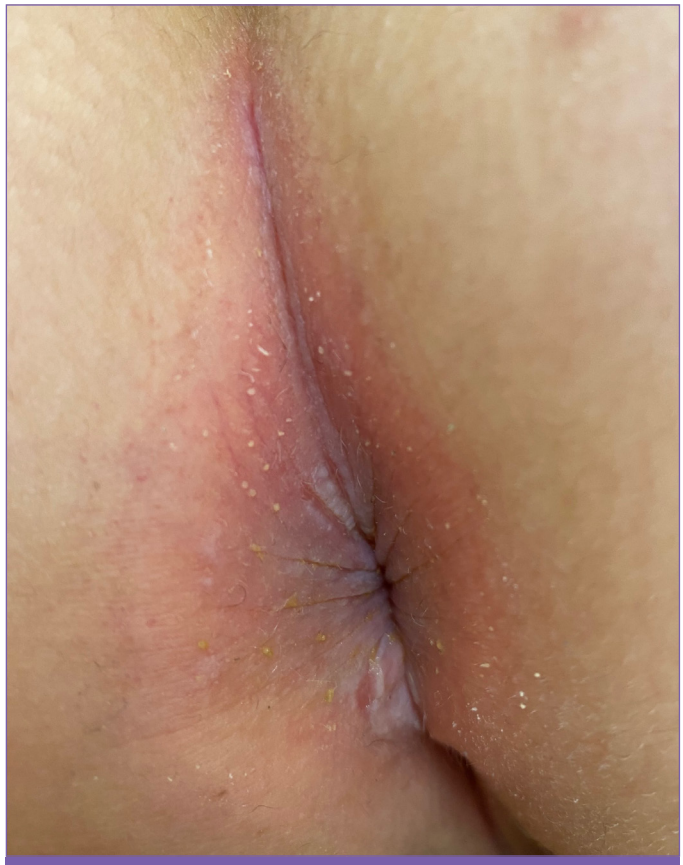

Figure 3. Perianal involvement of lichen sclerosus in a prepubertal girl. Note the erythema, sclerosis, fissures (intergluteal and perianal) and erosions. Authors declare patient consent was obtained for clinical photographs

with the soap substitution and the use of emollients [12]. The initially recommended treatment frequency and duration vary from once to twice daily and one to three months in different guidelines [7,12,40]. The European guideline recommends the use of topical corticosteroids twice daily in the first month of treatment and then decreasing the frequency to once daily in milder cases [40]. The British guideline recommendations differ according to gender. Female patients are recommended to use topical clobetasol propionate 0.05% once daily for the first month, alternative days in the second month and two to three times a day in the third month. Male patients are recommended to use topical clobetasol propionate 0.05% once daily for one to three months. The intralesional injection of triamcinolone acetonide is recommended in both genders in case of hyperkeratotic lesion given that malignancy has been excluded [12]. The usual amount to be used in each application is a fingertip unit; with a maximum of 10 g per month in order to avoid the steroid side affects such as epidermal atrophy and telangiectasias [40].

After the initial one to three months treatment with potent topical corticosteroids, maintenance treatment with either topical steroids or topical calcineurine inhibitors is recommended in order to prevent relapses [7,12,40]. The frequency of maintenance treatment to successfully remain lesion free varies according to each patient; some patients require once to twice monthly uses whereas others require once to twice weekly. The proactive application of one or twice weekly mid potency topical corticosteroids (eg, mometasone furoate 0.1%) was proven to be effective in maintenance treatment. A maximum of 30 g per 3 months topical corticosteroid use is recommended in maintenance in order to prevent the side effects of long-term topical corticosteroid use [40].

The use of ultrapotent topical corticosteroids (e.g., betamethasone dipropionate 0.05%, diflorasone diacetate 0.05% and clobetasol propionate 0.05%) twice daily for six to eight weeks is also the mainstay treatment in pediatric LS patients with minimal side effects. While mid potency topical corticosteroids such as (triamcinolone acetonide and mometasone furoate) have also been found to be effective, their use in pediatric LS cases is not first line [39].

Topical Calcineurin Inhibitors

The topical calcineurin inhibitors are the second-line treatment options in genital LS patients in whom topical glucocorticoids are non-responsive or not tolerated [42]. Topical calcineurin inhibitors may be used in the maintenance of lichen scleroatrophicus after an initial three months treatment with potent corticosteroids [7,40].

Topical pimecrolimus 1% cream is recommended to be used twice daily up to six months in genital LS patients [7]. Compared to clobetasol propionate 0.05% cream applied once daily, pimecrolimus 1% cream twice daily is less effective in the treatment of genital lichen scleroathrophicus [43]. Topical tacrolimus was used in its 0.1% preperation in most of the studies. Tacrolimus (0.1%)

Table 5. General treatment perspective of LS

General measures	Treatment	Surveillance
Avoid the contact of urine	1st line: Ultrapotent or potent topical corticosteriods	Follow-up for squamous intraepithelial neoplasia and cancer
Use of syndets instead of soaps		
Minimising the contact of irritants	Topical calcineurin inhibitors, retinoids, phototherapy, photodynamic treatment, systemic immunosupresion and circumsion for resistant cases	
Use of emollients		Biopsy if any suspicion

Table 6. Effective treatment modalities according to gender [40]

Female	Male
Topical steroids	Topical steroids
Intralesional steroids	Topical tacrolimus (0.03% and 0.1%)
Topical testosterone (2%)	Pimecrolimus (1%)
Topical progesterone (2% and 8%)	Circumcision
Cyclosporine	
Topical tacrolimus (0.03% and 0.1%)	
Pimecrolimus (1%)	
Retinoids	
Oxatomide	
Carbondioxide laser	
Perineotomy	

ointment is recommended twice daily for three months in patients with genital LS [7]. There is also a case of steroid-resistant genital LS which was successfully treated with tacrolimus 0.03% ointment [44]. Tacrolimus 0.03% ointment was shown to be effective and safe for the treatment of pediatric genital LS [45].

Phototherapy

Beattie et al. [46] investigated the treatment efficacy of ultraviolet-A-1 (UVA1) phototherapy in corticosteroid-resistant genital LS in seven female patients. Five of the patients achieved complete remission after treatment. UVA1 phototherapy is of benefit in the management of resistant vulvar LS cases [46]. Garrido-Colmenero et al. [47] recently reported a vulvar LS case that was successfully treated with narrowband ultraviolet-B, which was resistant to topical steroids, twice weekly, at a dose of 0.2 j/cm^2 for 5 months.

Circumcision

Circumcision is a treatment option for LS as well. The male genital LS patients who have not responded to a three months course of topical potent steroid treatment should be re-evaluated for the possiblities of phymosis, paraphymosis and burried penis (due to obesity) which would with old the application of topical steroids. Obese patients should be encouraged for weight loss. Patients with phymosis or paraphymosis should be referred to urology for circumcision. Circumcision may be considered in patients not responding to topical steroids as well [12]. Uretheroplasty or meatoplasty may be necessary in cases of extensive stenosis. Topical corticosteroids are recommended to be applied in the postsurgical period as well [48]. Nevertheless, it should be kept in mind that there is still the risk of squamous neoplasia development even in early-circumcised male genital LS patients [49].

Topical Testosterone

Testosterone, in a topical preparation of 2%, was used in the treatment of vulvar LS in several studies. Yet it is effective in the palliation of symptoms, Ayhan et al. [50] have shown that topical testosterone (2%) is not as effective as topical clobetasol propionate (0.05%) in the initial and maintenance treatments of vulvar LS. Still, premenopausal patients respond better, have higher remission and lower response rates to topical androgens than the postmenopausal patients [50,51].

Photodynamic Treatment

Photodynamic treatment is a treatment modality in which 5% 5-aminolevulinic acid is applied to the treatment area that is subsequently irradiated with a halogenic lamp (wavelenght of 590-760 nm) for 10 minutes. It is a beneficial treatment modality for vulvar LS. The greatest treatment benefit is seen in the reduction of subepithelial ecchymoses, telangiectasias, erosions and fissures. It has limited benefit in the atrophic lesions. Overall, it is a safe treatment alternative that promises good results in the treatment of vulvar LS [52,53].

Laser

Laser modalities are utilized in many different diagnoses. Recently, the use of non-ablative lasers in the treatment of vulvar LS has been investigated by Bizjak Ogrinc et al. [54] Nd: Yittrium Aluminium Garment Laser, R33 headpiece, was used with a spot size of 9 mm and a fluence of 90 j/cm^2. The patients received 3 sessions of laser treatment with 14 days intervals along with topical corticosteroids. Compared to the corticosteroid-only group, the combination of topical corticosteroid and laser led to greater reduction in burning, itching, pain, dyspareunia and sclerosis with minimal patient discomfort and maximal patient satisfaction [54]. Fractionated carbon dioxide laser may be used in the treatment of refractive vulvar LS cases as well. In a study by Balchander and Nyirjesy [55], patients received at least two sessions of laser treatment with at least monthly intervals. Two months after the last treatment session, patients reported a significant reduction in dysuria, dyspareunia, itching and vaginal pain as well as a reduction in the use of topical corticosteroids. Thus, fractionated carbon dioxide laser may be a treatment alternative in resistant cases [55].

Adalimumab

Similar to other inflammatory dermatoses, tumor necrosis factor-alpha (TNF-alpha) levels are high in LS. Adalimumab is a monoclonal anti-TNF-alpha antibody which is used in the treatment of inflammatory dermatoses. A patient with balanitis xerotica obliterans, refractive to treatment with topical steroids and topical calcineurin inhibitors, was treated with intralesional 40 mg adalimumab injections with two weeks interval for six months. Although the patient benefited from treatment, injections were painful and expensive. Relapse occurred eight weeks after treatment cessation. Nonetheless, anti-TNF agents are promising modalities for LS in the future [56].

Topical and Systemic Retinoids

There are many reports of topical and systemic retinoid use in female lichen sclerosis. Topical 0.025% tretinoin 5 days a week for one year and acitretin 20-30 mg/day for twelve weeks were both effective in the treatment of genital lichen sclerosis in women. Side effects of retinoid use were observed [57,58]. Only one study was perfomed in male genital lichen sclerosis patients, 35 mg/day acitretin was given for twenty weeks. Acitretin was found to be effective in the treatment of balanitis xerotica obliterans with tolerable side effects [59].

Cyclosporine

Cyclosporine is also a treatment alternative in refractory LS patients. Bulbul Baskan et al. [60] treated five refractory female genital LS patients with oral cyclosporine for three months with doses ranging from 3 to 4 mg/kg/day. Erythema and erosions improved significantly and the total symptom scores regressed. Patients experienced mild adverse effects such as nausea, hypertrichosis and mucositis. Oral cyclosporine is a safe and effective treatment alternative in vulvar LS patients refractory to treatment [60].

Prognosis

Prognosis of Vulvar Lichen Sclerosis

Cooper et al. [61] analysed 327 female genital LS patients with definitive histopathological diagnosis. Of these patients, 255 responded to the initial treatment of topical corticosteroids, 244 (96%) with improvement in symptoms, 168 (66%) symptom free, 76 (30%) partial response and 11 (4%) poor response. SCC has developed in 6 (2.4%) patients and scarring was significantly less often in girls. The lifelong remission rate of vulvar lichen sclerosis was 16% [61]. According to Bradford and Fischer [62], symptom remission due to topical corticosteroids is achieved in 98% of the compliant and 75% of the non-compliant patients. Progression with scarring was not observed in any of the compliant patients but in 35% of the non-compliant patients. None of the compliant patients developed squamous cell cancer; on the other hand five of the non-compliant patients developed SCC, which is statistically significant. Mild corticosteroid side effects were seen in 7% of the patients in the long-term follow-up. According to the authors, topical corticosteroid treatment has a protective effect against sclerosis and the development of squamous cell cancer in female lichen sclerosis patients [62].

SCC is the most important complication of vulvar lichen sclerosis. The risk of SCC arising from lichen sclerosis is 5%. The SCC arising within vulvar lichen sclerosis lesions arises within well-differentiated type vulvar intraepithelial neoplasia. If SCC is to arise in the background of vulvar lichen sclerosis, it becomes invasive within six months. The risk of SCC development within the vulvar LS lesion depends on the duration and severity of LS rather than the patient's age [63].

Prognosis of Balanitis Xerotica Obliterans

Nasca et al. [64] evaluated 86 male genital LS patients with a 10 years follow-up interval. Of these 86 patients, five had malignant transformation: three SCC, one erythroplasia of Queyrat and one verrucous carcinoma. The average lag time between the diagnosis of LS to malignant transformation was 17 years. Human papilloma virus (HPV) was present in four of these five patients. Thus, male patients with genital lichen sclerosis are at increased risk of malignant transformation and the risk is associated with HPV positivity [64]. Barbagli et al. [34] also reported a series of 130 male genital LS patients with 10 years follow-up. In their series, 11 (8.4%) of the patients showed malignant transformation: 7 (64%) SCC, 2 (18%) verrucous carcinoma, 1 (9%) erythroplasia of Queyrat and 1 (9%) SCC within verrucous carcinoma. Thus, long-term follow-up of male genital LS patients is mandatory [34].

