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Narrative Review

Main Causes of Skin Traumas and Damages in Patients with COVID-19

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Abstract

COVID-19 can affect multiple organs including heart and blood vessels, kidneys, gut, and brain. This study aimed to assess all aspects of skin traumas and damages in COVID-19. The main causes of skin trauma in COVID-19 and its consequences can be examined in four parts, including cutaneous manifestations that appear during COVID-19, drug reactions that occur during hospitalization or outpatient treatment of patients, skin damages caused by over-washing or rinsing with inappropriate detergents, or inappropriate use of personal protective equipment (mask, gloves,…), and changes the duration of COVID-19 in patients with autoimmune, chronic and inflammatory underlying skin diseases. The rate of skin manifestations in patients with COVID-19 in the range of 1.8%-20.4%, including vascular lesions (petechiae, purpura, livedo reticularis, pernio, and chilblain lesions), urticaria and maculopapular rash, and other less common skin manifestations such as erythema multiforme, pityriasis rosea, suite syndrome. These skin manifestations were commonly seen in men aged 45-89 years. The most lesions distribution (69.4%) was in the body, but in 19% of cases, lesions were observed in the hands and feet. Patients with COVID-19 receive multiple viral treatments, antibiotics, and various anti-inflammatory drugs. Receiving these drugs has led to cutaneous manifestations in some patients. Medical staff is prone to various traumatic skin conditions, due to the long-term use of personal protective equipment. These conditions include itching, redness, skin irritation, contact dermatitis, and worsening of underlying diseases. The effects of COVID-19 on the skin system can be serious and long-lasting. Adequate treatment and supportive therapy can prevent the long-lasting consequences and disability of the patient.

Keywords: Cutaneous Manifestations, COVID-19, Skin, Trauma, Review.

Introduction

The dermatological aspects of COVID-19

COVID-19 can affect multiple organs including heart and blood vessels, kidneys, gut, and brain. This study aimed to assess all aspects of skin traumas and damages in COVID-19.

The main causes of skin trauma in COVID-19 and its consequences can be examined in four following parts

1. Cutaneous manifestations that appear during COVID-19: Like other viral diseases such as scarlet fever, rubella, measles, meningococcus, etc. which are accompanied by certain skin manifestations. During COVID-19, skin signs and symptoms may occur, even in some of these signs and symptoms appear during the incubation period of COVID-19 (the first 14 days after the virus enters the body) and in this phase, these skin manifestations may be considered a diagnostic sign of COVID-19.[1]

The most common skin manifestations that have been seen during COVID-19 disease, include urticaria, maculopapular rash, exanthematous rash, chickenpox vesicles, petechiae pityriasis, multiform erythema, and acute hemorrhagic edema.

2. Drug reactions that occur during hospitalization or outpatient treatment of patients.[2]

3. Traumatic skin conditions, despite advising hygienic protocols, over-washing or rinsing with inappropriate detergents can cause irritating or allergic contact dermatitis in people, especially those with allergies. Also, inappropriate use of personal protective equipment (e.g. masks, gloves and shields) can cause skin lesions on the face and hands or aggravate the lesions of acne, seborrheic dermatitis, eczema, etc.[3]

4. COVID-19 in patients with autoimmune, chronic, and inflammatory underlying skin diseases such as psoriasis, lupus erythematosus, pemphigus, and scleroderma that use immunosuppressive drugs or biological drugs to control their disease and how to change the course of COVID-19.[4]

We now describe in detail each of the above four cases and the mechanism of skin lesions by presenting documents and articles related to each case:

Cutaneous manifestations of COVID-19:

Cutaneous manifestations of coronavirus

Keratinocytes, in addition to being a mechanical barrier against the penetration of microbes and foreign pathogens, play a vital role in the production of cutaneous immune responses. Keratinocytes can produce inflammatory and immunological mediators.[5] The first cytokines identified to be released by keratinocytes were interleukin-1. Later, keratinocytes were shown to be capable of secreting various soluble mediators, including immunosuppressive, inflammatory, immunomodulatory cytokines, and some inflammatory and antihypertensive, and anti-inflammatory drugs produced even at low concentrations may be effective on microbes.

