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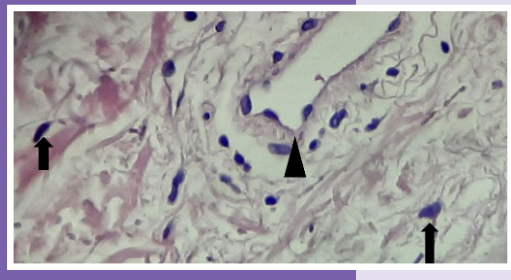

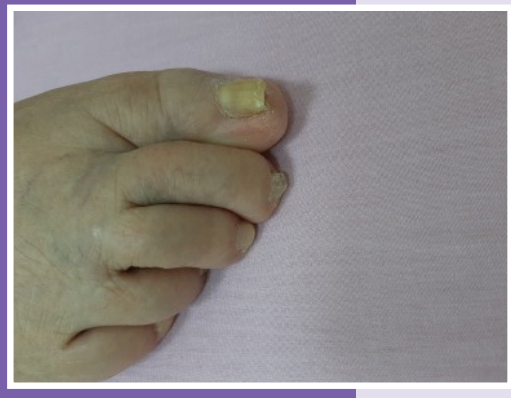

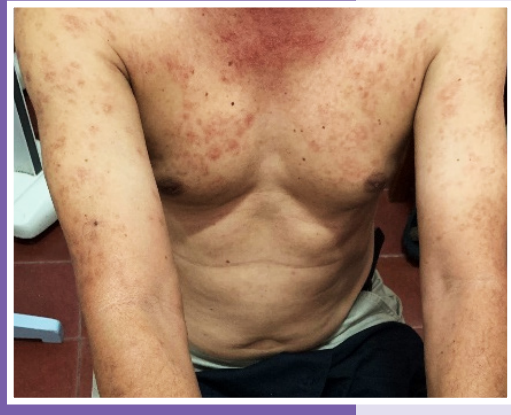

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the appendices

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REVIEW

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Collagen Supplementation

Defne Özkoca, Özge Aşkın

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ABSTRACT

The use of nutritional supplements for antiaging purposes has been rising in the past decade. Collagen is one of the most prevalent proteins in the human body. Aging is a multifactorial process; and the thinning and sagging of the skin is due to the loss of collagen and elastin fibers. Oral collagen supplementation, via collagen dipeptides and tripeptides triggers neocollagenesis. Therefore there is a rise in the market of collagen supllementation recently. This review article dwells on the biochemistry and sources of collagen as well as the recent studies about collagen supplementation.

Keywords: Anti-aging, Collagen, Supplementation

Introduction

Skin homeostasis is affected by nutrition. The use of nutritional supplements for antiaging purposes has been rising in the past decade and the estimated market value for nutritional supplementation in 2025 is 60 billion Turkish liras. Although the demand has been rising, enough evidence for the use of oral collagen supplementation in anti-aging is still lacking [1].

Biochemistry of Collagen

Collagen is one of the most prevalent proteins in the human body. It compromises one third of the human protein component, three quarters of the dry weight of human skin; and it is the most abundant component of the extracellular matrix. Collagen is a protein that is unique for its sturcture: Three polipeptide strands forming a helix [2]. Gelatin is a product that is produced when collagen is denatured by heat. Gelatin is used as a part of traditional medicine in Europe and China. Collagen hydrosylates, peptides of varying lengths, are produced by the further hydrolisis of gelatin. Collagen hydrosylates can be easily formulated into liquid drinks and jelly sticks due to its lower molecular weight and higher water solubility. In the human body, the collagen hydrosilates are further divided into dipeptides and tripeptides, which are resistant to degradation and are bioactive. The dipeptide and tripeptide degradation products of collagen are found in the human blood stream after oral collagen hydrosilate intake. Previously, animal studies have shown that these dipeptides are incorporated to the skin for two weeks. Furthermore, *in vitro* studies have demostrated that the ingestion of collagen hydrosilates induces mRNA transciption and translation of the protein and thus the collagen synthesis. Besides, it promotes anti-oxidative activity within the cells. Dipeptides induce chemotaxis, cell proliferation and the production of hyaluronic acid by fibroblasts. Thus, oral collagen supplementation has a potential therapeutic value for aging since it helps to produce stronger collagen fibers [1].

Aging

Aging is a multifactorial process. The reduction and repositioning of adipose tissue, bone remodelling and decreased production of collagen contribute to aging [3]. Histologically, aged skin shows abnormally deposited amorphous elastin fragments and fragmented collagen. The aged skin is lax, rough, shallow and has decreased elasticity [4]. First signs of dermal aging are shown in the human

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body around 30 years of age. Fine wrinkles ocur around the eyes and the mouth. The thinning and sagging of the skin is due to the loss of collagen and elastin fibers [5]. Oral collagen supplementation, via collagen dipeptides and tripeptides triggers neocollagenesis [1].

Sources of Collagen

The most commonly used source of collagen are the bovine and porcine sources. The age of the animal effectes the solubility of collagen obtained. Collagen of older animals are less soluble than that of the younger animals. The technology for acquiring collagen has been advancing as well. Bovine collagen, extracted as gelatin from the bovine bone, was used in the treatment of osteoarthitis previously. However, due to the increasing risk of bovine encephalopathy the use of this source has diminished. As a result the search for other sources of collagen began, which include vegetable source, algea and marine organisim including the fish [6].

The use of marine organisms is preferred in the cosmetic industry as a source of collagen. The marine organisms from which collagen can be extracted are jellyfish, sponges, seaurchin, octopus, cod, salmon and marine mammals. The biocompatibility and amino acid content of marine collagen is similar to that of bovine collagen. Yet, it has a lower molecular weight, is more soluble and has a lower potential for contamination or inflammatory reactions. In addition to these, type 1 collagen is more abundant in marine sources. The previous uses of marine collagen in the cosmetic industry were would healing, antimicrobial protection, prevention of loss of heat and humidity from the injured tissues [7,8]. The only limitation of the use of marine collagen is its possible contamination with heavy metals [9].

Previous Studies Regarding the Use of Oral Collagen Supplementation in Human Subjects

Collagen Hydrosilates

In 2006, Lee et al. [10] investigated the use of collagen hydrosilate in pressure ulcers with 89 patients. Each patient either received 15 g oral collagen three times daily or placebo. The investigators concluded that collagen hydrosilates were effective in the treatment of pressure ulsers compared to placebo [10].

Proksch et al. [11] investigated the use of 2.5 g oral bioactive collagen product use daily for the treatment of eye wrinkles in 116 healthy females. As a result of daily collagen use, procollagen type 1 and elastin has increased within the skin. There was a significant reduction in the periorbital wrinkles after the daily use of collagen hydrosilate. A year after, Proksch et al. [12] investigated the use of porcine collagen for impro ving skin elasticity. Sixty-nine females with dry forearm skin were divided into three groups of equal participants. The first group recevied 2.5 g oral daily porcine collagen hydrosilate, the second group received 5 g oral porcine collagen hydrosilate and the third group was the placebo group. The authors concluded that daily use of porcine collagen hydrosilates (2.5 g or 5 g) were effective in improving the skin quality and elasticity [11,12].

In 2014, Yoon et al. [13] compared the use of oral 2 mg astaxhantin and 3 g fish collagen hydrosilate to placeboin 44 women with wrinkles. Skin elasticy and transepidermal water loss improved significantly with the use of collagen hydrosilates. The expression of procollagen type 1 mRNA increased and the expression of the matrix metalloproteinases decrased as a result of collagen ingestion [13].

Asserin et al. [14] compared the use of porcine collagen to that of fish collagen in 33 women with dry skin. Ten grams of fish colllagen peptide, used daily was compared to 10 g porcine peptide used daily and the investigators report that fish collagen hydrosilate increased the skin moisture by 12 percent, whereas pig collagen hydrosilate increased the skin moisture by 28 percent. Asserin et al. [14] also compared the effect of fish collagen hydrosilates to placebo. They reported that the collagen density increased significantly and collagen fragmentation decreased significantly with the use of 10 g fish collagen hydrosilate daily compared to placebo [14].

Schunck et al. [15] gave 2.5 g porcine bioactive collagen peptide daily to 105 female patients with moderate cellulite. They reported a significant decrease in cellulite, reduced skin waviness and significantly improved dermal collagen density in women with normal weight. The effects were less pronounced in overwieght patients [15].