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.Ç.O., T.K.U., Design: M.Ç.O., T.K.U., Data Collection or Processing: M.Ç.O., T.K.U., Analysis or Interpretation: T.K.U., Literature Search: M.Ç.O., D.Ö., Writing: M.Ç.O., D.Ö., T.K.U.

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Approach Towards Patients Presenting with "Red Face": A Retrospective Study

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ABSTRACT

Background: Facial erythema (red face) is a common clinical finding, evident even to the untrained eye; however, a red face does not represent a single cutaneous disease. Red face can be caused by many different underlying conditions of varying severity, including infectious causes such as lupus vulgaris, dermatomyositis, lupus erythematosus, lupus pernio, allergic contact dermatitis, drug-induced erythema, and acne vulgaris.

Materials and Methods: However, this is not a classification method used in western dermatology. The files of the patients who applied to the Department of Dermatology between February 15 and May 15, 2022, were retrospectively analyzed. In this study, it was aimed to determine the distribution of diseases with red face in patients who applied to our center, to evaluate which skin findings are observed in these diseases and the treatments used in these patients.

Results: Two hundred sixty-two patients were included in the study. According to our results the mean age of the patients was 30.01±11,943 (2-89). In the study the distribution of the patients by sex included 94 men and 168 women. The mean age of the men in the study was 27.38±12,632 (2-89), and the mean age of the women was 31.48±11,313 (17-70). The distribution of the patients by Fitzpatrick skin type was assessed. Accordingly, Type 3 (n=92, 35.1%) skin type was the most common and type 1 (n=24, 9.2%) skin type was the least frequent. As a result, acne (n=73, 27.9%) and rosacea (n=100, 38.2%) were the most common in patients presenting with a red face.

Conclusion: "Red face" is a very common finding in dermatology clinics. Red face often due to changes in skin blood flow and sometimes accompanying inflammation a situation that arises. Wide differential diagnosis in patients presenting with a "red face" has a range.

Keywords: Red face, Facial erythema, Acne, Rosacea, Lupus erythematosus

Introduction

The term red face is used for lesions predominantly on the face that result due to the changes in cutaneous blood flow triggered by many different conditions. Facial erythema may also be a sign of other diseases. There are various diseases in the differential diagnosis of patients presenting with a red face. Diagnosis is based on lesions characteristics, features of the erythema, functional findings, and associated systemic manifestations. In most cases, the cause of a red face is a benign disease such as rosacea, contact dermatitis, photodermatosis, and climacterium, and a detailed history and physical examination are sufficient to make the diagnosis. Facial erythema may also present as a manifestation of drug allergies, heart disease, carcinoid syndrome, pheochromocytoma, mastocytosis, and anaphylaxis. Further laboratory testing, radiological or histopathological examination, may detect some rare causes such as medullary carcinoma of the thyroid, pancreatic islet cell tumor, and renal carcinoma. In this study, the differential diagnosis and approach to various conditions that cause "red face"

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are discussed. Dermatological diseases are classified according to a standard etiological approach (e.g. papulosquamous diseases, bullous dermatoses, pigmentation disorders, connective tissue diseases, etc.) [1,2,3].

Materials and Method

The files of the patients who applied to the Department of Dermatology between February 15 and May 15, 2022, were retrospectively analysed. Patients were given written consent forms before the study. In this study, it was aimed to determine the distribution of diseases with red face in patients who applied to our center, to evaluate which skin findings are observed in these diseases and the treatments used in these patients.

Patient age, gender, and Fitzpatrick skin score were evaluated from demographic data. Diseases to be included in the red face category were determined as acne, rosacea, connective tissue diseases, sarcoidosis, pseudolymphoma, pigmentation disorders, dysplastic lesions, inflammatory dermatoses, infections, cutaneous lymphomas, bullous diseases and vascular malformations. Undiagnosed red face patients were excluded from the study. The diseases were subgrouped and evaluated. Cutaneous findings of patients with red face were evaluated. The cutaneous findings include erythema, lichenification, papules, pustules, atrophy, macules, scales, nodules, patches, erosions, vesicles, hyperpigmentation, hypopigmentation and telangiectasia.

The approval of Istanbul Univeristy-Cerrahpasa, Cerrahpasa Faculty of Medicine Ethics Committee was taken before initiating the study (number: E-83045809-604.01.01-371606, date: 26.04.2022).

Statistical Analysis

For statistical analysis SPSS 25.0 windows program was used. Numbers and percentages for categorical variables in descriptive statistics; in numeric variables mean and standard deviation in normally distributed data, and in non-normally distributed data median, largest (maximum) and smallest values (minimum) were used. The limitations to our study were the number of patients taken into our study and due to the number referred patients to our clinic we had more rheumatology patients then usual.

Results

Two hundred sixty-two patients were included in the study (Figure 1). According to our results the mean age of the patients was 30.01±11,943 (2-89). In the study the distribution of the patients by sex included 94 men and 168 women. The mean age of the men in the study was 27.38±12,632 (2-89), and the mean age of the women was 31.48±11.313 (17-70) (Table 1). The distribution of the patients by Fitzpatrick skin type is shown in Table 2. Accordingly, Type 3 (n=92, 35.1%) skin type was the most common and Type 1 (n=24, 9.2%) skin type was the least frequent.

The distribution of diseases accompanying a red face is given in Table 3. As a result, acne (n=73, 27.9%) and rosacea (n=100, 38.2%) were the most common in patients presenting with a red face, meanwhile sarcoidosis (n=2,0.8%) and dysplastic lesions (n=2, 0.8%) were the least detected. There was no cases of pseudolymphoma and vascular malformation.

In our study 73 patients with acne were identified. Forty-four patients had acne vulgaris and 12 had nodulocystic acne (Figure 2). One hundred patients were identified with rosacea. Accordingly, 68 of these patients had erythematotelangiectatic type, 30 had papulopustular type, and 2 had phimatous type (Figure 3). Thirty-four patients with connective tissue disease were identified 12 patients had acute cutaneous lupus, 10 had systemic sclerosis, 8 had discoid lupus erythematosus (DLE) and lupus tumidus were detected in 4 of them (Figure 4).

Erythema was observed in all 73 (100%) acne patients, accompanied by erythema in 70 (95.9%), papules, pustules in 60 (82.2%) patients and nodules in 28 (38.4%). In rosacea, erythema was observed in all 100 patients (100%), papules in 44 (95.9%), pustules in 28 (82.2%) and nodules in 90 (91.8%) patients (Table 4). In connective tissue diseases, erythema was observed in all 35 patients (100%), 17 (51.5%) had telangiectasia, in 16 (46%) patients atrophy was observed, in 10 (29%) patients hyperpigmentation, in 8 (23%) patients hypopigmentation and papules were observed in 1 (2.9%)

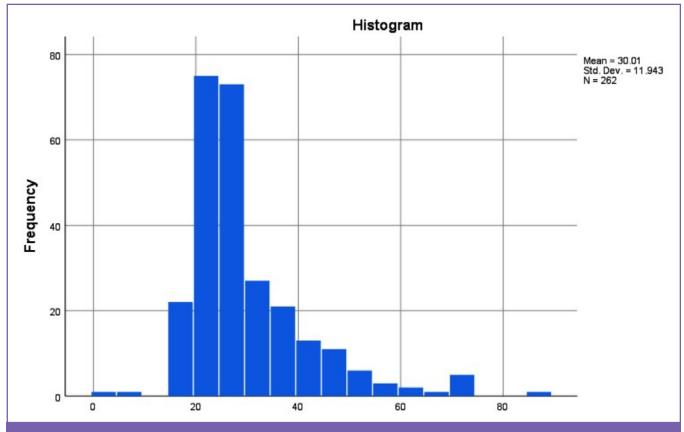

Figure 1. Distribution of frequency and age

Table 1. Mean ages of male and female patients

	Number (n)	Minimum	Maximum	Average	Standard deviation
Male	94	2	89	27.38	12,632
Female	168	17	70	31.48	11,313

patient (Table 5). In papulosquamous dermatoses, erythema was observed in all 28 patients (100%), scales were observed in 24 (85.7%) patients, lichenification and hyperpigmentation in 4 patients (14.3%), hypertrophy in 2 patients, macules and patches (7.1%) were not found. The distribution of skin findings in sarcoidosis is shown in Table 6. According to the results, erythema, nodules, patches and telangiectasia were observed in all 2 patients (100%). Skin findings observed in pigmentation disorders is shown in Table 7. All 8 patients (100%) had hyperpigmentation, 6 patients had hyperpigmentation patches and a maculae were observed in 2 patients. The distribution of skin findings observed in dysplastic lesions is shown in Table 8. Accordingly, hyperpigmentation, lichenification and telangiectasia were observed in all 2 patients (100%). The distribution of skin findings observed in inflammatory dermatoses is shown in Table 9.

Table 2. Distribution of the patients by Fitzpatrick skin type

	Frequency (n)	Percentage (%)
Type 1	24	9.2
Type 2	66	25.2
Type 3	92	35.1
Type 4	80	30.6
Total	262	100

Table 3. Distribution of diseases accompanying a red face

	Frequency (n)	Percentage (%)
Acne	73	27.9
Rosacea	100	38.2
Connective tissue diseases	35	13.4
Sarcoidosis	2	0.8
Pigmantation disorders	8	3.1
Dysplastic lesions	2	0.8
Inflammatory dermatosis	28	10.7
Infections	6	2.3
Cutaneous lymphomas	4	
Bullous diseases	6	

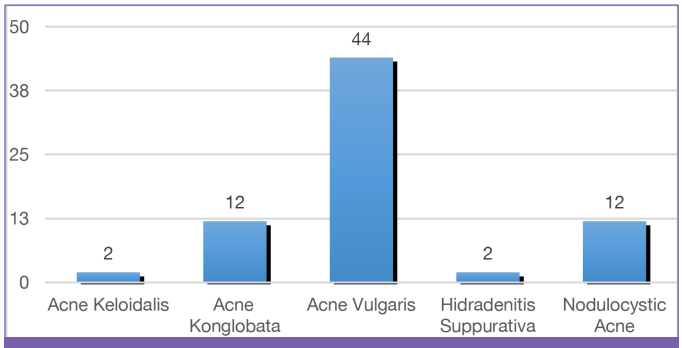

Figure 2. Distribution of acne subtypes

Erythema was observed in all 28 (100%) patients, and scales in 24 (85.7%) patients, lichenification and hyperpigmentation in 4 patients (14.3%), hypertrophy was observed in 2 patients (7.1%), macules and patches were not found. The distribution of skin findings observed in infectious diseases is given in Table 10. The distribution of skin findings observed in cutaneous lymphomas is shown in Table 11. Accordingly, in all 4 patients (100%), erythema, scales, nodule, patch and erosions were detected, hyperpigmentation was found in 2 (50%) patients. Accordingly, erythema in all 6 patients (100%), papules in 4 (67%), lichenification, pustules, macules, scaling and vesicles were detected in 2 of them (33%). The distribution of skin findings observed in bullous diseases is shown in Table 12. Accordingly, erythema and erosion were detected in all 6 patients (100%) and scaling in 4 patients (67%).