In addition to secreting cytokines, keratinocytes express immunological surface molecules and in some cases serve as targets of the immune response. Similar to other cells in the human nucleus, keratinocytes exhibit class 1 molecules, so they can be attacked by cytotoxic cells .[6]

Although keratinocytes do not secrete class 2 molecules under normal conditions, in the inflammatory phase they can express these class 2 molecules on their surface. The major inducer of class 2 molecules at the keratinocyte level is interferon-gamma. The expression of class 2 molecules on the keratinocytes surface is associated with high lymphocyte infiltration at the skin lesion site.[5]

What is the mechanism of skin lesions?

In describing the pathogenic mechanism proposed for skin lesions in COVID-19 patients, the role of the hyperactive immune response, complement activity, microvascular damage has been mentioned.[7] The pathophysiology of the disease is multifactorial, accompanied by the innate immune response, increased coagulation, pulmonary and neurological damage.[8] In coronary heart disease, the virus that is present in the blood vessels of the skin of patients with COVID-19 disease is thought to cause lymphocytic vasculitis. Keratinocytes may be secondary targets.[1] In other words, in the skin, in the first stage of the disease, after activation by the virus, numerous accumulations of Langerhans cells occur in the epidermis.[9]The innate immune system in the skin is one of the first elements to react against infectious agents.[10] It can cause a worsening of the condition and even death of a person.[8]

These cytokines stimulate liver cells and liver cells release late-phase proteins into the bloodstream.[11] The role of acute-phase proteins is to opsonize pathogens. This protein is a good marker for disease progression and is a reliable marker for inflammatory or infectious processes. CRP binds to phosphorylcholine lipopolysaccharide in microbial cell membranes and activates chemokines leukocytes and phagocytosis and causes spontaneous vasculitis.[12] Investigation of recently published studies suggests the role of systemic vasculitis and cytokine-mediated coagulation diseases as major causes of organ failure in severe COVID patients.[13]

Vascular damage may be due to direct damage to endothelial cells by the virus or due to the inflammatory response of the host.[14] Skin biopsy of patients with microvascular thrombosis in dermal vessels has been observed.[15] Many secondary skin lesions are due to obstruction of small and medium vessels due to micro thrombosis formation or the formation of antigen-antibody complex.[16] In the manifestations of skin livedo reticularis, accumulation of micro thrombosis originating from other organs causes a decrease in blood flow in the skin. Complementary thrombogenic vasculopathy has also been reported.[1]

The same explanation may be given for hypoxemic damage that occurs in other vital organs such as the lungs, heart, brain, and kidneys.[15]

These systemic conditions may be accompanied by cutaneous lesions that show multiple manifestations in the skin and cause various changes in histopathology. These lesions can be caused by the angiotensin-converting type 2 receptor.[8] The angiotensin-2-converting enzyme is an essential receptor for binding COVID-19 to the cell.[17]

Angiotensin 2-converting receptor enzyme is also present on keratinocytes, and the skin can be a potential target for the COVID-19 virus directly.[18] However, it is not yet clear exactly whether the skin symptoms are due to a primary skin infection or a secondary manifestation of a lung infection in the skin. A combination of such mechanisms may be involved in the development of skin lesions in COVID-19 patients. The morbidity and mortality of COVID-19 disease can be reduced by increasing the activity of the cellular immune system and reducing the activity of the humoral

immune system. Along with the prevention of tissue hypoxia and the establishment of appropriate tissue perfusion, the use of antiviral immunomodulators, antioxidants, anticoagulants, and coagulants are also effective in curing this disease.[15]

Skin manifestations of COVID-19 patients

Patients with COVID-19 disease mainly experience various symptoms such as fever, fatigue, dry cough, anorexia, indigestion, rhinorrhea, shortness of breath, etc. The first study was performed at Lecco Hospital in Lombardy, Italy.

From the collected data (88 patients), 18 patients (20.4%) developed cutaneous manifestations. In 8 patients, skin involvement was observed in 10 patients after hospitalization. The skin manifestations were erythematous rash (14 patients), widespread urticaria (three patients), and vesicles such as chickenpox (one patient). The trunk of the area was mostly involved. The itching was slight or absent, and the lesions usually healed within a few days and had nothing to do with the severity of the disease. It has been reported that the skin manifestations were similar to the skin involvement that occurs during common viral infections.[19] Of course, there is a lot of variation in the skin manifestations associated with COVID-19. Based on the findings of published articles,[20] the dermatological manifestations of COVID-19 can be divided into 4 groups:

1. Exanthema including papulovesicular lesions, morbilliform rash, chicken-like lesions (Figure-1).
2. Vascular including petechiae, purpura, lesions of livedo reticularis, pernio, chilblain.
3. Urticaria and maculopapular rash.
4. Other less common skin manifestations such as erythema multiforme, pityriasis rosea, suite syndrome, etc.