Genovese et al. [16] investigated the use of oral 50 mL blend of 5 g fish collagen bioactive peptides, hyaluronic acid, borage oil, N-acetylglucose amine and antioxidants on 120 healthy volunteers. They reported that skin elasticity improved significantly with the use of collagen [16].

Collagen Tripeptides

Choi et al. [17] investigated the use of oral 3%, 15 g collagen tripeptide for the treatment of post-laser erythema and skin elasticity in 8 females that have recieved laser therapy. The authors reported that the collegen supplementation led to faster recovery of post-laser erythema and skin hydration starting at the third day of treatment; and increased skin elasticity by the 14th day of treatment [17]. In another study, Choi et al. [17] compared the use of oral 3%, 15 g collagen alone or along with vitamin C supplementation 500 mg dailiy in 24 female and 8 male patients with wrinkles. They concluded that daily collagen peptide supplementation improves skin elasticty and hydration; however, the synchronous intake of vitamin C supplementation does not enhance this effect [18].

Collagen Dipeptides

Inoue et al. [19] investigated the use of oral fish collagen in 85 female patients for the improvement of facial skin moisture, elasticity,

wrinkles and roughness. They compared the use of collagen hydrosilates with low (0.5 mg) and high (10 mg) dipeptide content. The authors concluded that oral collagen hyrdosilate solutions with higher dipeptide content were superior to those with lower dipeptide content in the treatment of decreased skin moisture and elasticity, wrinkles and roughness due to aging [19].

Hexsel et al. [20] researched the efficacy of oral collagen supplementation in improving nail brittleness. Twenty-five patients with brittle nail syndrome received 2.5 g oral daily collagen supplementation for 24 weeks. Bioactive collagen peptides decreased the nail break rate by 42% and increased the nail growth rate by 12%. Eighty percent of the patients were satisfied with the results. Thus, oral collagen supplementation is effective in treating brittle nails [20].

A Shift in Perspective: Marine Collagen Sources

Due the possible adverse effects faced with the use of bovine collagen sources, the resaerchers have shifted to a newer perspective and started investigating the marine sources [6]. Marine collagen peptides have high homology to human collagen, they are safe, stable, highly biocompatable and have high bioavalibilty through the gastrointestinal tract. However, due to the increased hydroxyproline levels in collagen, marine sources have the potential of causing higher oxidative stress. Besides, they can activate innate immune response through the activation of neutrophils and macrophages via the toll-like receptors which leads to NADPH activation and the production of reactive oxygen species [21].

De Luca et al. [21] investigated the use of marine collagen peptides acquired from the fish skin on the skin quality in 41 healthy volunteers. Each participant received marine collagen peptides combined with coenzyme Q, grape skin extract, seleinum and luteolin. Skin properties such as the moisture, elasticity, sebum production, and biological age were assed subjectively; and the ultrasonic markers such as the epidermal/dermal thickness and acoustic density were assesed objectively. The authors concluded that marine collagen peptides improved the skin properties measured by both objective and subjective parameters. Furthermore, the addition of plant derived antioxidants (coenzyme Q, grape skin extract, selenium and luteolin) were beneficial in reducing the oxidative stress. Thus, the combination of marine collagen peptides with the skin targeting anti-oxidants is effective and safe for improving skin properties [21].

Costa et al. [22] investigated the use of marine collagen for improving skin wrinkles in male patients. Forthy-seven male pateints received two tablets of the following content: marine protein (105 mg), vitamin C (27 mg), grape seed extract (13.75 mg), zinc (2 mg), and tomato extract (14.38 mg) every day for 180 consecutive days. As a result of the treatment, the facial erythema and pH decreased significantly, skin hydration increased significantly and the dermal density measured by ultrasound increased significantly. Thus, marine collagen supplement containing biomarine complex, vitamin C, grape seed extract, zinc, and tomato extract was effective in improving skin quality in men [22].

An animal study on hairless mice has previously shown that collagen hydrosilates derived from the type 1 collagen in the fish skin, promoted the recovery of collagen fibers from degraded collagen and enhanced the formation of normal elastic fibers rather than the abnormal elastic fibers which were due to the solar elastosis due the ultraviolet B damage. This effect was caused by the reduction of matrix metalloproteinases which degrade collagen and gelatins. This reduces skin wrinkling and transepidermal water loss; and increases skin elasticty and hydration. Kim et al. [23] investigated the use of collagen hydrosilates derived from the sutchi catfish's skin (Pangasius hypophthalmus), with >15% tripeptide content in the treatment of photoaged skin. Sixty-four female volunteers, ages ranging from 40 to 60 years received 1g low molecular weight collagen hydrosilate daily for 12 weeks. The authors concluded that the skin hydration and elasticity were significantly higher and wrinkling was less pronounced in the treatment group than in the placebo group. Thus, the low molecular weigh collagen peptides obrtained from sutchi catfish can be used as a supplement for improving skin hydration, elasticity and wrinkling [23].

Sangsuwan and Asawanonda [24] conducted a study about the use of oral collagen supplement obtained from the fish scale and skin. Thirty-six post menopausal female patients were randomized into two groups, the first group received 5 g oral collagen hydrosilate derived from fish skin and scale; the second group received placebo. Authors reported that the skin elasticty of the cheeks (representing the sun exposed areas) imporved significantly after using the collagen supplementation for 4 weeks. Furthermore, the effects continued 4 weeks after the supplementation was discontinued [24].

Some other studies regarding the use of marine derived collagen were performed using enzymatic hydrolysis as well. It was shown that commercially available fish type I collagen hydrolysate from amino collagen (Meiji Seika, Tokyo, Japan) improved skin hydration in 25 female Japanese patients after using for 6 weeks. Collagen peptides stabilized orthosilicic acids rejuvenised the skin and caused no side effects, hypersensitiy or systemic symptoms. Marine sponge collagen also rejuvenised the skin via increasing cell proliferation and photoprotection [25]. Other uses of marine organism include the uses in skin regenerative medicine such as wound healing, prevention of biofilm formation and bacterial contamination [26].

Ethics

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Authorship Contributions

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

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The Management of Autoimmune Bullous Skin Disorders in the Era of COVID-19 Pandemic: A Single Center, Retrospective, Cross-sectional Study

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ABSTRACT

Background: Coronavirus disease-2019 (COVID-19), a serious pulmonary illness caused by the highlycontagious novel coronavirus, is a global pandemic. In this retrospective study, we aimed to demonstrate the COVID-19 prevelance and treatment course of the patients with bullous skin disorders.

Materials and Methods: A total of 151 patients with bullous skin disorders who admitted toour department between the dates of October 2019-October 2020 were enrolled in this study. The statistical analysis was performed with the SPSS-21.

Results: One hundred twenty five patients were taking systemic steroid treatments and 113 patients were under the treatment of adjuvant treatment including azathioprine (AZA), mycophenolate mofetil (MMF) and dapsone. Eighteen patients received a minimum of a two-cure rituximab treatment, and 15 patients a minimum of a three-cure intravenous immunoglobulins (IVIG) treatment the year before the start of the pandemic. Only 4 of the 151 patients had a COVID-19 infection history where all of them experienced a mild disease without hospitalization.

Conclusion: As there is no consensus as to the immunosuppressive and biological treatments for autoimmune bullous diseases during the COVID-19 pandemic and we think that the maintenance of a systemic steroid treatment does not increase the incidence rate and the severity of the COVID-19 infection. The immunosuppressive agents including AZA and MMF should be discontinued for the COVID-19 infected patients since no data are showing their beneficial effect for the course of COVID-19 up until now. IVIG can be considered as a therapeutic option for the COVID-19-infected autoimmune bullous disease patients.

Keywords: Azathioprine, Bullous pemphigoid, Bullous skin disorders, Pemphigus vulgaris

Introduction

Coronavirus disease-2019 (COVID-19), is a worldwide pandemic that usually manifests itself as a respiratory tract infection. The most common symptoms are fever, dyspnea, cough, and myalgia. A sore throat, diarrhea, a loss of taste and smell are among the other symptoms [1]. Although most patients develop mild symptoms, pneumonia and a multi-organ failure can also be seen especially in high-risk patients. The studies have shown that the male gender as well as having diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and hypertension increase the risk of severe infections [2]. Bullous diseases are mucocutaneous blistering disorders in which systemic steroids and immunosuppressive drugs are used in the treatment. The most encountered bullous diseases are pemphigus vulgaris, pemphigus foliaceous, bullous

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pemphigoid, mucosal pemphigoid, dermatitis herpetiformis, epidermolysis bullosa acquisita, and linear immunoglobulin A (IgA) dermatosis. There are no clinical data that indicate whether the systemic steroids and immunosuppressive agents are safe during the COVID-19 pandemic. In this study, we aimed to demonstrate the COVID-19 prevalence among bullous patients in our clinic and the treatment process of those patients.