Discussion

Red face is a very common finding in dermatology clinics. Red face often occurs due to changes in cutaneous blood flow and sometimes accompanies inflammation [4]. Wide range of differential diagnosis is observed in patients presenting with a red face. The diagnosis of red face is often established with the history of the disease, the morphology of the erythema, clinical findings and accompanying systemic symptoms together. established by the evaluation. Sometimes to confirm the diagnosis in these patients

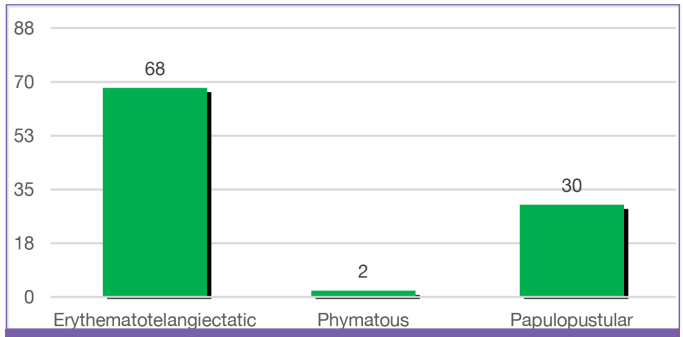

Figure 3. Distribution of rosacea subtypes

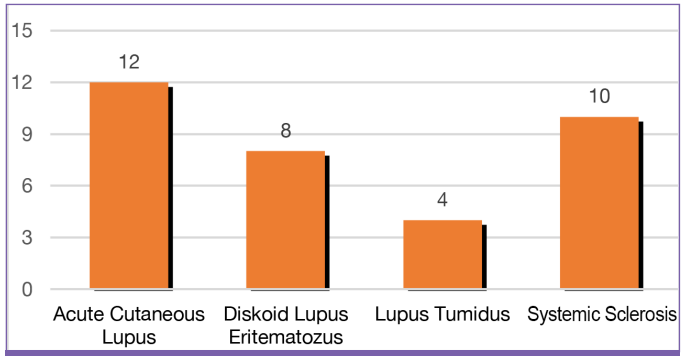

Figure 4. Distribution of subtypes of connective tissue diseases

laboratory tests or histopathological examination may be required. "Red face" or facial erythema may be a manifestation of non-dermatological systemic diseases such as neuroendocrine tumors, fever, hyperthermia, menopause, alcohol, drugs (eg. vancomycin) hyperthyroidism, hypersensitivity reactions, pheochromocytoma or superior vena cava syndrome. Red face is what we call dermatoses involving the facial area. The aim of our study is to divide the diseases that cause facial erythema into groups and accompany them categorise them according to their clinical findings. Among these diseases, especially acne, papulosquamous diseases such as rosacea, atopic dermatitis (AD) and seborrheic dermatitis, sarcoidosis granulomatous diseases such as tuberculosis, infectious

Table 4. Distribution of clinical findings in acne patients

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	73	0	73	100
Lichenification	73	0	0	0
Papule	73	0	70	95.9
Pustule	73	0	60	82.2
Atrophy	73	0	2	2.7
Hypertrophy	73	0	4	5.5
Macule	73	0	0	0
Scale	73	0	0	0
Nodule	73	0	28	38.4
Patch	73	0	0	0
Erosion	73	0	0	0
Vesicule	73	0	0	0
Hyperpigmentation	73	0	0	0
Hypopigmentation	73	0	0	0
Telangiectasia	66	7	0	0

Table 5. Distribution of clinical findings in connective tissue diseases

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	35	0	35	100
Lichenification	35	0	0	0
Papule	35	0	1	2.9
Pustule	35	0	0	0
Atrophy	35	0	12	34.3
Hyperpigmentation	35	0	0	0
Macule	35	0	0	0
Scale	35	0	0	0
Nodule	35	0	0	0
Patches	35	0	16	46
Erosion	35	0	0	0
Vesicule	35	0	0	0
Hyperpigmentation	35	0	10	29
Hypopigmentation	35	0	8	23
Telengiectasia	33	2	17	51.5

Table 6. Distribution of clinical findings in sarcoidosis

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	2	0	2	100
Lichenification	2	0	0	0
Papule	2	0	0	0
Pustule	2	0	0	0
Atrophy	2	0	0	0
Hypertrophy	2	0	0	0
Macule	2	0	0	0
Scale	2	0	0	0
Nodule	2	0	2	100
Patch	2	0	2	100
Erosion	2	0	0	0
Vesicule	2	0	0	0
Hyperpigmentation	2	0	0	0
Hypoppigmentation	2	0	0	0
Telangiectasia	2	0	2	100

Table 7. Distribution of clinical findings in pigmentation disorders

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	8	0	0	0
Lichenification	8	0	0	0
Papule	8	0	0	0
Pustule	8	0	0	0
Atrophy	8	0	0	0
Hypertrophy	8	0	0	0
Macule	8	0	2	25
Scale	8	0	0	0
Nodule	8	0	0	0
Patch	8	0	6	75
Erosion	8	0	0	0
Vesicule	8	0	0	0
Hyperpigmentation	8	0	8	100
Hypopigmentation	8	0	0	0
Telangiectasia	8	0	0	0

causes, pigmentation disorders, connective tissue diseases, photodermatoses, lymphocytic infiltrates and neoplastic diseases such as actinic keratosis, basal cell carcinoma (BCC), squamous cell carcinoma were divided into groups.

In our retrospective study, 64.1% of the patients presenting with a red face had an age range of between 20-40. In the literature female patients had a higher rate of applying to health care services compared to male patients [5]. Our study is also included in the literature supports the findings.

The most common skin type in the patients was Fitzpatrick 2-4. In a study in 2015 conducted in Turkey, Fitzpatrick 4 skin type was found to be the most common followed by Fitzpatrick 3 skin type [6]. Fitzpatrick 3-5 skin type increases susceptibility towards solar lentigos, melasma or postinflammatory hyperpigmentation. Meanwhile patients with Fitzpatrick 1-2 are more prone to rosacea.

Rosacea is a common chronic inflammatory skin condition affecting the face area, and it was the main common disease cause of red face detected in our study. There are four subtypes: these include erythematotelangiectatic, papulopustular, phymatous and ocular types. The severity, disease course, and percentage of rosacea in affected areas differ. Erythematotelangiectatic is the most common subtype rosacea was observed, followed by papulopustular rosacea. One hundred rosacea patients participated to our study; 68 of them had erythematotelangiectatic (ETTR) type, 30 papulopustular type and 2 phymatous type were detected. We observed that the most common subtype of rosacea is ETTR. In 2016 Tan et al. [7] made a large-scale, multicenter retrospective study and the most common subtype observed was ETTR. Our study was consistent with literature; the most common cause of red face or facial erythema being rosacea and in a patient presenting with "red face" is rosacea is first diagnosis that should come to mind [8]. Among the connective tissue diseases, acute cutaneous disease is the most frequently applied to our clinic followed by systemic sclerosis and the third

Table 8. Distribution of clinical findings in dysplastic lesions

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	2	0	2	100
Lichenification	2	0	2	100
Papule	2	0	0	0
Pustule	2	0	0	0
Atrophy	2	0	0	0
Hypertrophy	2	0	0	0
Macule	2	0	0	0
Scale	2	0	0	0
Nodule	2	0	0	0
Patch	2	0	0	0
Erosion	2	0	0	0
Vesicule	2	0	0	0
Hyperpigmentation	2	0	0	0
Hypopigmentation	2	0	0	0
Telangiectasia	2	0	2	100

Table 9. Distribution of clinical findings in inflammatory dermatoses

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	28	0	28	100
Lichenification	28	0	4	14.3
Papule	28	0	0	0
Pustule	28	0	0	0
Atrophy	28	0	0	0
Hypertrophy	28	0	2	7.1
Macule	28	0	2	7.1
Scale	28	0	24	85.7
Nodule	28	0	0	0
Patches	28	0	2	7.1
Erosions	28	0	0	0
Vesicules	28	0	0	0
Hyperpigmentation	28	0	4	14.3
Hypopigmentation	28	0	0	0
Telangiectasia	28	0	0	0

Table 10. Distribution of clinical findings in infectious diseases

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	6	0	6	100
Lichenificaton	6	0	2	33
Papule	6	0	4	67
Pustule	6	0	2	33
Atrophy	6	0	0	0
Hypertrophy	6	0	0	0
Macule	6	0	2	33
Scale	6	0	2	33
Nodule	6	0	0	0
Patch	6	0	0	0
Erosion	6	0	0	0
Vesicule	6	0	2	33
Hyperpigmentation	6	0	0	0
Hypopigmentation	6	0	0	0
Telangiectasia	6	0	0	0

most common cause was DLE. Due to our clinic working closely with rheumatology connective tissue patients were referred to us frequently. According to the results, erythema was observed in all 35 patients, telangiectasia in 17 patients, atrophy in 16 patients, and 10 patients had hyperpigmentation, hypopigmentation was seen 8 patients and papule in 1 patient. Most of these patients were affected

Table 11. Distribution of clinical findings in cutaneous lymphomas

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	4	0	4	100
Lichenification	4	0	0	0
Papule	4	0	0	0
Pustule	4	0	0	0
Atrophy	4	0	0	0
Hypeertrophy	4	0	0	0
Macule	4	0	0	0
Scale	4	0	4	100
Nodule	4	0	4	100
Patch	4	0	4	100
Erosion	4	0	4	100
Vesicule	4	0	0	0
Hyperpigmentation	4	0	2	50
Hypopigmentation	4	0	0	0
Telangiectasia	4	0	0	0

Table 12. Distribution of clinical findings in bullous diseases

	N		Number of patients with symptoms (n)	Percentage of patients with symptoms (%)
	Total patients	Lost data		
Erythema	6	0	6	100
Lichenification	6	0	0	0
Papule	6	0	0	0
Pustule	6	0	0	0
Atrophy	6	0	0	0
Hypertrophy	6	0	0	0
Macule	6	0	0	0
Scale	6	0	4	67
Nodule	6	0	0	0
Patches	6	0	0	0
Erosion	6	0	6	100
Vesicule	6	0	0	0
Hyperpigmentation	6	0	0	0
Hypopigmentation	6	0	0	0
Telangiectasia	6	0	0	0

with acute cutaneous lupus due to systemic lupus erythematosus (SLE). Patients with SLE presented with typical malar rash. Malar rash in SLE is characterized with bilateral erythema. It is often repetitive, occurs after sun exposure and passes without scarring. Two different subtypes of acute cutaneous lupus erythematosus (ACLE) have been identified: generalized ACLE and localized ACLE. Unlike localized ACLE, malar rash is accompanied in generalized ACLE.

SLE may present with a generalized morbiliform rash on the trunk and is as termed photosensitive lupus dermatitis or maculopapular rash of lupus [9]. The second cause of connective tissue diseases that frequently causes erythema on the face is systemic sclerosis, the most common clinic presentation on the face erythematous mat telangiectasias and facial fibrosis [10].

Mat telangiectasias, especially in limited systemic sclerosis is accompanied by esophageal dysmotility, dilated nail bed capillaries, sclerodactyly and calcinosis cutis accompanies [11]. In DLE, the lesion is characterised by brown hyperpigmentation around the circumference with hypopigmentation in the middle. Due to scarring DLE may cause extensive cosmetic morbidity. Often cicatricial alopecias are referred to our hair disorders outpatient clinic, therefore ACLE and SS are more commonly observed.

The number of patients presenting with sarcoidosis was low. Two patients admitted to our clinic presented with papulonodular sarcoidosis. All the patients (100%) presented erythema, nodules, patches and telangiectasia was observed. Especially lupus pernio and plaque sarcoidosis are associated with severe systemic disease. Papulonodular sarcoidosis is characterized by purple-brown papules and nodules especially on the face and the extremities.

Most of our patients presenting with pigmentation disorders had melasma. Hyperpigmentation was observed in all patients (100%) and in 6 patients patch and maculae were observed in 2 patients. Our cosmetology and laser unit is the reason melasma patients were frequently applying.

Melasma is a disorder an acquired hyperpigmentation that affecting up to 30% of women who were pregnant. The clinical pattern is symmetrical, with irregular borders, light or dark. It is characterized by brown hyperpigmented patches. Increased hyperpigmentation in summer is one of the hallmarks of this disorder [12].

The disease observed from the dysplastic lesions group was BCC and 2 patients applied during the study period. In all of these patients (100%) hyperpigmentation, lichenification and telangiectasia have been observed. BCC of the skin, most common in the fair-skinned adult population over 50 years of age is cancer. Its incidence is increasing worldwide and ultraviolet exposure is the main carcinogenic factor. In some genodermatoses, there may be a predisposition to the formation of BCC.

In inflammatory dermatoses group seborrheic dermatitis is the

most common disease, followed by AD. Erythema was observed in all of this patient group, scales in 24 patients, lichenification in 4 and hyperpigmentation 2 patients, hypertrophy, macula and patch in 2 patients. Seborrheic dermatitis is a skin disease that can be seen frequently in all age groups.

Characteristic symptoms are facial erythema, scaling, and pruritus. Most commonly on the scalp, face and seen in the presternal region. Clinical diagnosis of seborrheic dermatitis depends on the localization of the lesions and appearance. The most probable known cause is the inflammation of the skin caused by a response to malassezia furfur. AD, also known as atopic eczema is a chronic relapsing inflammatory skin disease. The incidence of AD in developed countries has increased 2 or 3 times and accounts for approximately 15% to 20% of children and 1% of adults worldwide. Pruritus, typical localizations and it's chronic course makes the diagnosis of the disease. Upper lip cheilitis, centrofacial pallor and periocular or periorbital eczematous lesions are common.

In our study tuberculosis was the most common infectious disease which caused "red face". Lupus vulgaris was followed by herpes labialis. In our study erythema was observed in all patients, papules in 4, lichenification in 2 patients, pustules, macules, scales and vesicles were detected. The face is one of the most affected areas in lupus vulgaris and often, patients present with hard, dry plaques on an erythematous background [13].