Figure-1. Cutaneous manifestations of COVID-19

What is the prevalence of skin lesions in COVID-19 patients?

It has been found in a review of 57 articles on skin manifestations in patients with COVID-19 from 19 December 2019 to Jun 2020 is ranged from 1.8% to 20.4%,[14] including erythema, papule or pustule (similar to pernio), urticarial lesions, and livedo-venous necrosis and they were commonly seen in men aged 45 to 89 years.

However, in a small number of cases in children, manifestations of popular vesicles, ocular lesions, similar to Kawasaki-like and pernio lesions have been observed.[14] Most patients were male with an average age range 4.5-89 years. The distribution of lesions was essentially localized in the trunk and extremities. The median duration of the lesions was several days and resolved spontaneously. Skin lesions may not be apparent until COVID-19 is exacerbated in individuals. However, in some patients, it appears 2 to 5 days before the onset of COVID-19 symptoms.[14] According to a previous study in Canada, the most common cutaneous manifestations were maculopapular exanthema (morbilliform), which was seen in 36.1% of people. Other skin manifestations in the mentioned study were papular vesicle rash (34%), urticaria (9.7%), painful acral red papules (15.3%), livedo reticularis (2.8%), and petechiae (1.4%).[1] The mean age of patients was 53.6 years (between 15-84 years). 38.9% of men and 27.8% of women made up the patient. The COVID-19 diagnosis was confirmed in 97.2% and 2.8% were suspected of COVID-19.[1]

In a study on 507 COVID-19 patients with cutaneous manifestations, the average age of these patients was 49 years, and women accounted for 60% of the patients. Polymorphic varietal and pernio-like skin lesions and urticarial lesions were the most common cases.[17]

In another study, 52 patients with COVID-19 disease showed skin manifestations in certain age groups. Patients with skin complaints of 55-64 years and 65-74 years showed no difference in sex. However, the relationship between morbidity and dermatological findings was significant. Patients admitted to the intensive care unit showed a higher rate in terms of skin lesions.[21] Reported lesions of these patients included scaly erythematous rash (32.7%), maculopapular rash (23%), urticarial lesions (13.5%), purpuric petechiae rash (7.7%), necrosis (7.7%), and enanthema, and degenerative stomatitis (5.8%), vesicular rash (5.8%)) was pernio (1.9%) and pruritus (1.9%).[20]

Following the COVID-19 pandemic, the number of reports of patients with Kawasaki andpityriasis rosea increased significantly.[10] Human herpesvirus type 6 is involved in the pathogenesis of these two diseases and it is assumed that the Coronavirus is effective in reactivating human herpes type 6 virus.[10]

Location of skin lesions in COVID-19 patients

The distribution of most lesions (69.4%) was observed in the body, but in 19% of cases, lesions were observed in the hands and feet.[1]

Time of skin lesions in COVID-19 patients

The skin lesions were observed from three days before to 13 days after the diagnosis of COVID-19. So that in 12.5% of the cases the skin lesions had developed before the pulmonary symptoms. In 69.4% of the cases, skin lesions appeared after the onset of pulmonary symptoms and in 18.1%, the onset of skin symptoms was not reported.[1] In another study, skin lesions appeared in 507 patients with COVID-19 during 1 - 30 days after the onset of systemic symptoms.[17]

Time of skin biopsy in COVID-19 patients

Of patients with COVID-19 who developed skin lesions after pulmonary symptoms, 74% underwent skin biopsy within 7 days, and in 6% of cases a biopsy was performed.[1]

Histological results of skin biopsy

Skin biopsies performed on patients with COVID-19 who tested positive and those with skin lesions who tested negative with a high risk of COVID-19 infection. In all cases, the presence of prominent dilated blood vessels at the top of the swollen endothelium, blood vessels surrounded by red blood cells, lymphocyte infiltration (mainly cytotoxic cells) and eosinophils around the vessels were observed. In 2 cases, diffuse coagulopathy was present in the cutaneous vascular network.[7]