Materials and Method

This study was conducted between October 2019 and October 2020 and one hundred fifty one patients diagnosed with a bullous disease at our bullous diseases outpatient clinic were included. The bullous disease diagnosis was made based on histopathology, direct immunofluorescence and ELISA results. The demographical and clinical features of all patients were noted. The treatment courses and prevalence of COVID-19 infections were retrieved from the medical records. The information of the patients who did not visit the clinic in the last 6 months was obtained via telephone calls. The patients with positive polymerase chain reaction (PCR) tests or computerized tomographies suggesting COVID-19 infection were regarded as having a COVID-19 infection.

Statistical Analysis

The statistical analysis was performed with SPSS-21. The descriptive statistic method and frequency analysis were used for the data distribution.

Ethical Statement

Before commencement of the study, the approval was taken from Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (approval number: 151638, date: 17.11.2020).

Results

The demographical and clinical data of the patients who participated in the study are listed in Table 1. Of the patients 122 (80.8%) were diagnosed with pemphigus vulgaris, 13 (8.6%) with bullous pemphigoid, 4 (2.6%) with pemphigus foliaceus, 4 (2.6%) with dermatitis herpetiformis, 3 (2%) with mucous membrane pemphigoid, 1 (0.7%) with pemphigus vegetans, 1 (0.7%) with linear IgA bullous dermatosis, 1 (0.7%) with epidermolysis bullosa acquisita, 1 (0.7%) with subcorneal pustular dermatosis, and 1 (0.7%) with paraneoplastic pemphigus. The mean age of the patients was 53, with 84 (55.6%) of them being females and the remaining 67 (44.4%) males. The average duration of the bullous disease was 5.2±3.9 years. The number of patients visiting the clinic in the last 6 months was 94 (62.3%) while that of those not visiting 67 (37.7%). Of the 151 patients, 125 were taking systemic steroid treatments. Among the patients taking systemic steroid treatments, 43 were receiving methylprednisolone ≥16 mg/day. As for the treatment processes of the patients; of the 151 patients 26 did not receive any systemic steroid treatment, 104 patients who were on systemic steroid treatments were given a lower treatment dosage while 12 patients continued to receive the same dosage, 8 patients either started to receive steroid treatments or their treatment dosage was increased upon the occurrence of an active illness and one patient uncontrollably terminated the steroid treatment on his own. Moreover, of the 151 patients, 38 did not receive any adjuvant treatment, 93 were already receiving an adjuvant treatment and kept receiving it at the same dosage, and 10 terminated the treatment on their own. The adjuvant treatment dosage was reduced or discontinued for 9 patients, and one patient started to receive an adjuvant treatment due to active illness. Eighteen of the patients received a minimum of a two-cure rituximab treatment during last year, and another 15 patients a minimum of a three-cure intravenous immunoglobulins (IVIG) treatment in the last year. Of the 122 patients diagnosed with pemphigus vulgaris, 15 patients did not receive any systemic steroid treatment, 90 patients were given a treatment with a lower systemic

Table 1. Clinical characteristics of patients

Characteristics	No (%)
Number of patients	151
Average duration of disease, years, mean (min-max)	5.2 (0.5-19.0)
Age of patients, years, mean (min-max)	53 (21.0-87.0)
Sex	
Female	84 (55.6)
Male	67 (44.4)
Subgroup of patients	
Pemphigus vulgaris	122 (80.8)
Pemphigus foliaceus	4 (2.6)
Pemphigus vejetans	1 (0.7)
Bullous pemphigoid	13 (8.6)
Dermatitis herpetiformis	4 (2.6)
Lineer IgA bullous dermatosis	1 (0.7)
Mucosal membrane pemphigoid	3 (2)
Subcorneal pustuler dermatosis	1 (0.7)
Paraneoplastic pemphigus	1 (0.7)
Epidermolysis bullosa	1 (0.7)
Patients having COVID-19 infection	4 (0.02)
Patients receiving steroid treatment	125 (82.7)
Patients receiving adjuvant treatment	113 (74.8)
Patients having history of rituximab treatment over the last year	18 (11.9)
Patients having history of IVIG treatment over the last year	15 (0.1)

min-max: Minimum-maximum, IgA: Immunoglobulin A, COVID-19: Coronavirus disease-2019, IVIG: Intravenous immunoglobulins

steroid dosage and 10 continued to receive the same dosage while 6 patients were given a higher dosage, and finally, one patient terminated the treatment on his own. Only 4 of the 151 patients had a COVID-19 infection history where all of them experienced a mild disease with flu-like symptoms. The ages of COVID-19 infected patients were 38, 45, 49 and 52 respectively. All of the patients had pemphigus vulgaris and were taking methylprednisolone treatment greater than 16 mg/day when they were diagnosed with COVID-19. Three of those patients were taking azathioprine (AZA) 150 mg/day which was discontinued during COVID-19. Two of the patients had a history of 2-cure rituximab treatment in the last year and the other one received a 3-cure IVIG treatment in the last year. None of the patients required any hospitalization due to COVID-19.

Discussion

The COVID-19 infection has emerged as a pandemic infection by the World Health Organization in March 2020 and the number of patients infected with COVID-19 is still on the increase worldwide. The emergence of the COVID-19 infection affected the management of several diseases, also autoimmune bullous skin diseases have been affected during this pandemic. Autoimmune bullous disorders are potentially life-threatening disorders that require long-term immunosuppressive and immunomodulatory therapies. The immunosuppressive treatments used for autoimmune bullous diseases including systemic steroids and steroid-sparing agents [rituximab, AZA, mycophenolate mofetil (MMF)] may potentially increase the risk of viral infections [3,4,5,6,7,8]. However, there is no consensus as to the safety of these treatments during the COVID-19 pandemic for the autoimmune bullous disease patients who are already receiving immunosuppressive and/or biologic treatments or who require a new treatment to control their active diseases. Among the autoimmune bullous diseases, the treatment of pemphigus vulgaris is more challenging since the need for an immunosuppressive treatment is inevitable.

Systemic steroids are the first line treatment for many autoimmune bullous diseases, especially for pemphigus vulgaris [9]. It is known that systemic steroids increase the risk of infection in a dose-dependent manner. However, the current studies showed that the anti-inflammatory effects of systemic steroids may have a role in suppressing the cytokine storm in the COVID-19 infection via decreasing the pro-inflammatory cytokines [10,11,12,13]. These studies support that COVID-19 induced lung inflammation may benefit from systemic steroid treatment. As for autoimmune bullous disease treatment, Kasperkiewicz et al. [14] recommended that immunomodulatory therapy including systemic steroids should be continued if necessary. The patients should be informed about social distancing and hygiene rules. They also recommend that a prednisolone dosage of ≤10 mg/day can be continued for the autoimmune bullous patients infected with COVID-19. For the dosages of over 10 mg/day, they suggest that the dose be tapered following risk evaluations both for COVID-19 and autoimmune bullous diseases [14]. An abrupt cessation of systemic steroid treatments should be avoided due to the risk of adrenal insufficiency and the recurrence of an autoimmune bullous disease. In our clinic, one hundred twenty-five patients out of 151 autoimmune bullous disease patients were receiving systemic steroid treatments during the COVID-19 pandemic. The dose of the systemic steroid therapy was tapered for 104 patients properly. The dosage remained the same for twelve patients receiving less than 8 mg/day methylprednisolone. Three patients with the previous pemphigus vulgaris diagnosis were started a methylprednisolone dosage of over 16 mg/day due to the activation of their diseases. Three patients were diagnosed with pemphigus vulgaris during the pandemic and they started to receive a methylprednisolone dosage of over 24 mg/day. Two patients, one with a previous linear IgA dermatosis and one with an epidermolysis bullosa acquisita started to receive ≥16 mg/day methylprednisolone due to the widespread activation of the disease.