Mycosis fungoides (MF)/sezary syndrome, was the most common cutaneous lymphoma found in our study. In all of our 4 patients who applied with lymphoma, erythema, scales, nodules, patches, erosions were observed and meanwhile hyperpigmentation was observed in 2 patients. MF is the most common cutaneous T-cell lymphoma. Typically, neoplastic T-cells are localized in the skin and causes patches, plaques, tumors, or erythroderma. The diagnosis of MF is quite may be difficult due to variable clinical and histological findings. Molecular biology facilitates the diagnosis. However, MF could be confused with a wide variety of skin diseases which makes clinical experience very important. Especially at the beginning, it manifests itself with erythematous brown scaly plaques, later the disease progresses to erythematous, scaly plaques or tumoral lesions in the later stages of the disease.

On the other hand, folliculotropic MF and erythrodermic MF often involve the face characterised by diffuse erythema, scaling and alopecia [14].

Pemphigus is the most common bullous disease and 6 patients have presented to our clinic. Erythema and erosion were detected in all of our patients, and scales was detected in 4 patients has been done. Pemphigus is a disease characterised by intraepithelial bullae, acantholysis of the mucosa and skin and it is associated with high mortality and morbidity [15]. Pemphigus vulgaris commonly presents with loose bullae or erosions involving the skin or mucosa may be seen in patients [16].

Study Limitations

However, the subtype of pemphigus foliaceus, which causes erythema and scaling in the face area is also known as pemphigus erythematosus or seborrheic pemphigus. Having a bullous diseases out patient clinic pemphigus patients rarely apply to our primary outpatient clinics.

Conclusion

When we looked at the literature the frequency associated with the diseases causing red face wasn't much studied and there was no algorithm related to its approach. In your study we investigated the frequency, clinical findings, first-choice treatment steps and we looked at the Fitzpatrick skin type found in these patients. There were 94 men and 168 women participating in our study. Diseases that caused "red face" rosacea was the most common, followed by acne and its subgroups, and connective tissue is the third.

A larger retrospective study is needed to optimise our approach to patients presenting with facial erythema or "red face".

Ethics

Ethics Committee Approval: The approval of Istanbul Univeristy-Cerrahpasa, Cerrahpasa Faculty of Medicine Ethics Committee was taken before initiating the study (number: E-83045809-604.01.01-371606, date: 26.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: D.D.A., B.E., Design: B.E., Data Collection or Processing: D.D.A., Analysis or Interpretation: D.D.A., Literature Search: D.D.A., Writing: D.D.A.

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

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ORIGINAL ARTICLE

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Low Dose UVA-1 Treatment in Atopic Dermatitis: Does Treatment Response Depend on Age and Gender?

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ABSTRACT

Background: UVA-1 is one of the anti-inflammatory treatment alternatives for atopic dermatitis.

Materials and Methods: The aim of this study is to evaluate the efficacy of low dose UVA-1treatment in atopic dermatitis. The patient files of the 19 atopic dermatitis patients who received low dose UVA-1 (10-15 J/cm^2, 5 days a week) treatment were analysed retrospectively.

Results: The complete remission rate was 84%. The mean of the cumulative dose was 236.05 J and the mean of treatment sessions was 16.1. Mann-Whitney U test showed that there is no relationship between age and treatment response (p=1.00). Fischer's extract test showed that there is no relationship between gender and treatment response (p=0.582).

Conclusion: It was concluded that low dose UVA-1 is an efficacous treatment for atopic dermatitis regardless of the patient's age and gender. A lower cumulative dose with a greater number of treatment sessions is required for low dose UVA-1 compared to high dose UVA-1 in the treatment of atopic dermatitis.

Keywords: Atopic dermatitis, Low dose, Phototherapy, UVA-1

Introduction

Atopic dermatitis is one of the most commonly encountered chronic inflammatory skin diseases. The treatment of atopic dermatitis has three crucial steps: avoiding the triggering factors, increasing the barrier function of the skin and anti-inflammatory treatment. Phototherapy, including narrow band ultraviolet-B (nbUVB) and ultraviolet-A1 (UVA-1), is one of the anti-inflammatory treatment alternatives [1,2]. There is limited data in the literature regarding the use of UVA-1 in the treatment of atopic dermatitis. The aim of this study is to evaluate the treatment efficacy of low dose UVA-1 in atopic dermatitis; and to determine the effect of age and gender on the treatment response.

Materials and Methods

Inclusion Criteria and Data Acquisition

Patients with the definitive diagnosis of atopic dermatitis, who have received UVA-1 phototherapy between January 2005 and November 2020, at the photherapy unit of İstanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Dermatology and Venerology were included in this retrospective study. The treatment indications for UVA-1 were having an acute attack, generalised skin eruption and thick infiltrative plaques. Patients with photosensitive disorders; pregnant and lactating patients; and those who cannot abide with the treatment protocol were excluded from this study. The age, gender, number of treatment sessions received, previous

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treatment modalities, comorbid diseases, maximum dose reached, cumulative dosage and the treatment response were noted from the patient files.

Treatment Parameters

Low dose UVA-1 treatment, with doses ranging from 10-15 J/cm^2, was given to every patient 5 days per week. (Waldmann Medizintechnik, UV7001). The approval of İstanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Ethics Commitee was taken before the initiation of the study (03.12.2020-158710).

Statistical Analysis

SPSS version 21 was used for the statistical analysis. Mann-U Whitney and Fisher's extract tests were used for the statistical analysis.

Results

Demographics

A total of 19 patients were included in this study: 10 females and 9 males. The mean age of the patients was 28.1 years; the youngest patient was 11 years old and the eldest patient was 60 years old. Comorbid asthma was present in three patients, hypothyroidsm in two patients, familial mediterranean fever in two patients and Netherton syndrome in two patients.

Treatment Response

The mean number of total treatment sessions was 16.1; maximum of 27 and minimum of 10. The mean cumulative dose of 236.05 J, minimum cumulative dose of 100 J and a maximum cumulative dose of 600 J were reached. Sixteen of the patients reached full remission whereas treatment modality was changed in three patients due to unresponsiveness.

Mann-Whitney U test was used to reveal that there is no relationship between age and treatment response (p=1.00). Fischer's extract test was used to reveal that there is no relationship between gender and treatment response (p=0.582).

Discussion

Atopic dermatitis is an inflammatory disease. Phototherapy is a helpful treatment for atopic dermatitis via photoimmunosupression and photoimmunomodulation. Phototherapy modalities that have been previously used in the treatment of atopic dermatitis are nbUVB (311-313 nm), broad band UVB (290-320 nm), UVB, Goeckerman regimen, excimer laser (308 nm), UVA, UVA-1 (340-400 nm), psoralens plus UVA and combined UVA/UVB (280-400 nm). Previously, a systematic review has reached the conclusion that medium dose UVA-1 is the most effective photherapy modality in the treatment of acute flares of atopic dermatitis, whereas, UVB is better at the chronic disease. Due its greater wavelength, UVA-1 penetrates deeper into the dermis and superficial vessels compared to UVB; therefore it suppresses the activity of Langerhans cells in the skin. It is effective in the treatment of acute flares in particular. It was shown that high dose UVA-1 (80-130 J/cm^2) and medium dose UVA-1 (40-80 J/cm^2) are equally effective and superior to low dose UVA-1 (<40 J/cm^2) in the treatment of atopic dermatitis in fair skinned individuals [3,4,5,6]. High dose UVA-1 is more effective than medium dose UVA-1 in dark-skinned individuals [7]. Due to increased heat emitted from the high dose UVA-1 lamps, treatment intolerances have been observed. This led to the introduction of cold-light UVA lamps that filter the infrared radiation [6]. UVA-1 and cold light UVA-1 therapies offer prolonged therapeutic benefits due to the decrease in eosinophilic cationic protein and soluble interleukin-2 and interleukin-4 receptors in the sera of patients, compared to UVB therapy. Cold light UVA-1 is superior to conventional UVA-1 treatment in terms of both anti-inflammatory efficacy and side effects since it produces less heat-induced blood flow to the irridiated area [8,9]. All available UVA-1 modalities are compared in Table 1. The therapeutic effects of UVA-1 phototherapy are prolonged up to 3 months [10].

High dose UVA-1 has been used as an efficacious treatment modality for acute exacerbations of atopic dermatitis since 1992 [11,12]. A multicenter trial has shown that high dose UVA-1 treatment is superior than topical high potency corticosteroids in the treatment severe atopic dermatitis; and it can be used as a mono-therapy in the treatment of acute exacerbations [13]. A recent study on the Asian population also investigated the efficacy of high-dose UVA-1 therapy on acute exacerbations of atopic dermatitis. A total of 16 patients were treated with an average cumulative dose of 968.8 J/cm^2 with an average of 9.7 treatment sessions of high dose (100 J/cm^2) UVA-1 phototherapy. Nine (56.3%) of these patients had complete and five (31.2%) of these patients had partial remission [14]. In our study, on the caucasian population, a mean cumulative dose of 236 J/cm^2 was reached on an average of 16.1 treatment sesions. Sixteen of the patients (84.2%) reached complete remision. Compared to high dose UVA-1, a lower average cumulative dose is reached in low dose UVA-1 treatment; however, the mean number of treatment sessions is more in low dose UVA-1 compared to high dose UVA-1 treatment. The two modalities are compared in Table 2.

Table 1. The comparison of different UVA-1 modalities [3,4,5,6,7,8,9]

Treatment modality	Dose (J/cm^2)	Efficacy
High dose UVA-1	80-130	Standard
Medium dose UVA-1	40-80	As efficacious as high dose
Low dose UVA-1	10-15	Less eficacious than high dose
Cold light therapy	45	More efficacicous than high dose

UVA: Ultraviolet-A-1

Table 2. Cumulative dose and average treatment sessions of high dose vs low dose UVA-1 [14]

Modality	Treatment dose (J/cm²)	Cumulatie dose (J)	Average number of treatment sessions
High dose UVA-1	100	968.8	9.7
Low Dose UVA-1	10-15	236	16.1

UVA: Ultraviolet-A-1

The medium dose UVA-1 treatment was found to be equally effective with high dose UVA-1 treatment [3-6]. A recent study on medium dose UVA-1's efficacy on acute attacks of atopic dermatitis has shown that medium dose UVA-1 (45 J/cm²) therapy improves the quality of life of atopic dermatitis patients by decreasing the severity of disease and exerting antipruritic effects [15]. Medium dose UVA-1 cold light therapy (45J/cm²), when given for 4 weeks, was found to be superior than conventional medium dose UVA-1 therapy given for 3 weeks [16]. When compared to medium dose UVA-1 (50 J/cm²), low dose UVA-1 (10 J/cm²) was found to be less effective on acute exacerbations of atopic dermatitis, given 5 times a week for 3 weeks [17]. Later, it was reported that even doses as low as 30 J/cm² were sufficient to control acute attacks of atopic dermatitis and the cumulative dose was the important treatment parameter that determines the treatment efficacy [18].

To our knowledge, our patient series was the first study to evaluate the efficacy of low dose UVA-1 treatment on acute attacks of atopic dermatitis, without comparing it to other dosing regimens. We have reported a complete remission rate of 84%. The mean number of treatment sessions was greater compared to higher dose UVA-1. Furthermore, our study was the first study to reveal that treatment response to UVA-1 in atopic dermatitis patients was independent of both age and gender.

Study Limitations

The limited sample size and the lack of Scoring Atopic Dermatitis scores are the main limitations of this study.

Conclusion

It was concluded that low dose UVA-1 is an efficacous treatment for atopic dermatitis regardless of the patient's age and gender. A lower cumulative dose with a greater number of treatment sessions is required for low dose UVA-1 compared to high dose UVA-1 in the treatment of atopic dermatitis.

Ethics

Ethics Committee Approval: The approval of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Ethics Commitee was taken before the initiation of the study (03.12.2020-158710).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Ö., T.K.Ü.U., Concept: D.Ö., T.K.Ü.U., Z.K., Design: D.Ö., T.K.Ü.U., Z.K., Data Collection or Processing: D.Ö., T.K.Ü.U., Analysis or Interpretation: D.Ö., N.C., Z.K., Literature Search: D.Ö., Z.K., Writing: D.Ö., Z.K.

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ORIGINAL ARTICLE

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Higher Serum Ceruloplasmin Levels May Indicate the Role of Oxidative Stress in Onychomycosis

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ABSTRACT

Background: Onychomycosis is the most common nail infection in the world. The most common causative agents are dermatophytes; however, the disease may appear due to non-dermatophytic molds and yeasts. Ceruloplasmin also takes part in defense mechanisms against oxidative stress. Ceruloplasmin is considered to be associated with approximately 80% of oxidative events in the plasma. The aim of the present study was to evaluate ceruloplasmin level in onychomycosis and to review the association with the parameters of the disease.

Materials and Methods: This is a prospective cross-sectional study and included 112 healthy volunteers and 102 patients followed up with the diagnosis of onychomycosis in the dermatology clinic of Ankara City Hospital between October 2021 and March 2022.

Results: The patients and control group were similar in terms of age and gender. The mean serum ceruloplasmin level in patients (866.6 U/L) was significantly higher than the control group (800.6 U/L) ($p=0.025$). A positive correlation was detected between the duration of the disease and ceruloplasmin levels. Serum ceruloplasmin levels were higher in patients with longer disease duration ($p=0.002$, $r=0.31$). The disease severity of the patients enrolled in the study was scored according to the onychomycosis severity index. Similarly, ceruloplasmin levels were correlated with disease severity ($p<0.001$, $r=0.43$).

Conclusion: Consequently, we believe that higher ceruloplasmin levels in the patients may indicate oxidative stress on tinea unguium. Ceruloplasmin may be a potential marker of disease severity and activity in onychomycosis.

Keywords: Onychomycosis, Ceruloplasmin, Oxidative stress

Introduction

Onychomycosis is the most frequent nail infection in the world and causes thickening and staining of the influenced nail plate. Although it may be detected in any age, the prevalence increases along with aging [1]. Organisms that cause onychomycosis can be categorized as dermatophytes, non-dermatophyte molds and yeasts [2]. Dermatophytes are accepted as the prevaling infectious organisms in onychomycosis; however, non-dermatophyte molds are also reported with increased incidence, especially in hot climates. The uncomplicated dermatophyte infection of the nail is called tinea unguium. The majority (60% to 70%) of dermatophytic nail infections are caused by Epidermophyton floccosum, Trichophyton rubrum and Trichophyton mentagrophytes [1]. The factors that predispose onychomycosis involve advanced age, diabetes mellitus, HIV infection, Down syndrome, psoriasis, peripheral vascular disorders, and traumatic nail disorders [2]. Oxidative stress is an injury in which redox imbalance occurs as a result of

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an increase in destructive free radicals, a decrease in antioxidants and antioxidant defense pathways [3]. Different biomarkers have been detected in oxidative stress to date. Ceruloplasmin is a serum ferroxidase that contains more than 95% of the copper found in plasma. Ceruloplasmin belongs to the group of positive acute phase proteins and acts in defense mechanisms against oxidative stress. The ability of ceruloplasmin to trap transition metal ions appears with preventing the formation of superoxide anion. Ceruloplasmin performs many catalytic functions similar to glutathione peroxidase activity and acts as an oxidase against a wide range of organic substrates. Today, ceruloplasmin is considered to be associated with approximately 80% of oxidative events in the plasma [4].

In our study we aimed to evaluate ceruloplasmin level in onychomycosis and appraise it as an oxidative stress marker in onychomycosis and to review the association with the parameters of the disease.

Materials and Methods

Study design and patients

This is a prospective cross-sectional study and included patients followed up with the diagnosis of onychomycosis in the dermatology clinic of Ankara City Hospital between October 2021 and March 2022, and healthy subjects without any concomitant disease. The diagnosis was confirmed by direct microscopic examination for all patients through a 20% potassium hydroxide preparation. The patients with concomitant systemic or cutaneous diseases, those who received any systemic treatment (e.g., anti-seizure drugs, oral contraceptives) in the last 1 month, and smokers were excluded from the study. The age, gender, disease duration, location and onychomycosis severity scores of the patients were recorded.

Our study was carried out in conformity with the Declaration of Helsinki and approval of the Ethical Committee of Ankara City Hospital was obtained (number: 2027, date: 06.10.2021). Written informed consents were obtained from the patients and volunteers.

Sampling and Measurements

Venous blood samples collected from the patient and control groups after at least 8 hours of fasting were centrifuged at 1,500 rpm for 10 minutes, and the separated serum was stored in a deep freezer at -80 degrees Celsius.

Ceruloplasmin ferroxidase activity levels were measured by the method described by Neselioglu et al. [5]. This is an automated and colorimetric method lying on the enzymatic oxidation of ferrous iron ions (Fe^{2+}) to ferric ions (Fe^{3+}).

Statistical Analysis

The SPSS 23.0 package program was used for data analysis. Categorical variables were shown as numbers and percentages, and numerical variables were expressed as mean (standard deviation) or median [(IQR) interquartile range]. The Kolmogorow-Smirnow test was used to assess whether numeric variables comply with normal distribution. Numerical variables with normal distribution were compared with Student's t-test, and numerical variables without normal distribution were compared with Mann-Whitney U test. The chi-square test was used to compare categoric variables. The correlation between numeric variables was examined through Pearson's or Spearman Analysis. Any p value <0.05 was accepted as statistically significant.

Results

The study included 102 patients followed-up due to onychomycosis and 112 healthy volunteers.

The patients and control group participants were similar in terms of age (p=0.45) and gender (p=0.18) (Table 1).

The onychomycosis subtype detected in all cases was distal lateral subungual onychomycosis. The location of the onychomycosis was foot in 95.1% of the patients whereas 4.9% of the patients had both hand and feet involvement.

Comparison of serum ceruloplasmin levels of the patient and control groups: The mean serum ceruloplasmin level was 866.6±231.9 U/L in the patient group, and 800.6±189.4 U/L in the control group. Ceruloplasmin level was considerably higher in the patient group than in the control group (p=0.025) (Figure 1).

The association between serum ceruloplasmin levels and demographic and clinical characteristics of patients: Serum ceruloplasmin levels were significantly higher in females. (930.1 vs 758.1, p<0.001) There was not any correlation detected between the age and ceruloplasmin levels (p=0.088, r=0.12). A positive correlation was detected between the duration of the disease and ceruloplasmin levels. The median duration of the disease was calculated as 18 (IQR: 9-36) months. Serum ceruloplasmin levels were higher in patients with longer illness duration (p=0.002, r=0.31) (Figure 2).

The disease severity of the patients enrolled in the study was scored according to onychomycosis severity index (OSI) created by Carney et al. [6] The OSI score is available by multiplying area of

Table 1. The distribution of demographic data

	Patient N (%)	Control N (%)	p-value
Gender			0.18
Female	39 (38.2)	53 (47.3)	
Male	63 (61.8)	59 (52.7)	
Age (years), mean (SD)	48.6 ±14.6	47.3 ±12.8	0.45

SD: Standard deviation

involvement (range 1-5) by the score for the closeness of disease to the matrix (range 1-5). Ten points are affixed for the presence of a longitudinal streak or dermatophytoma or for greater than 2 mm of subungual hyperkeratosis. Mild onychomycosis accounts for a score of 1-5, moderate 6-15, severe 16-35. The OSI scores of the patients in this study were between 3 and 33. Median OSI was calculated at 13 (IQR: 7-21). Similarly, ceruloplasmin levels were correlated with disease severity ($p<0.001$, $r=0.43$) (Figure 3). The mean ceruloplasmin levels in patients with onychomycosis on both hands and feet were 1254.8±320.3 U/L and 846.6±209.9 U/L in patients with onychomycosis on the feet alone. Such difference between the groups was statistically significant ($p<0.001$) (Figure 4).

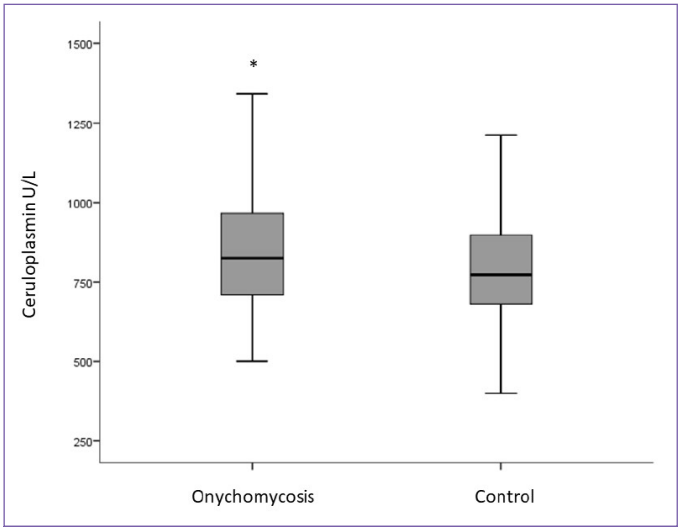

Figure 1. Ceruloplasmin levels in the patient and control groups

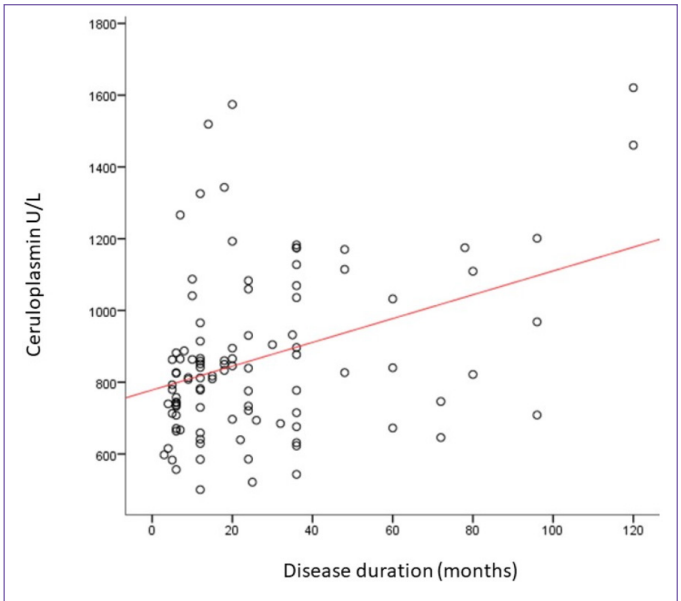

Figure 2. Ceruloplasmin levels and disease duration of the patients

Discussion

Onychomycosis consists of 50% of all nail diseases. Although the prevalence varies according to regions, Gupta et al. [7] analyzed the studies conducted in 2016 and detected the global prevalence of onychomycosis as 5.5%. Onychomycosis may appear at any age; however, the incidence increases with age. Although dermatophytes are the most common microorganisms in onychomycosis, non-dermatophytic molds such as Scopulariopsis brevicaulis, Acremonium spp., Aspergillus spp. may also be detected. Mixed dermatophytic-non dermatophytic infection may also be detected. The presence of non-dermatophytic molds in onychomycosis has often been associated with treatment failure and recurrence due to missed diagnosis. Onychomycosis caused by yeast is most

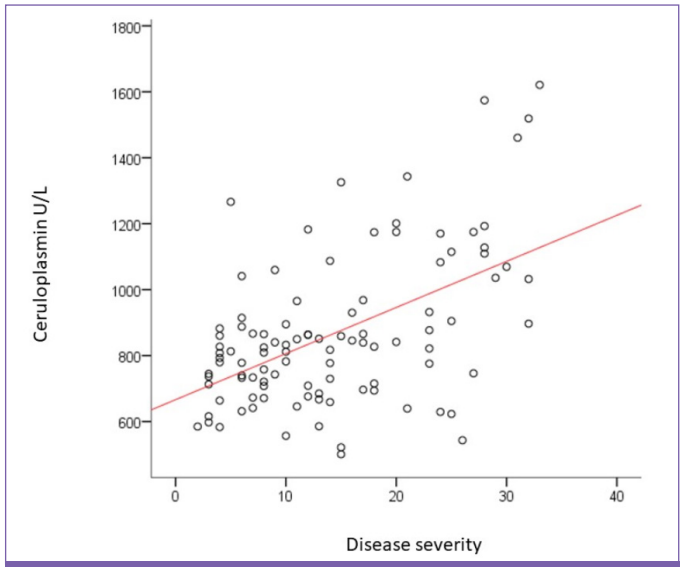

Figure 3. Ceruloplasmin levels and disease severity of the patients

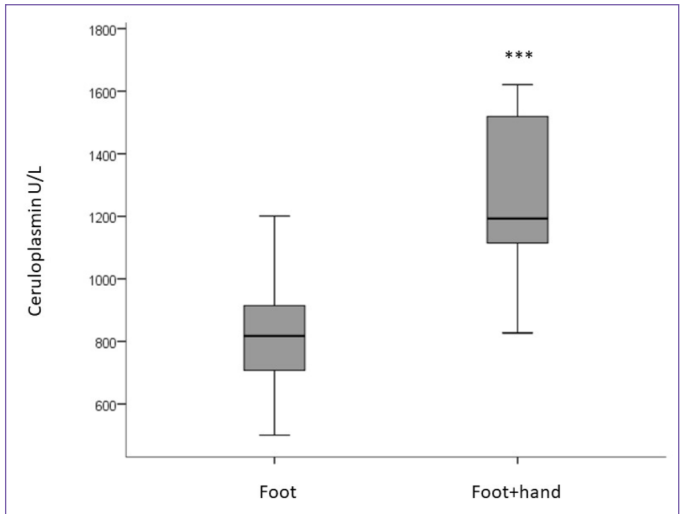

Figure 4. Ceruloplasmin levels and localization of the disease

commonly caused by Candida spp. on fingernails of people who are intensely in contact with water [1]. The presence of oxidative stress has previously been studied in many dermatological diseases such as telogen effluvium [8], seborrheic dermatitis [9], vitiligo [10], skin cancer [11], lichen planus [12], atopic dermatitis [12], and pemphigus vulgaris [13]. Different biochemical markers have been reviewed in aforesaid studies [8,9,10,11,12,13]. We used ceruloplasmin in order to demonstrate the role of oxidative stress in tinea unguium. Half lives of free radicals are as short as several minutes; therefore, in vivo quantity measurement is very difficult. Various markers have been used to assess oxidative stress, however none of them are considered as ideal biomolecules [14].