Four patients who had a previous history of pemphigus vulgaris experienced the COVID-19 infection and diagnosis was made either with a PCR test or a computerized tomography while they were receiving a methylprednisolone dosage of ≥16 mg/day. All experienced mild diseases with flu-like symptoms and the steroid therapy dose were tapered during and after the COVID-19 infection period without an abrupt cessation.

AZA and MMF are the first choices of a steroid-sparing treatment for the pemphigus vulgaris patients [9]. Although, there are limited data for the safety of AZA and MMF during the COVID-19 pandemic, Kasperkiewicz et al. [14] recommended the maintenance of these two agents unless patients were infected with COVID-19. The study performed by Russel et al. [11] showed that MMF may prove harmful during the COVID-19 infection. The study by Hormati et al. [15] showed that the AZA treatment did not decrease the severity of the COVID-19 infection. Similarly, Shakshouk et al. [16] suggested that the intake of these drugs be ceased in COVID-19-infected patients. The guidelines from the European Academy of Dermatology and Venereology states that AZA and MMF may increase the severity of the COVID-19 infection, and therefore the treatment with these two agents may be discontinued in patients with the diagnosis of COVID-19 [17]. In our clinic, we also discontinued the AZA therapy for the COVID-19-infected patients. Eighty-four patients who were already receiving adjuvant treatment with AZA or MMF remained at the same dosage.

Rituximab is a chimeric monoclonal IgG1 antibody targeting CD20 receptors on the mature B-cells. It is especially used for the recalcitrant pemphigus vulgaris cases when other treatments fail to control the disease and used for the patients who can not use systemic steroids due to their side effects or comorbidities [9]. Rituximab is associated with the activation of the hepatitis B virus, tuberculosis, and pneumocystis pneumonia [18]. It causes depletion in the B-cells in which the regeneration of B-cell immunity may take months. Therefore, Shakshouk et al. [16] pointed out that the generation of the COVID-19 specific plasma cells can be affected for the patients who were treated with rituximab especially in the last year. They recommended postponing the rituximab treatment as long as possible during the COVID-19 pandemic [16]. On the other hand, Schultz et al. [19] put forward the hypothesis that rituximab may decrease the severity of the COVID-19 infection via decreasing antiviral IgG which was shown to induce a lung injury. However, in an expert study, Kasperkiewicz et al. [14] recommended that the rituximab treatment be postponed during COVID-19 due to the risk of COVID-19-specific plasma cell suppression following rituximab. In our clinic, eighteen patients diagnosed with pemphigus vulgaris have received at least a two-cure rituximab treatment in the last year. Two of those patients were diagnosed with the COVID-19 infection after they received rituximab treatment. They had only mild symptoms, were treated with 5-day favipiravir, and did not require hospitalization [20].

Intravenous immunoglobulin (IVIG) is a biological agent that can be used for autoimmune bullous disease treatments. It is especially used for pemphigus vulgaris patients to maintain a long-term clinical remission [21]. Current studies showed that the IVIG treatment may have a place in the treatment of the COVID-19 infection via suppressing the cytokine storm [22,23,24]. Therefore, IVIG can be an option for patients with pemphigus vulgaris who necessitate treatment during the COVID-19 infection. The risk of thromboembolism should be kept in mind, non-etheless, since both IVIG and COVID-19 are associated with an increased risk of thromboembolism [25,26,27]. Fifteen patients received a minimum of a three-cure IVIG treatment in the last year in our clinic. One of the patients with pemphigus vulgaris had been treated with 3-cure IVIG treatment last year before having the COVID-19 infection. He had mild symptoms which improved following 5-day favipiravir treatment.

Dapsone, also known as diaminodiphenyl sulfone, is a drug that is widely used in autoimmune bullous diseases especially for bullous pemphigoid and mucosal membrane pemphigoid [28]. The current studies hypothesized that dapsone may have a role in the treatment of COVID-19 infection-induced cytokine storm via inhibiting neutrophil chemotaxis and signaling of certain interleukins including IL-1, IL-6, IL-8 [29,30]. Dapsone is not considered to increase the risk of infections, thus it may be continued or started in appropriate patients during the COVID-19 pandemic [14,15,16,17]. In our clinic, six patients with bullous pemphigoid and three patients with mucosal membrane pemphigoid were under treatment with dapsone 100 mg/day. One patient with bullous pemphigoid discontinued therapy on his own. None of the patients had documented COVID-19 infection.

Study Limitation

The limited sample size of COVID-19 infected patients are the main limitation of this study.

Conclusion

There is no consensus as to the immunosuppressive and biological treatments for autoimmune bullous diseases during the COVID-19 pandemic. Based on the results of our study, we think that the maintenance of a systemic steroid treatment does not increase the incidence rate and the severity of the COVID-19 infection. However, it should be noted that the number of the COVID-19 cases was limited. Although we did not observe any increment in the severity of the COVID-19 infection for patients who received the rituximab treatment in the last 1 year, we still recommend the rituximab treatment only for cases in which the benefit is greater than the risk of the COVID-19 infection. If possible, the treatment with AZA and MMF should be discontinued for the COVID-19 infected patients since the data showing their reliability during COVID-19 infection are limited. On the other hand, IVIG can be considered as a therapeutic option for the COVID-19-infected autoimmune bullous disease patients.

Ethics

Ethics Committee Approval: Before commencement of the study, the approval was taken from Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (approval number: 151638, date: 17.11.2020).

Informed Consent: Retrospective study.

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Authorship Contributions

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

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ORIGINAL ARTICLE

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Q-switched 1064 nm Nd:YAG Laser Therapy in Onychomycosis

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ABSTRACT

Background: Recently, laser therapy in onychomycosis has become an alternative treatment because it is a minimally invasive procedure and positive results can be obtained in a few sessions. Our aim in our study was to evaluate the results of Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG) laser in the treatment of patients followed up with the diagnosis of onychomycosis.

Materials and Methods: Twenty-six patients with a diagnosis of onychomycosis were included in the study. Q-switched Nd:YAG laser treatment was applied for a total of three sessions every two weeks. The patients were re-evaluated one month after the last session.

Results: The most common type of onychomycosis was the distal lateral (73.1%) type. The average of the onychomycosis score index values, which were measured to evaluate the clinical response, decreased significantly after the treatment (p=0.001).

Conclusion: Q-Switched Nd:YAG (1064 nm) laser is a safe method in onychomycosis patients. It can be recommended especially in patients who do not want to use oral antifungals or have contraindications. Longer sessions may be required for effectiveness.

Keywords: Q-switched Nd:YAG laser, Onychomycosis, Nail

Introduction

Onychomycosis is a fungal infection of the nail caused by dermatophytes, non-dermatophytic molds or candida species. Although it is seen in 10% of the population in general, it is observed in more than 50% of those over the age of 70 [1]. Clinical findings, microscopic examination and mycological culture are used in diagnosis. When onychomycosis is not treated, a non-cosmetic appearance, pain and secondary bacterial infections of the nails may occur. In treatment, chemical debridement, topical antifungals and systemic antifungals are used alone or in combination [2]. In recent years, laser therapy has become an alternative treatment for onychomycosis. Most laser systems use heat effects or work with the breakdown of fungal structures and the production of toxic reactive oxygen species, thereby disrupting the mitochondrial membrane potential [3].

In the literature, there are onychomycosis treatment results with various laser types [4,5,6]. Carbon dioxide (CO_2) laser, kills fungi by directly disrupting the tissues [7]. On the other hand, the CO_2 laser is no longer used due to its pain and trauma side effects. In a study, it was shown that a long-pulse neodymium-doped yttrium aluminum garnet (Nd:YAG) laser with a wavelength of 1064 nm could cure 52% of 154 infected nails in 33 onychomycosis patients [8]. Another approach is the idea that fungal hyphae can be destroyed with extremely short pulses of a Q-switched laser [9].

However, studies with more case series are needed to select the standard treatment plan and the best dose regimen. Our aim in

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our study is to evaluate the results of Q-switched Nd:YAG laser in the treatment of onychomycosis and compare them with the data in the literature.

Materials and Method

Twenty-six patients diagnosed with onychomycosis after clinical and microscopic examination were included in the study. Demographic characteristics, nail fungus type, treatment history and onychomycosis score index (OSI) values of the cases were recorded. Informed consent form consent was obtained from the patients. Pregnant women, cases with subungual hematoma or nevoid formation in the nail, and participants with diseases affecting the nail plate (such as lichen planus or atopic dermatitis) were not included in the study. Clinical and mycological evaluations were performed before the treatment and one month after the last session of the laser treatment (Figure 1).

Determining Onychomycosis Severity

The nail area held (1-10=1, 11-25%=2%, 26-50=3, 51-75%=4%, 76-100=5), the proximity of the disease to the matrix (matrix involvement=5), whether it is >2 mm dermatophytoma or subungual hyperkeratosis (absent=0, present=10) are evaluated and the obtained scores are collected [10].

Laser Therapy

Q-switched 1064 nm Nd:YAG Laser (Lutronic, Spectra) was applied to the patients for three sessions with an interval of two weeks. The parameters used were determined as, 8 J/cm^2, spot size 4 mm and frequency 5-Hz. Laser scanning was performed on the nail plate, proximal and lateral nail folds and hyponychium. No anesthetic was applied before the laser. The endpoint during laser application was that the patient felt pain. No side effects were observed during or after laser application in the patients. Patients who completed three sessions of treatment were re-evaluated one month after the last session. Patients were instructed not to use any other antifungal therapy during this treatment. No side effects were detected in the patients who were called for control one month after the treatment.

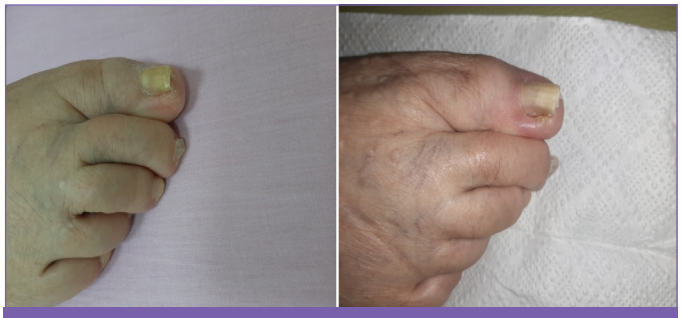

Figure 1. Pre-treatment and post-treatment images

Before starting the study, approval was obtained from the Malatya Clinical Research Ethics Committee (decision no: 2019/13, date: 06.02.2019).

Statistical Analysis

All data were expressed as mean ± standard deviation and statistically analyzed with SPSS 19.0 (SPSS Inc. USA). The clinical profile of the patients was analyzed with the chi-square test for qualitative variables. Student's t-test was used to compare quantitative variables. A probability level of 5% was considered statistically significant ($p<0.05$).

Results

Demographic and clinical data are shown in Table 1. A total of 26 patients were included in the study. The mean age of the patients was 50.6±12 years. Sixteen (61.5%) of the patients were female and 10 (38.5%) were male. Three patients had hand involvement, one patient had both hands and feet, and all the remaining patients had foot involvement. The most common type of onychomycosis was distal lateral (73.1%), and the second most common type was total dystrophic (26.9%).

After treatment, culture growth was detected in all patients except three patients. The most abundant fungal type in culture was dermatophytes. All of the dermatophytes were trichophyton species. Candida grew in pretreatment culture in only one patient.

All of the patients were in the moderate and severe groups according to the OSI scoring. While 24 patients were evaluated as moderate according to the OSI scoring, two patients were in the severe group. After treatment, the OSI values of two patients decreased from severe to moderate. After treatment, nine patients continued to be in the severe group according to the OSI assessment, but their scores decreased. A statistically significant decrease was found in the mean of OSI values measured before and after treatment (p=0.001) (Table 2).

Table 1. Demographic and clinical data

		Number (n)	%
	Female	16	61.5
	Male	10	38.5
Onychomycosis type	Distal lateral	19	73.1
	Total dystrophic	7	26.9

Table 2. Onychomycosis severity index scores

	Mean ± SD	Median (min-max)	p-value
Before treatment	25.7±7.0	26 (9-35)	0.001
After treatment	22.2±6.9	22 (9-35)	

min-max: Minimum-maximum, SD: Standard deviation

Discussion

Onychomycosis is a difficult disease to treat. Because the infection is embedded in the nail. Topical antifungal agents hardly penetrate the nail plate and do not provide local therapeutic effect. Systemic oral antifungal agents are not suitable for some patients with abnormal liver function [2,11,12]. Laser therapy appears to be a promising new treatment regimen with its low side-effect profile and easy applicability.

The incidence of onychomycosis increases with age and is most common in the age range of 40-60 years [13]. The age of the patients included in our study was 50.6±12 years, consistent with the literature. The majority of the patients were women (61.5%). In our study, dermatophytes were detected most frequently in fungal culture. Elmorsy et al. [14], in their study comparing the efficacy of Q-switched Nd:YAG laser and long pulse Nd:YAG laser in the treatment of onychomycosis, found candida as the most common agent.

Although a significant decrease was detected in OSI scores after laser treatment in our study, culture positivity was detected in all patients, except three, as a result of the culture performed one month after the treatment. It was thought that this may be related to the early detection of the culture and the low specificity of the fungus culture [15]. The low negative rates in fungal culture in the early period may be due to the fact that laser energy does not kill all fungal colonies in the infected nail and limits their ability to proliferate and survive [16]. In their study, Elmorsy et al. [14] reported that in 10 onychomycosis patients who applied five sessions of laser treatment with 1064 nm Q-switched Nd:YAG laser once a month, they found the rate of mycological clearance as 30% immediately after the last laser session and 50% at the 6-month follow-up [n]. Kim et al. [17] found clinical improvement with Nd:YAG laser treatment in onychomycosis patients as 47.6% and 57.1% at 12 and 24 weeks, respectively. In a study comparing the number of 1064 nm Nd-YAG laser applications to onychomycosis patients, the efficacy was found to be higher in the group with more applications and in patients with milder disease severity [18].

In the literature, it has been reported that the mycological and clinical efficacy of combining topical drugs with laser therapy is significantly higher than laser therapy alone [19]. In a clinical study in which the efficacy of Q-Switched Nd:YAG (1064 nm) laser in the treatment of onychomycosis was compared with oral itraconazole, one group of patients received weekly laser treatment and the other group received itracanazole treatment for 3 months. It was found that Q-switched Nd:YAG laser (1064 nm) application in onychomycosis patients was more effective than itraconazole in 3-month treatment, and both methods were effective in one-year follow-up [20].

The exact mechanism of laser therapy in onychomycosis is still under investigation. Various laser and light sources used in the treatment of onychomycosis have the potential to destroy dermatophytes by various methods, including photothermal and photochemical effects. Q-switched Nd-YAG lasers exert both selective photothermal and photomechanical effects on the fungus. It is thought that denaturing one or more molecules in the pathogen in this way can inactivate the fungi [21]. Another possible mechanism is to stimulate the immune system response to attack the organism. All of these hypotheses describe how the host cells surrounding the infected tissue are protected from this attack with little or no damage [22].

In our study, the patients did not have any complaints other than mild pain during the procedure, and no side effects were observed during and after the procedure. Similar side effects have been reported in the literature, most commonly mild, tolerable pain. In a study comparing the effectiveness of long-pulsed Nd:YAG (1064 nm) laser and Q-Switched Nd:YAG (1064 nm) laser in onychomycosis, it was found that Q-Switched Nd:YAG laser has fewer side effects than long pulse Nd:YAG laser in terms of pain intensity during the procedure [14].

Study Limitations

The low number of participants and the short follow-up period are the limitations of our study.

Conclusion

We believe that Q Switched Nd:YAG (1064 nm) laser is a safe treatment method in patients with onychomycosis. It can be recommended especially in patients who do not want to use oral antifungals or who have contraindications. However, we think that longer sessions and longer follow-up periods may be needed for effectiveness.

Ethics

Ethics Committee Approval: Before starting the study, approval was obtained from the Malatya Clinical Research Ethics Committee (decision no: 2019/13, date: 06.02.2019).

Informed Consent: Informed consent form consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Retrospective Evaluation of Patients Diagnosed with Hidradenitis Suppurativa According to Hurley Stages

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease with a prevalence ranging from less than 1% to 4% in the population. The disease affects the apocrine glands and is poorly understood. HS lesions are typically found in intertriginous areas. Genetic and environmental factors, such as high body mass index (BMI) and smoking, are believed to contribute to lesion development. The lesions are classified into three Hurley stages, and treatment varies according to the stage of the disease.