Since ceruloplasmin belongs to a positive acute phase protein group, plasma concentration increases by 50% following exposure to an injury. Such response developed after a stimulus that initiates the acute phase reaction appears within 24 to 28 hours. Ceruloplasmin is also involved in defense mechanisms against oxidative stress. Ceruloplasmin prevents the formation of superoxide anion due to the ability to bind transition metal ions and acts as a protective antioxidant in free radical reactions. It catalyzes the oxidation reaction of ferrous ions (Fe^{2+}) to ferric ions (Fe^{3+}). Ceruloplasmin is the principal copper oxidase in the plasma. It mediates the transport of most of the serum copper. It stabilizes the activity of superoxide dismutase enzyme which is the key enzyme of the antioxidant barrier of the body [4,15].

The only study on the role of oxidative stress in tinea unguium is the study conducted by Metin et al. [16]. The thiol/disulfide homeostasis was investigated in 52 patients with onychomycosis and 50 healthy individuals in the aforesaid study. It was observed that the thiol/disulfide balance in the patient group shifted in favor of disulfide indicating the oxidative stress. It was suggested in this study that oxidative stress may have a role in the pathogenesis of onychomycosis [16]. Novikova and Zlotnikova [17] investigated ceruloplasmin levels in patients with chronic recurrent and severe form of herpes infection. They found that ceruloplasmin levels were higher during disease exacerbation and remission periods when confronted with the control group. The ceruloplasmin level in the remission period was found higher than the level in the exacerbation period in that study, and this was attributed to the endogenous antioxidant effect of ceruloplasmin [17]. Kocyigit et al. [18] examined serum trace elements and their associated enzyme values in cutaneous leishmaniasis and found that ceruloplasmin level were more elevated in the patient group than in the control group. Cwynar et al. [4] measured malondialdehyde and ceruloplasmin levels in the blood in order to evaluate the oxidative stress in patients with alopecia areata and found that ceruloplasmin levels were greater in patients with alopecia areata when compared to the control group, and they attributed this to the oxidant/anti-oxidant system imbalance in alopecia areata. Kirmit et al. [15] reported in their study to appreciate the oxidative stress status in psoriasis that ferroxidase levels were higher in the patient group than the control group, and this increase may have occurred as a compensatory response to oxidative stress.

It is known that medications can affect the levels of ceruloplasmin [17]. For that reason we avoided the participants who took any medications from our study. Also high estrogen and progesterone levels can cause high ceruloplasmin levels which suggests that ceruloplasmin levels are influenced by gender [17]. However, our patient and control groups were statistically similar in regards to gender which showed a parallel distribution of males and females in both groups. Ceruloplasmin levels were found significantly higher in the patients than in the control group in our study; and they were correlated with both disease severity and disease duration. The ceruloplasmin level was detected higher in patients with hand and foot involvement where the disease is relatively severer than in those with foot involvement only.

Study Limitations

The principal limitation of our study was lack of other biomarkers of the oxidative stress. Single center design of the study and the small sample size of the patients were the other limitations of our study.

Conclusion

Consequently, we believe that higher ceruloplasmin levels in the patients may indicate the oxidative stress on onychomycosis. However, further studies with larger patient series are needed. An investigation of the effects of systemic antifungals used in the treatment of tinea unguium on ceruloplasmin levels may be the subject of a further study. Furthermore, we believe that ceruloplasmin in onychomycosis may be a potential marker of disease severity and activity due to a strong statistical correlation.

Ethics

Ethics Committee Approval: Our study was carried out in conformity with the Declaration of Helsinki and approval of the Ethical Committee of University of Helath Sciences Turkey, Ankara City Hospital was obtained (number: 2027, date: 06.10.2021).

Informed Consent: Written informed consents were obtained from the patients and volunteers.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: F.Erd., Design: F.Erd., Data Collection or Processing: F.Erd., F.E., E.F.O., Ö.E., Analysis or Interpretation: Y.H., F.Erd., Ö.E., Literature Search: F.Erd., A.Y.İ., Writing: F.Erd.

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

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CASE REPORT

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COVID-19 Vaccine Induced Bullous Pemphigoid: Case Report and Review of the Literature

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ABSTRACT

Bullous pemphigoid (BP) is a subepidermal blistering disease most commonly observed in older patients. There are some trigger factors identified such as infections, drug intake, and physical agents. The coronavirus disease-2019 (COVID-19) vaccines are a new suspected factor that may induce BP. Recently few cases of new-onset BP after vaccines were reported. We describe a 41-year-old patient who presented with bullous lesions gradually spreading to the whole body after the Pfizer COVID-19 vaccine. To identify all new-onset cases of BP after vaccination, we review the relevant literature and we found 14 previous cases reported. There are similarities between clinical and immunopathological findings in cases. After conducting a literature review, we suggest that vaccine-induced BP have a more refractory course as compared with the spontaneous occurring BP. The results of our study also support that BP may be observed more often after the mRNA syndrome-coronavirus-2 vaccine rather than the inactivated COVID-19 vaccine due to the induction of greater immune response.

Keywords: Bullous, Pemphigoid, COVID-19, Vaccine, New, Onset

Introduction

Bullous pemphigoid (BP) is a common acquired autoimmune blistering disease that is observed generally in elderly individuals. It's characterized by autoantibody formation against basement membrane structural BP180 and BP230 proteins. Only less than 15% of BP patients, there are triggering factors identified such as viral infections, drug use, physical agents [1]. Rarely, there are cases triggered after influenza, tetanus, and meningococcal vaccines [2]. There are a few cases that developed after the coronavirus disease-2019 (COVID-19) vaccination. Herein, we report a patient who developed bullous pemphigoid right after the first dose of the Pfizer mRNA syndrome-coronavirus-2 (SARS-CoV-2) vaccine.

Case Report

A 41-year-old woman visited our clinic with pruritic bullous lesions on her trunk and extremities including the palmoplantar region. The patient had no history of infection or drug use, but the rashes began to appear 2 weeks after receiving the first dose of Pfizer mRNA SARS-CoV-2 vaccine. The patient had used high potency topical steroids (propionate of clobetasol 0.05% cream) for 3 months, but her complaints did not regress. On dermatological examination, there were widespread erythematous annular plaques and blisters on her trunk and extremities including the palmoplantar region, there was no oral mucosal involvement (Figure 1). Histopathology from a bullous lesion demonstrated subepidermal blisters accompanied by eosinophilic infiltration in the dermal-epidermal junction and superficial dermis. A direct immunofluorescence study showed the linear deposition of immunoglobulin G and C3 at the basement membrane zone (Figure 2). The patient was diagnosed with BP based on histopathological and clinical findings, and the patient was started on 1 mg/kg/day prednisolone treatment. In the 2nd week of the treatment, the patient's lesions completely resolved. The

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patient in this manuscript has given written informed consent to publication of her case details.

Discussion and Review of the Literature

Although the etiopathogenesis of BP is not clear, it has been hypothesized that in genetically predisposed individuals, there is an alteration in the basement membrane by the effect of certain triggers such as burns, trauma, drug intake, and neurological diseases. It could be possible that there is a similar association between vaccination and the occurrence of BP. Vaccine-induced inflammation may induce the disease by changing the basement membrane structure followed by the production of autoantibodies targeting the basement membrane [3].

We evaluated all accessible cases of new-onset BP triggered by the COVID-19 vaccine published in the English language till the cut-off date of 22nd December 2021. A database search (Pubmed, Google Scholar, Wiley Online Library) using the keywords 'bullous, pemphigoid, COVID-19, vaccine, new, onset' elicited 14 reports of new-onset BP triggered by COVID-19 vaccine. Inclusion criteria is that in the direct immunofluorescence, there needs to be IgG or C3 deposition in the basement membrane. We excluded cases that were diagnosed as BP before vaccination. No restrictions were implemented regarding patient age. A summary of the clinical and immunopathologic findings from our current case and the 14 reported cases in the literature are shown in Table 1.

Six (40%) of the patients were female and, the median age was 74.9 years (range 41-97 years). This suggests that COVID-19 vaccine-induced BP is characterized by the old age of onset as the spontaneous occurring BP. The youngest age of onset is 41 that is observed in our present case. Fourteen out of 15 patients developed the disease after the mRNA vaccine (Pfizer, Moderna, AstraZeneca 10,2,1 patients respectively). Only one patient was

Table 1. Clinical and immunopathologic findings in patients with new-onset bullous pemphigoid after COVID-19 vaccine

Author	Age	Sex	Comorbidities	Vaccine-dose	Flare after 2nd dose	Onset	DIF	Treatment	Outcome
Our case	41	Female	None	Pfizer-dose 1	X*	2w	+	OCS	2w
Nakamura et al. [2]	83	Female	Xerotic eczema	Pfizer-dose 2	-	3d	+	IVCS, IVIG	2w
Young et al. [4]	68	Male	None	Pfizer-dose 1	Flare	3w	+	TCS	3m
Agharbi et al. [5]	77	Male	None	Astrazeneca-Dose1	X*	1d	+	DCN, TCS	Favorable response**
Perez- Lopez et al. [6]	78	Female	DM, Alzheimer	Pfizer- dose1	Flare	3d	+	OCS, TCS	2w
Bostan et al. [7]	67	Male	BPH, DM*	Inactivated vaccine-dose1	Flare	5w	+	OCS, OMA	No regression
Dell'Antonia et al. [8]	83	Male	Ht	Pfizer- dose1	Flare	1w	+	OCS, TCS	3w
Tomayko et al. [9]	97	Female	Psoriasis	pfizer- dose2	-	2d	+	DCN, NAM, TCS	2w
Tomayko et al. [9]	75	Male	Eczema	Pfizer-dose2	-	10d	+	OCS, NAM, DCN, TCS	3w
Tomayko et al. [9]	64	Male	None	Pfizer- dose2	-	14d	+	TCS	4w
Tomayko et al. [9]	82	Male	Eczema	Pfizer- dose2	-	1d	+	TCS	2w
Tomayko et al. [9]	95	Female	Nonmelanoma skin cancer	Pfizer-dose1	No flare	5d	+	NAM, DCN, TCS	8w
Tomayko et al. [9]	87	Male	Stasis dermatitis, Alzheimer disease	Moderna-Dose2	-	21d	+	OCS, NAM, DCN	No regression
Tomayko et al. [9]	42	Female	Hand eczema	Moderna-Dose2	-	3d	+	IVCS, IMCS, TCS	No regression
Tomayko et al. [9]	85	Male	Dementia	Pfizer-dose1	No flare	5d	+	OCS	No regression

*This patient was using vildagliptin for diabetes mellitus, **The patient was treated by high potency topical corticosteroid and systemic doxycycline. Favorable outcome was reported but full response time is unknown, X: *The patient didn't receive the 2nd dose of COVID-19 vaccine. DIF: Direct immunofluorescense, DM: Diabetes mellitus, BPH: Benign prostate hyperplasia d:days, w:weeks, m: months OCS: Oral corticosteroid, IVCS: Intravenous corticosteroid, IMCS: Intramuscular corticosteroid, IVIG: Intravenous immunoglobulin, TCS: Topical corticosteroid, DCN: Doxycycline, NAM: Nicotinamide OMA: Omalizumab

reported whose diagnosis of BP was confirmed after the inactivated COVID-19 vaccine. In this patient, prolonged use of vildagliptin for diabetes mellitus was thought as the cause of the refractory course of the disease [7]. These observations raise the question of why BP is observed more often after the mRNA vaccine rather than the inactivated vaccine. Talotta [10] hypothesized that the COVID-19 mRNA vaccine increases the risk of autoimmunity by activating endosomal pattern recognition receptors, producing cross-reactive autoantibodies. Moreover, the generation of type 1 IFN response may cause the disruption of immunological self-tolerance and, therefore, trigger autoimmunity. These findings remind us of a significant question of whether BP is induced by an adjuvant of the vaccine itself and is there any association between the high level of autoantibodies and the development of BP. In a study by Lim et al. [11], it was shown that there were higher concentrations of neutralizing antibodies against SARS-CoV-2 in patients who received mRNA vaccine than in those who received the inactivated COVID-19 vaccine. These results support that compared with the inactivated vaccine, the mRNA vaccine may trigger a greater immune response.