Materials and Methods: This study aimed to evaluate the factors that contribute to the development of HS and the treatments administered based on the Hurley stages. The purpose was to assess the factors associated with an increased risk of HS and examine the treatment approaches specific to each Hurley stage. Between the years 2018 and 2022, a retrospective evaluation was conducted on a total of 31 patients who were followed in our HS outpatient clinic at the Department of Dermatology and Venereology, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine. The evaluation focused on gender distribution, smoking rates, BMI, and the treatments received, categorized according to the Hurley stages.

Results: When we retrospectively examined the data of 31 patients, 21 were male, and 10 were female. The mean age of male patients was 36, while the mean age of female patients was 30.9. Among the patients, 19% were classified as Hurley stage 1, 29% as Hurley stage 2, and 51% as Hurley stage 3. The smoking rates were 50% in Hurley stage 1, 55% in Hurley stage 2, and 62% in Hurley stage 3. When comparing BMI, the mean BMI was 26.16 kg/m^2 in Hurley stage 1, 27.66 kg/m^2 in Hurley stage 2, and 31.25 kg/m^2 in Hurley stage 3. In terms of treatment, 66% of Hurley stage 1 patients received systemic antibiotic treatment, while all patients in Hurley stage 2 and 3 received systemic antibiotic therapy. None of the Hurley stage 1 patients used adalimumab, while the rate of adalimumab use was 33% in Hurley stage 2 and 42% in Hurley stage 3.

Conclusion: When examining the patients who presented to our clinic, it was observed that HS disease is more prevalent among men, smokers, and individuals with a higher BMI. However, further studies with larger patient cohorts are still necessary to validate these findings.

Keywords: Hidradenitis suppurativa, Hurley stage, Smoking, Body mass index

Introduction

Hidradenitis suppurativa (HS) is a chronic and recurrent inflammatory skin disease with a prevalence ranging from less than 1% to 4% in the population [1,2]. Numerous studies have reported a higher prevalence of HS in women compared to men [3,4,5]. It is predominantly observed in individuals in their second and third decades of life [3,4,5]. HS affects the apocrine glands, and its etiology is believed to involve follicular occlusion, although it remains poorly understood [6]. The disease commonly manifests in intertriginous areas such as the axilla, inguinal, inframammary, perianal, and perineal regions, and less frequently in the scrotum, vulva, pubic area, and abdomen [7]. Lesions associated with HS may

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cause pain, discharge, and malodor, which can have significant psychosocial impacts on patients [8]. Typical HS lesions include nodules, abscesses, fistulas, skin tunnels, comedones, and scars [8,9]. HS lesions are classified into three Hurley stages [10,11]. Hurley stage 1 is characterized by the development of abscesses without scar or tunnel formation, while Hurley stage 2 involves abscesses frequently accompanied by tunnels and scars. Hurley stage 3 is characterized by diffuse involvement [10,11]. Genetic factors, as well as physical factors such as friction and pressure, are believed to contribute to lesion development [12,13,14,15]. Research has shown that HS is more prevalent in individuals with a high body mass index (BMI) and in smokers [16,17]. The management and treatment of HS patients vary according to the Hurley stage.

Materials and Methods

This retrospective study included patients who were diagnosed with HS and presented to the HS follow-up Clinic at the Department of Dermatology and Venereology, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine between January 1, 2018, and June 15, 2022.

Statistical Analysis

The registered data of the patients in the HS clinic were retrospectively analyzed. Patient characteristics such as age, gender, Hurley stages, smoking status corresponding to these stages, treatments received, and BMI were assessed retrospectively.

The approval of Istanbul Univeristy-Cerrahpasa, Cerrahpasa Faculty of Medicine Ethics Committee was taken before initiating the study (number: E-83045809-604.01.01-649573, date: 21.03.2023).

Results

In this study, 31 patients diagnosed with HS whose data were accessible followed at HS clinic between 2018 and 2022 were included. Of the total 31 patients included in the study, 21 were male (67.74%) and 10 were female (32.25%). The mean age of male patients included in the study was 36, while the mean age of female patients was 30.9. At the time of diagnosis, 19.35% of all patients included in the study were Hurley stage 1, 29.03% were Hurley stage 2, and 51.61% were Hurley stage 3. The patients we followed in our HS outpatient clinic were predominantly hurley stage 3. Of the Hurley stage 1 patients, 50% had a history of smoking, while 55.55% of Hurley stage 2 patients and 62.5% of Hurley stage 3 patients had a smoking history. The mean BMI was 26.16 kg/m^2 for Hurley stage 1 patients, 27.66 kg/m^2 for Hurley stage 2 patients, and 31.25 kg/m^2 for hurley stage 3 patients. The smoking rates and BMI of the patients included in the study according to hurley stages are shown in Table 1. While 66% of Hurley stage 1 patients had a history of using systemic antibiotics, all Hurley stage 2 and 3 patients had a history of systemic antibiotic use. None of the Hurley stage 1 patients had a history of using adalimumab, whereas the rate of adalimumab use was 33.33% in Hurley stage 2 and 43.75% in Hurley stage 3. The treatments received by the patients are shown in Table 2.

Discussion

According to research and studies, factors contributing to the pathogenesis of HS and the reasons for its increased incidence have been identified. A study conducted in the United Kingdom, which included undiagnosed patients, reported an incidence rate of 0.77 [18]. Studies conducted in North America and Europe have shown that HS is more common in women [19,20,21]. In a study conducted in France, it was found that the incidence of HS disease in women was approximately 3.6 times higher than in men [22]. However, in our clinic, we observed a higher incidence in men than in women among the patients who sought medical care. Similarly, another study conducted in Korea found a higher incidence rate of HS in men [23]. The difference in HS incidence rates between genders among European and Asian countries is associated with smoking habits [24]. In our study, the number of male smokers was higher than that of female smokers (55.5% male, 44.5% female).

Studies have observed a positive correlation between smoking and the development of HS. Patients with HS were found to smoke or have a smoking history at the time of diagnosis [25]. A retrospective study conducted in the United States found a higher incidence rate of HS in smokers compared to non-smokers [26]. Nicotine and other tobacco components have been identified as potential contributing factors to follicular occlusion, neutrophil chemotaxis, TNF-alpha production by keratinocytes, and stimulatory effects on Th17 cells [27,28]. In our study, the number of smokers and non-smokers was equal in Hurley stage 1, but the ratio of smokers to non-smokers was higher in Hurley stages 2 and 3. Furthermore, some studies have shown that a smoking history increases disease severity [29,30]. A multicenter study conducted in Turkey and published in 2021 revealed that the incidence rate in men is higher than in women and that it leads to more severe disease in smokers [31]. In

Table 1. Smoking rates and body mass index of the patients

Hurley stage	Smokers	Body mass index
1	50%	26.16 kg/m^2
2	55.55%	27.66 kg/m^2
3	62.5%	31.25 kg/m^2

Table 2. Treatments administered

Hurley stage	Systemic antibiotic	Adalimumab
1	66%	-
2	100%	33.33%
3	100%	43.75%

our study, the highest proportion of heavy smokers was observed in Hurley stage 3, and we observed that smoking increases disease severity.

The relationship between HS and BMI has been investigated in numerous studies. Although the results are conflicting, many studies have found a positive correlation between HS and BMI [32]. Our study also yielded similar results. The average BMI of Hurley stage 1 patients was 26.16 kg/m^2, stage 2 patients had 27.66 kg/m^2, and stage 3 patients had 31.25 kg/m^2. BMI was found to be above the normal range in all stages, and the average BMI increased with higher stages. Our study also supports the positive correlation between HS and BMI. However, it is important to note that both factors are influenced by many other factors, and the causes of HS are still not fully understood.

When the data of the patients followed in our hospital's HS clinic were examined according to Hurley stages and the treatments administered, it was observed that 66% of Hurley stage 1 patients received systemic antibiotic treatment, while all patients in Hurley stages 2 and 3 were treated with systemic antibiotics. In a study of 154 patients who did not respond to oral antibiotic therapy, the efficacy of adalimumab treatment was evaluated. The study included patients with moderate and severe HS. The results showed that patients with high BMI had more severe HS symptoms, and adalimumab treatment resulted in better outcomes for these patients [33].