In eight patients (53.3%), the rashes appeared after the first dose of vaccine, while seven (46.6%) patients developed the disease after the second dose. Of the 8 patients who developed the rashes after the first vaccine, 6 of them received the booster dose of COVID-19 vaccine. Four (66.6%) of 6 patients experienced a flare-up of blisters. Two (33.3%) of 6 patients tolerated the second dose and had no worsening of the disease. Tomayko et al. [9] hypothesized that rapid onset of rash after the first dose of vaccine may be related to exacerbation of a preexisting subclinical autoreactivity by temporary

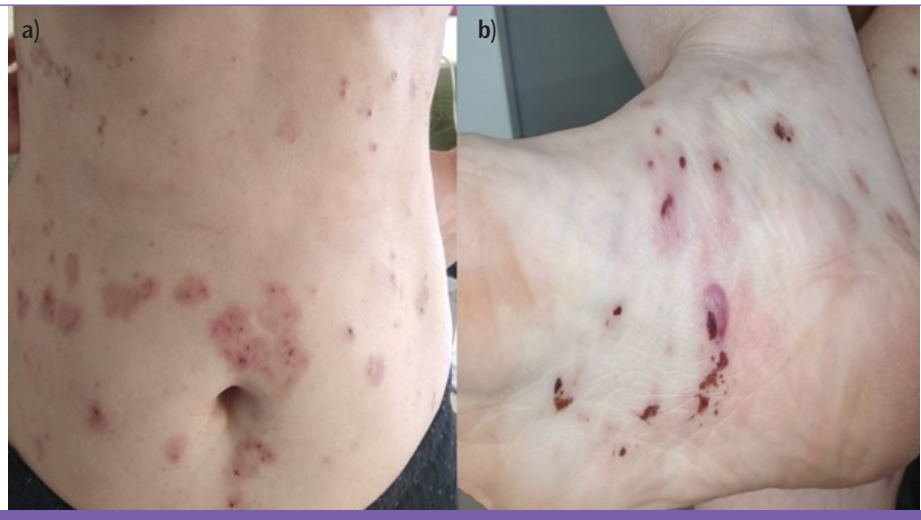

Figure 1. Clinical images, a) Excoriated annular plaques on anterior trunk, b) excoriated papules on erythematous base and a blister on right plantar region

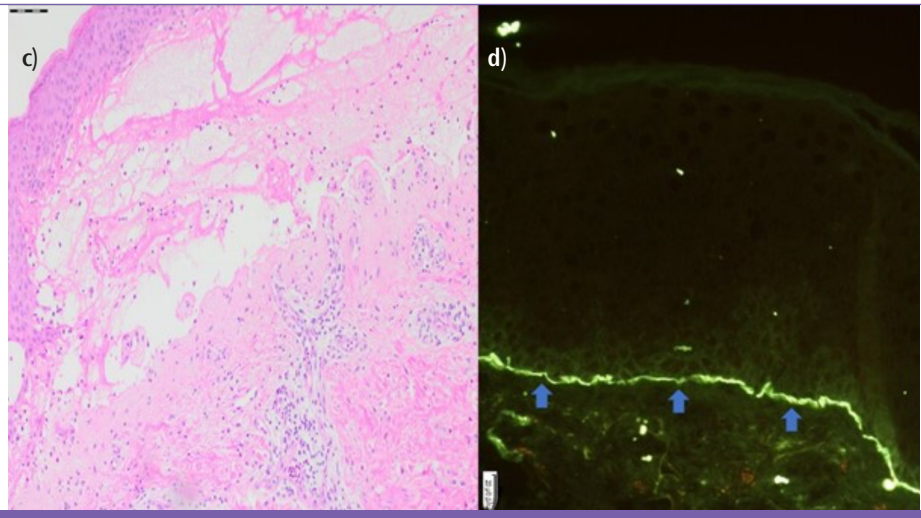

Figure 2. Histopatological images, c) Subepidermal bulla formation with eosinophil infiltration in the dermal-epidermal junction, (H&E stain X100), d) Linear deposition of IgG noted on direct immunflourescence as indicated by the blue arrows

activation of the immune system by vaccines. Also, the longer the time between vaccination and the onset of the disease, the less likely the patient would have subclinical autoantibodies. According to our review, there is no correlation between rapid disease onset and the flare-up of the disease after the second dose of the vaccine. The latency between vaccine and disease onset and the existence of subclinical autoantibodies remains to be proven.

Including the present case, the median latency period between vaccine application and the appearance of the symptoms is 9, 8 days. In recent studies, the latency period was reported between 1 day to 1 month in influenza vaccine-induced disease onset [3]. In our study the longest latency period, 5 weeks, is observed after the inactivated COVID-19 vaccine. This is a quite remarkable finding and needs to be elucidated. Histopathology was similar in all patients and direct immunofluorescence was IgG or C3 positive in all cases. In 11 (73.3%) out of 15 patients had a considerable clinical response with different therapy modalities (range 2 to 12 weeks). However, in four patients, there was a failure to control disease activity and new blisters continued to develop. Among the 11 patients who showed a significant response to the treatment, 3 patients (27.2%) were treated by high potency topical steroids alone and 8 patients (72.7%) had improvement in clinical findings with systemic treatment (combinations of topical and systemic corticosteroids, doxycycline, nicotinamide, omalizumab, intravenous immunoglobulin therapy). In a single-center retrospective study which included 96 BP patients with a mean age of 84 years, while 62% of patients had resolution of blisters with topical steroid alone, 25% of patients had additional systemic treatment due to failure of treatment or relapses [12]. In contrary to this study, a higher percentage of patients needed further systemic therapy to control the disease in our study. It's conceivable that vaccine-induced BP is more likely to have a refractory course as compared with the spontaneous occurring BP. Therefore, these patients should be closely followed up.

Conclusion

Recently, few cases of BP after COVID-19 vaccination were reported. By reporting the cases, new side effects can be recognized and the frequency of side effects can be determined and included in the prospectus information. The accumulating evidence suggests that vaccine-induced BP is more resistant to treatment than spontaneous BP and long-term follow-up of patients is required. The COVID-19 vaccine has been newly used in humans and with the increase of our knowledge about different types of vaccines, personalized vaccine dosing or schedules may be developed in the future.

Ethics

Informed Consent: The patient in this manuscript has given written informed consent to publication of her case details.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., Concept: A.S., İ.İ.K., E.A., Design: P.Ü., E.A., Data Collection or Processing: P.Ü., A.S., Analysis or Interpretation: P.Ü., İ.İ.K., Literature Search: P.Ü., A.S., Writing: P.Ü.

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

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

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CASE REPORT

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Variable Clinical Features of Temporal Triangular Alopecia

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ABSTRACT

Temporal triangular alopecia (TTA), in other words congenital triangular alopecia, is an asymptomatic, non-cicatricial, permanent type of alopecia. Although it is often localized unilaterally in the frontotemporal region, it can occur bilaterally. Despite various associations with TTA have been reported, its association with sebaceous nevus has not been reported so far. In this article, we aim to report a possible association between TTA and sebaceous nevus and to report a pinkish background as a trichoscopic finding of TTA in addition to previously described trichoscopic findings.

Keywords: Nevus sebaceus, Temporal triangular alopecia, Trichoscopy

Introduction

Temporal triangular alopecia (TTA), in other words congenital triangular alopecia, is an asymptomatic, non-cicatricial, permanent type of alopecia. Although it is often localized unilaterally in the frontotemporal region, it can occur bilaterally [1]. Some associations have been reported as leukonychia, wooly hair, Down syndrome, sectorial hyperpigmentation of iris, epilepsy, mental retardation, phakomatosis pigmentovascularis, aplasia cutis congenita, congenital heart disease, bone and tooth abnormalities [1,2]. In this study, we aim to report a new possible association with TTA and nevus sebaceous and describe our cases with TTA clinically and trichoscopically.

Case 1

A 30-year-old man applied our clinic with hair loss. He had a 3x1.5 cm triangular alopecic patch (Figure 1a) and a verrucous plaque, on his temporal and parieta-occipital area, respectively. Both lesions were asymptomatic and present since birth. On the triangular alopecic area, pigmented vellus hairs in different thicknesses surrounded by terminal hairs and white hairs were found trichoscopically (Figure 1b). The lesion was diagnosed with TTA. The trichoscopy of the yellow verrucous plaque (Figure 2a) revealed transparent yellowish fingerlike projections (Figure 2b). The skin punch biopsy of the verrucous plaque was histopathologically compatible with nevus sebaceous.

Case 2

A thirty-nine-year-old woman was admitted to our clinic with 3x2 cm-sized, triangular alopecic patches, extending to the anterior scalp line, on both temporal areas (Figure 3a,b), since infancy. Trichoscopically, on a pinkish background, empty follicules, yellow dots, white hairs, pigmented vellus hairs with length and diameter diversity, surrounded by terminal hairs were detected (Figure 3c,d).

Case 3

A fourteen-year-old male patient applied to our dermatology outpatient clinic with a lancet shaped, 4x1 cm-sized alopecic patch on the left frontotemporal region (Figure 4a), since infancy. On trichoscopic evaluation pigmented vellus hairs of different length and epidermal scale on a pinkish background were detected.

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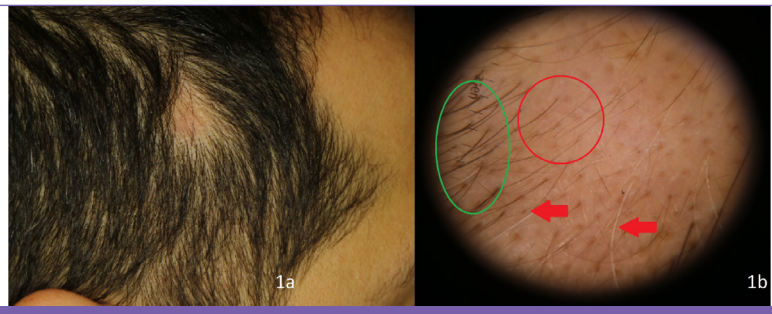

Figure 1. a. Triangular alopecic area, b. pigmented vellus hairs in different thickness (red circle) surrounded by terminal hairs (green circle) and white hairs (red arrows)

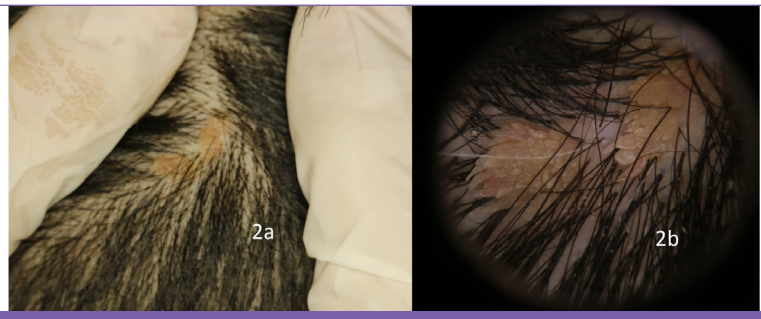

Figure 2. a. Yellow verrucous plaque, b. transparent yellowish fingerlike projections

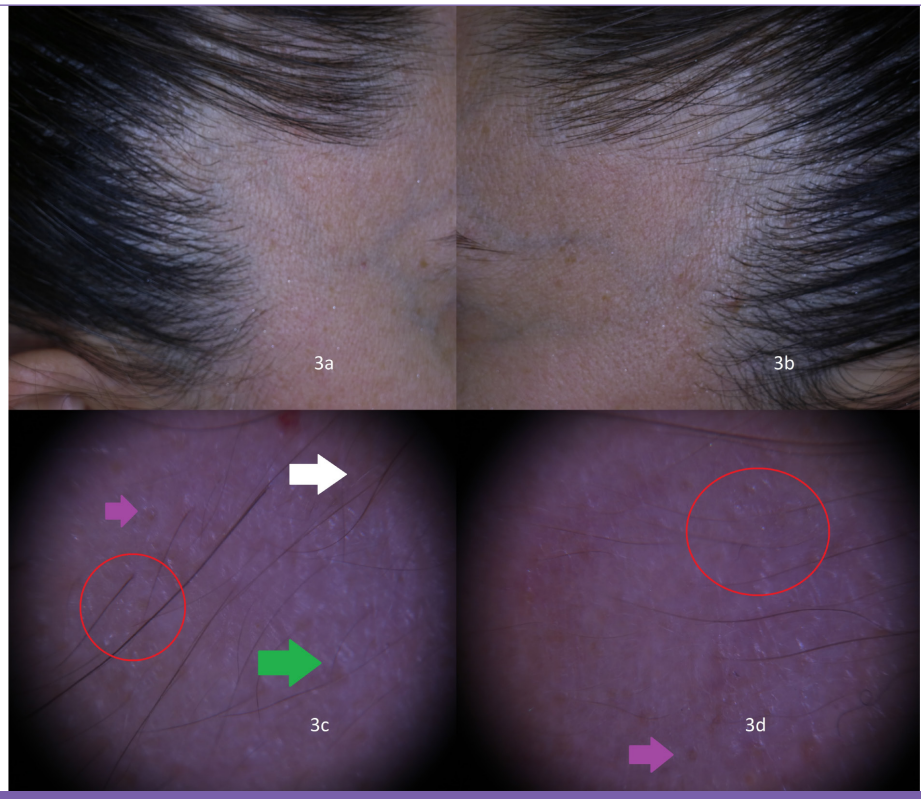

Figure 3. a,b. Alopecic areas were triangular shape 3x2 cm in size extending to the anterior scalp line, c,d. pigmented vellus hairs of different length and diversity, empty follicules, yellow dots, white hairs on pinkish background

Case 4

A twenty-year-old male patient presented with the complaint of an alopecic area since childhood. On dermatological examination, in the right frontotemporal region, a 3x1 cm lancet-shaped alopecic region was found (Figure 5).

Discussion

TTA is a kind of non-cicatricial alopecia that is often diagnosed in childhood and is usually observed in the frontotemporal region [3]. Although various associations have been reported in the literature, as far as we know, its association with nevus sebaceous has not been reported far.

Nevus sebaceous is a kind of hamartoma that is classically localized on the face or scalp [4]. Although it often occurs as an isolated lesion as in our TTA patient, especially extensive lesions can be accompanied by other system malformations such as brain, kidneys, bones, and heart [4]. The occurrence of two rare entities in the same patient on the scalp may be coincidental. In the light of cases to be reported in the future, conditions that may accompany isolated lesions will be revealed.

In the literature, white hairs, white dots, vellus hairs surrounded by terminal hairs, empty follicles and diameter diversity are described as common trichoscopic features of TTA [1,5]. In addition to the features described, we observed a pinkish background in two of our cases (case 2,3). In the literature, an arboriform vascular pattern and arborizing red lines were reported [1,5]. In our opinion, the pinkish color can be associated with vascular structures that we could not observe because of their deeply localization or insufficient illumination.

TTA is usually diagnosed in early childhood, rarely it can be diagnosed in adulthood [6]. Other childhood non-cicatricial alopecias like alopecia areata, aplasia cutis congenita, tractional

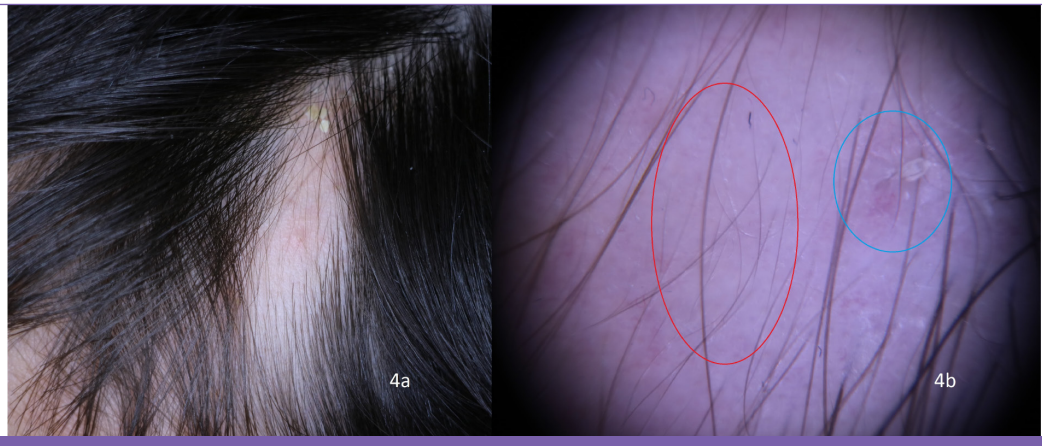

Figure 4. a. A lancet-shaped alopecic patch measuring 4x1 cm in size, b. Different lengths pigmented vellus hairs and epidermal scale on pinkish background

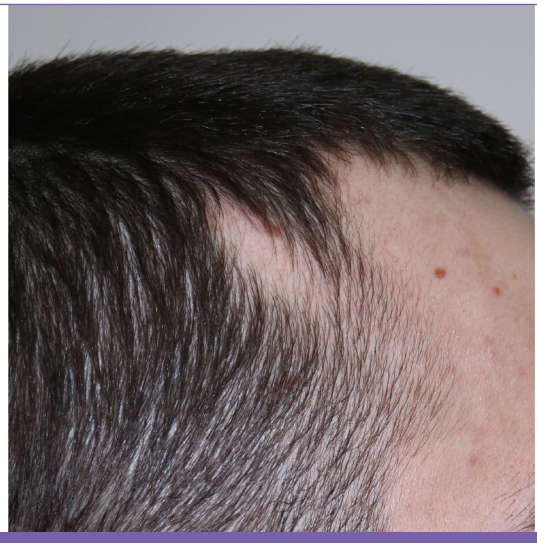

Figure 5. A lancet-shaped alopecic region, 3x1 cm in diameter, in the right frontotemporal region

alopecia, trichotillomania should be ruled out [1]. Absence of trichoscopic features of alopecia areata such as yellow dots, black dots, exclamation mark hairs, flame hairs, tapered hairs, pigtail hairs is distinctive [7]. Trichoscopy can also differentiate aplasia cutis congenita and TTA. Translucent appearance and absence of skin appendages are characteristic features of aplasia cutis congenita [5]. In contrast, eccrine pores are observed as white dots and numerous vellus hairs are seen in TTA [5].

In conclusion, trichoscopy is a non-invasive and useful method that can be used in the diagnosis of TTA and a pinkish background may take part as a trichoscopic feature. Evaluation of cases with TTA in terms of the presence of nevus sebaceous will be useful to find out the frequency of this association.

Ethics

Informed Consent: Patient consent has been obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.A., G.G., A.Ş.S., Concept: G.A., Design: G.A., A.Ş.S., Data Collection or Processing: G.A., G.G., Literature Search: G.G., A.Ş.S., Writing: G.A.

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

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Concurrent Herpes Zoster and Psoriasis After mRNA COVID-19 Vaccine (BNT162b2): A case Report

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Keywords: COVID-19 vaccine, mRNA vaccine, Psoriasis, Herpes zoster, Zona, VZV

Dear Editor,

With the increase in coronavirus disease-2019 (COVID-19) vaccination rates, different cutaneous side effects of vaccines are encountered. These reactions are generally mild and do not constitute an obstacle to vaccination. While reactions such as local injection site reactions, urticaria, morbilliform rash are more common due to mRNA COVID-19 vaccines (BNT162b2, mRNA-1,273); pernio/chilblains, cosmetic filling reactions, zoster, herpes simplex exacerbations, and pityriasis rosea-like reactions have also been observed [1]. Newly diagnosed psoriasis cases after mRNA COVID-19 vaccine have been reported rarely [2]. An article has recently been published reporting three cases of psoriasis exacerbated after mRNA vaccine [3]. As far as we could scan, there is no case of both herpes zoster (HZ) and psoriasis development in the same patient after mRNA vaccination. Here, we present a case of simultaneous development of HZ and psoriasis after mRNA COVID-19 vaccine. Informed consent form was obtained from the patient for this study.

A 62-year-old male patient presented with painful wounds on the right side of his torso and dandruff wounds on his hands and arms. The patient had no previously known additional disease and did not have any medication that he used regularly. In his detailed anamnesis, it was understood that the patient had the first dose of mRNA COVID-19 vaccine (BNT162b2) two weeks ago and his

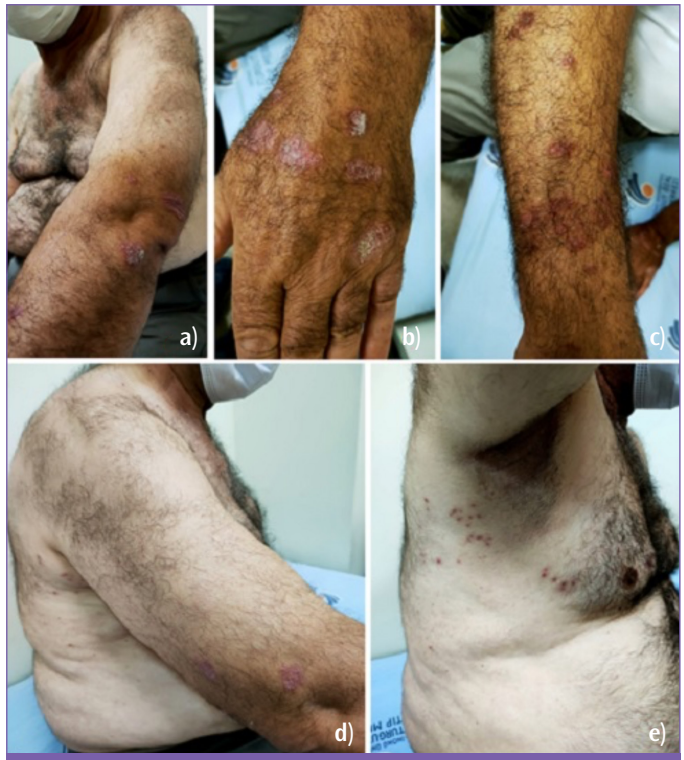

Figure 1. Psoriatic plaques on the dorsal surface of both hands, forearms, and elbow extensor surfaces (a,b,c). Erythematous vesicles and crusted center papules in the area compatible with the T-8 dermatome (d,e)

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complaints started about three days after the vaccine. Before his complaints started, the patient had no history of infection, drug therapy, emotional stress, or physical trauma. Dermatological examination revealed psoriatic plaques on the dorsal surface of both hands, forearms, and elbow extensor surfaces (Figure 1a,b,c), and erythematous vesicles and crusted center papules were found in the area compatible with the T-8 dermatome on the right half of the body (Figure 1d,e). Lesions on the trunk were compatible with HZ, and lesions on the extremities were compatible with psoriasis. For HZ, valacyclovir 1 g tablet three times a day, topical steroid cream and urea-based moisturizers were recommended for psoriasis lesions.

It has been reported that vaccines such as hepatitis A, influenza, rabies, and Japanese encephalitis trigger HZ. Recently, HZ cases have been reported after vaccination within creasing COVID-19 vaccination rates. Our case had new onset psoriasis concurrent with HZ. Psoriasis is a multifactorial disease in which genetic and environmental factors play a role. The innate and adaptive immune system plays a role in the pathogenesis. Dendritic cells and type-I interferon (IFN) produced by them play an active role in innate immunity, and Th-1 and Th-17 and tumor necrosis factor (TNF)-alpha, IL-23, IL-17 play an active role in adaptive immunity. Onset or exacerbations of psoriasis have rarely been reported after some vaccines (influenza and tetanus-diphtheria) [3,4]. Reported cases of psoriasis occur immediately after vaccination and are usually in the form of guttate psoriasis [3,4]. It has been determined that more than half of HZ cases due to COVID-19 vaccines occur in the first five days after vaccination, and most of them occur within two weeks [5]. In our case, plaque psoriasis and HZ appeared within a few days after vaccination, which was consistent with the literature. In clinical studies form RNA COVID-19 vaccines, it has been shown that IL-2, IL-12, TNF-alpha and IFN-gamma levels increase after vaccination [6]. In experiments performed in mouse models, it has been shown that there is an increased Th-1 and Th-17 immune response after influenza vaccination [7]. These studies show that the immune response after vaccination may trigger psoriasis. The relationship between mRNA COVID-19 vaccines and varicella-zoster virus (VZV) reactivation is thought to be mediated by the toll like receptor-3, 7 of innate immunity [8]. COVID-19 vaccination can activate T and B cell immunity by leading to the production of type-I IFNs and other inflammatory cytokines, and negatively affect antigen expression and cause VZV reactivation [9]. The coexistence of these two diseases in our patient indicates that there may be a common immune pathogenesis.

Ethics

Ethics Informed Consent: Informed consent form was obtained from the patient for this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.A., D.T., N.A., Design: S.A., D.T., N.A., Data Collection or Processing: S.A., D.T., N.A., Analysis or Interpretation: S.A., D.T., N.A., Literature Search: S.A., D.T., Writing: S.A.

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

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

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