More studies with larger sample sizes are needed to obtain clearer data on HS.

Study Limitations

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

Conclusion

It is important to conduct a thorough physical examination and gather a detailed medical history when patients with a diagnosis of HS seek care at the outpatient clinic. HS is a disease that has a higher prevalence in individuals who are obese and smoke. Our study yielded similar results, however, further research with a larger sample size is necessary to enhance our understanding of the epidemiological characteristics of patients and to establish appropriate treatment strategies.

Ethics

Ethics Committee Approval: The approval of Istanbul Univeristy-Cerrahpasa, Cerrahpasa Faculty of Medicine Ethics Committee was taken before initiating the study (number: E-83045809-604.01.01-649573, date: 21.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Z.A.F., B.E., Design: B.E., Data Collection or Processing: Ö.S., B.R., Analysis or Interpretation: Z.A.F., B.E., Literature Search: Z.A.F., Ö.S., Writing: Ö.S., B.R.

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CASE REPORT

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Telangiectasia Macularis Eruptiva Perstans: a Case Report and Review Literature

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ABSTRACT

Telangiectasia macularis eruptiva perstans (TMEP) is a rare variant of cutaneous mastocytosis with adults predominantly. It is characterized by erythematous or yellow-brown macules with telangiectasias on the trunk and upper limbs. Diagnosis is based on the appearance of skin lesions and histopathological findings. Dermoscopy is a useful diagnostic tool, as it can show a characteristic reticular pattern. We will report a TMEP case, focusing on clinical findings, dermoscopy, histopathology, and immunohistochemistry examination.

Keywords: Telangiectasia macularis eruptiva perstans, Dermoscopy, Histopathology, Immunohistochemistry

Introduction

Mastocytosis is a group of diseases characterized by abnormal proliferation and accumulation of mast cells within various organs [1]. These cells release histamine and other inflammatory mediators, which can result in pruritus, flushing, nausea, vomiting, abdominal pain, diarrhea, vascular instability, and headache [1,2]. Mastocytosis can be classified as either cutaneous mastocytosis (CM) or systemic mastocytosis, the latter of which can affect the bone marrow, liver, spleen, lymph nodes, and digestive tract [1,2,3,4].

CM is characterized by the proliferation and accumulation of mast cells in the skin [5,6,7,8]. There are three main types: maculopapular cutaneous mastocytosis (MPCM), diffuse CM, and solitary mastocytoma [1,7]. Maculopapular CM is further divided into papular/plaque variants, urticaria pigmentosa (UP), and telangiectasia macularis eruptiva perstans (TMEP) [4]. The diagnosis of CM is confirmed by dermal infiltration of mast cells, visualized with hematoxylin and eosin staining, or by using special stains such as Giemsa, Toluidin blue, or Astra blue [1,3,4].

TMEP is a rare variant of skin mastocytosis, occurring in <1% of patients. It most commonly occurs in adults, although some cases have been reported in children [6,9]. Diagnosis of TMEP is based on clinical findings and histological examination, with the final diagnosis by immunohistochemistry with tryptase and c-kit [7]. Recently, dermoscopy was reported as diagnostic equipment [3] because it reveals a characteristic reticular pattern [4,7,9]. Here, we describe a case of TMEP focusing on clinical, dermoscopic, histopathological, and immunohistochemical findings.

Case Report

A 51-year-old man has been experiencing an erythematous skin rash on his chest, back, and upper limbs for 11 years. The lesions typically improve within a few months, but leave hyperchromic lesions. He reports no itchiness associated with the rash. He denies experiencing fever, chest pain, abdominal pain, weight loss, diarrhea, syncope, bone pain, joint pain, or oral ulcers. He has been treated with anti-allergic and antihistamine tablets, as well as corticosteroid cream,

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with no improvement. He has no personal history of allergies, nor are there any allergies reported in his family. He has a history of hypertension and has been on amlodipine for the past three years. The physical examination revealed no abnormalities.

Dermatological status on the chest, back, and upper limbs showed erythematous-brownish macules with size 0.5 to 3 cm, confluent residual hyperchromic macules, and telangiectasis (Figures 1, 2, 3). Darier's sign is negative, and dermoscopy reveals mild erythema, thin tortuous linear vessels, and a delicate pigment network on a yellow-brown background (Figure 4). There was no abnormality on a blood, renal, or liver function test. Histopathology revealed edema in the superficial dermis with inflammatory cells containing lymphocyte and mast cells in the blood vessel's perivascular, periadnexal, and telangiectasis (Figures 5, 6). Giemsa stain showed mast cells in perivascular and periadnexal (Figure 7), highlighted on CD117 immunohistochemical stain (Figures 8, 9).

The patient was diagnosed with TMEP and received treatment with cetirizine 10 mg once daily and ketotifen 1 mg twice daily. Additionally, the patient was advised to avoid histamine-releasing agents such as alcohol, anticholinergic drugs, aspirin, non-steroidal anti-inflammatory drugs, heat, friction, and opioids. Although the patient showed improvement with medication, further evaluation is needed to determine the possibility of systemic involvement. Written informed consent was obtained from the patient.

Discussion

The skin manifestation in TMEP is non-pruritic and tends to be confluent and persistent. Darier's sign is usually negative or weakly positive because of the lesion's lower density of mast cells [6,10]. The mechanism of telangiectasia and erythematous lesions in TMEP is a local release of mediators and angiogenic factors from activated mast cells, which cause permanent vasodilation [4]. The molecular pathogenesis of TMEP remains unclear; several studies have reported

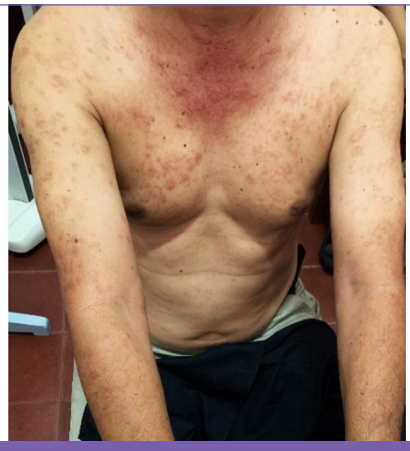

Figure 1. Dermatological status on the chest and upper limb showed erythematous-brownish macules

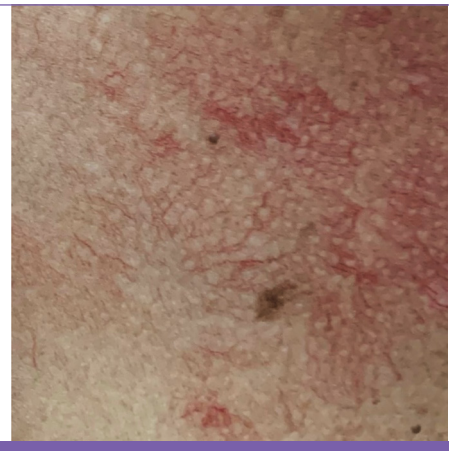

Figure 3. A close-up view of a skin lesion on the chest showed multiple telangiectases

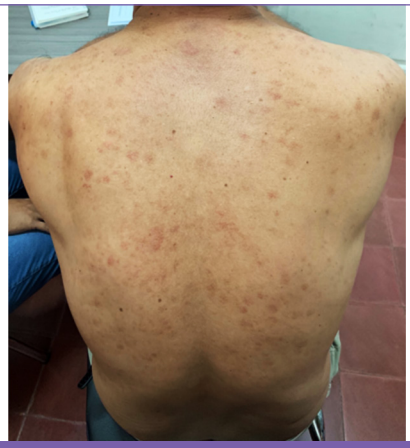

Figure 2. Dermatological status on the back showed erythematous-brownish macules

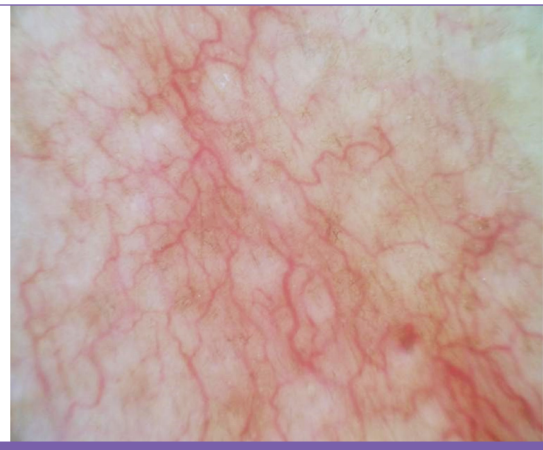

Figure 4. Dermoscopy reveals mild erythema, thin tortuous linear vessels, and a delicate pigment network on a yellow-brown background

point mutations in the *KIT* gene [5,10]. KIT is a type III tyrosinase kinase expressed on mast cells and melanocytes and is a major growth factor of mast cells. A cohort study of 34 TMEP patients detected that 12 patients (35.3%) show the KIT mutations at codon 816 [10].

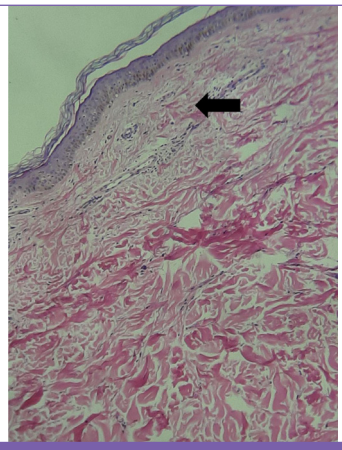

Figure 5. The histopathologic finding with hematoxylin-eosin staining (magnification 100x) revealed edema in the superficial dermis with inflammatory cells containing lymphocyte and mast cells in the perivascular, periadnexal, and telangiectatic vein

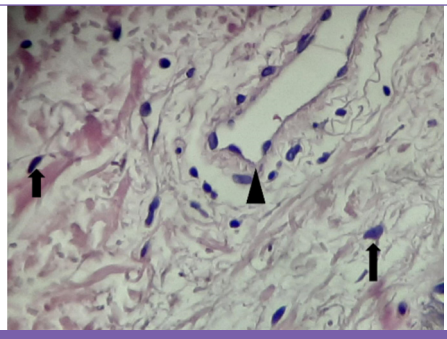

Figure 6. A close-up view showed the mast cell and dilatated blood vessel (magnification 400x)

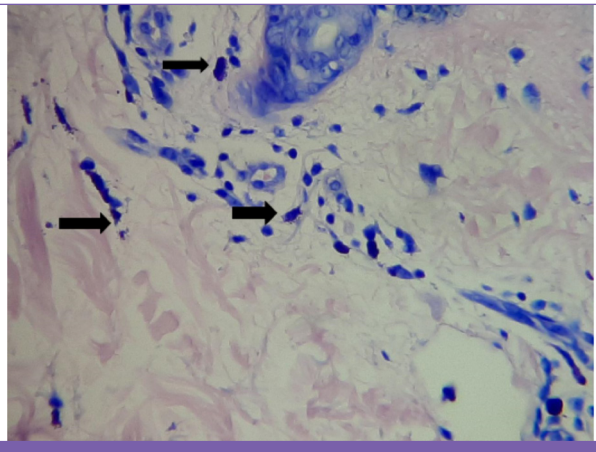

Figure 7. Giemsa stain showed mast cells in perivascular and periadnexal

Dermoscopy, *in vivo* epiluminescence microscopy, is a non-invasive method that provides a rapid and easy evaluation of the color and microstructure of the epidermis, dermo-epidermal junction, and papillary dermis [3,7]. This method not only aids in diagnosing CM but can also differentiate between TMEP and CM variants or other exanthematous skin diseases [3,4]. Akay et al. [4] reported dermoscopy patterns of CM with pigmented network and reticular vascular patterns [9]. The pigmented network was observed mainly in MPCM and UP cases. The reticular vascular pattern was in the TMEP case, corresponding to dilatation and vascular proliferation associated with mast cells in the dermis [4,6,7,9].

Histopathologically the mast cell infiltration of TMEP is predominantly located in the upper third of the dermis and usually clusters around dilated capillaries and superficial venule plexuses [1,4,6]. When the mast cell numbers were within the normal range, the specific stain highlighted these cells, including

Figure 8. Mast cell was highlighted with CD117 immunohistochemical stain (magnification 100x)

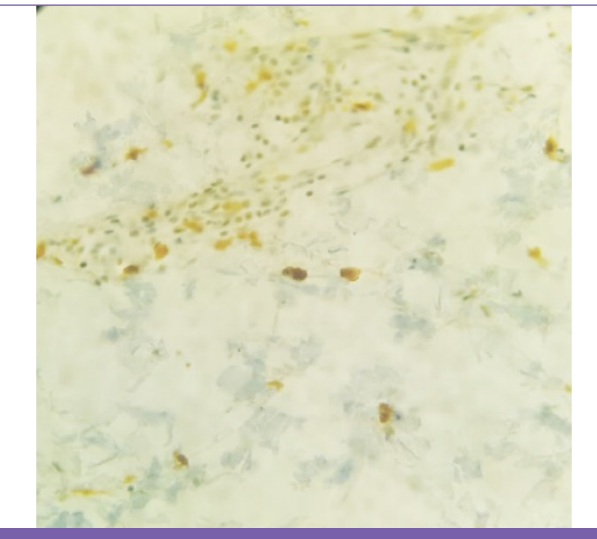

Figure 9. Mast cell was highlighted with CD117 immunohistochemical stain (magnification 400x)

Giemsa and immunohistochemistry with CD117 [6]. Mast cells constitutively express type III receptor tyrosine kinase *KIT* (CD117). It is encoded by c-kit proto-oncogene and is involved in mast cell development and survival. *KIT* activation changes result in mast cell accumulation, abnormal migration, and activation in various tissues. This mutation in CM indicates a condition of more aggressive mastocytosis [6].

Diagnosis of TMEP, in our case, is according to the correlation between clinical manifestation, dermoscopic examination, histopathological results, and immunohistochemistry. The clinical finding showed small, irregular reddish-brown telangiectatic macules on the predilection areas (chest, back, and upper limbs), with dermoscopy findings matching the pattern in the TMEP case. The biopsy result showed mast cell infiltration in the upper third of the dermis and around dilated capillaries, highlighted by Giemsa and immunochemistry with CD117 staining.

CM management aims to avoid and to treat symptoms caused by mast cell mediator release [6]. An essential first step is to avoid provocative events such as certain foods, sunlight, heat, cold, alcohol, drugs, or allergens [1,8]. First-line agents include systemic antihistamines [6]. Ketotifen, an antihistamine and mast-cell stabilizer, one of the best treatments for CM, was given once every evening due to its sedative effect. Bilastine, the second generation of H1-antihistamine, was given as a substitutive every morning due to its higher affinity for histamine H1 receptor than cetirizine, lack of cardiac toxicity, and sedation [6]. Second-line treatments include topical calcineurin inhibitors, oral sodium cromolyn, phototherapy, and mast cell degranulation inhibitors [1,6]. Topical glucocorticoids improve pruritus, whealing, and infiltration and can use for limited symptomatic lesions [6,8]. Phototherapy with psoralen ultraviolet A or ultraviolet B therapy can help reduce pruritus and skin symptoms [8]. Total body electron beam therapy has also been reported effective for TMEP treatment [8]. Five hundred eighty-five nm flashlamp-pulsed dye laser reduces the lesions' vascularity [6,8]. The leukotriene antagonists, such as montelukast, have been used for pediatric cases and have shown promising results [1,8].

Most cases of TMEP are confined to the skin; however, systemic involvement may occur in 35-50% of patients within six years or more after onset. The risk increases with age, so it is necessary to monitor patients regularly [5,6]. Several laboratory tests and diagnostic imaging studies can assist in the routine evaluation and establish systemic involvement. Diagnostic recommendations for baseline evaluation of adult mastocytosis patients are complete blood count, liver function tests, serum chemistry and tryptase, bone marrow biopsy, and aspirate. Abdominal ultrasound or CT scan, gastrointestinal endoscopy, bone X-ray, or scan are additional investigations for the initial evaluation of a mastocytosis patient, especially if a systemic involvement is suspected [2]. In our case, TMEP still needs further evaluation possibility of systemic involvement.

Conclusion

In this case, the diagnosis of TMEP is according to the correlation between clinical findings, dermoscopic examination, histopathological results, and immunohistochemistry with CD117. Our case was treated with cetirizine and ketotifen, and we were also advised to avoid histamine-releasing substances. Although the patient showed improvement with medication, further evaluation is needed to assess the possibility of systemic involvement.

Ethics

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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