The relationship between the severity of COVID-19 disease and skin lesions

A correlation was observed between COVID-19 and the severity of skin lesions was observed in five studies, which was seen in 23 patients, but this correlation was not observed in 21 patients (91.3% of cases).[1]

Healing of skin lesions in COVID-19 patients

In all patients, the skin lesions disappeared spontaneously within 10 days. In another article from Italy, out of 88 patients surveyed, 20% of them who tested positive for COVID-19 suffered from skin lesions. The most common skin lesions among the patients were erythematous rash (77%), urticarial (14%), and vesicular lesions (5%).[1]

Mucosal lesions in COVID-19 patients

In a study on 52 patients with COVI-19, Enanthema and stomatitis (5.8%) were observed.[20] A case study reported a patient with COVID-19 with oral mucosal manifestations in the form of oral pain, desquamative gingivitis, ulcer, and oral blisters, which was published in May 2020, 22. In April 2020, 2, mucosal lesions in the form of ulcer in the gingival margin were reported among 375 patients COVID-19 with cutaneous manifestations.[21]

Infection of skin and mucous membranes in children

Children can transmit the virus to others. Infants and toddlers can also get COVID-19 infection from their family members without being exposed to the outside environment. Some studies suggest that the virus causes mild symptoms in children. Some studies have shown that children, like adults, may experience life-threatening complications.[23]

What is a COVID-19 toe?

Proven perineal and pernio-like skin lesions have also been reported in several articles.[24] Pernio shows an abnormal inflammatory response to vascular ischemia caused by prolonged vasoconstriction, which manifests as a macular papule reddish to purple color in the acral regions of the fingers and toes. They are often symmetrical, and in severe cases, blisters and ulcers can occur. Patients complain of burning, itching, or pain in the lesions. Most lesions are disappeared within 1-3 weeks.[25]

Findings of acral ischemia may be due to increased coagulation in COVID-19 patients. In the biopsy of this pernicious lesion of the skin, COVID-19 virus particles were observed in the eccrine sweat glands with prominent inflammation around the eccrine sweat glands.[23]

Also, in 7 children with peritonectomy, a skin biopsy was performed and immunohistochemistry was performed in all of them, and electron microscopy was performed in one case. Histological findings in favor of peripheral viral body particle were observed on electron microscopy of skin biopsies in these patients.[26]

In Spain, out of 375 patients with suspected or confirmed COVID-19, pernicious lesions were observed in 19% of patients. These people were almost young and had mild coronary symptoms and had skin lesions at the end of the illness.[27] SARS-CoV-2 virus has been implicated as the etiologic agent of pernicious and it has been suggested that

some pathogenic mechanisms such as delayed response to viral infection in genetically predisposed individuals cause pernicious in these individuals. The gamma interferon response in young patients induces the virus to multiply and microangiopathic changes.[28] It may also be due to the association between pernicious lesions and the immune chain phenomenon following a viral infection in a group of patients.[29] Many histopathologic manifestations of pernicious, including keratinocyte necrosis, dermal edema, lymphocyte infiltration around vessels and peripheral sweat glands, micro thrombosis, vascular endothelial changes, fibrin deposition, fibrin deposition, immunoreactions on vessels was similar to idiopathic pernio and autoimmune pernio. It is directly positive with a higher rate of vascular changes and immunofluorescence. However, the role of the SARS-Cov-2 virus in this puzzle is not yet well understood.[30]

To evaluate the pathogenesis of ocular lesions, 20 patients (7 females and 13 males) in the age range of 1-18 years were examined.

Biopsy of six patients showed the histological characteristics of pernicious, but no evidence of COVID-19 was found in the tests.[31] Positive swaps from the nasopharynx have rarely been observed. Therefore, no relationship between pernio and COVID-19 has been reported in some previous studies.[32]

A larger sample study was performed on 31 patients with perniosis. Nasal swabs were taken from all patients and 22 patients underwent skin biopsy. Blood tests and COVID-19-specific antibodies were evaluated in all patients. Most of them were young and adolescents and 19 patients were women. In the histology of skin samples, evidence of micro thrombosis and lymphocytic infiltrate was observed according to chilblain. Immunofluorescence in seven patients showed small vessel vasculitis. Antibody titer in one patient was positive and nasal swabs for negative for specific COVID-19test. Blood tests were normal. Therefore, the appearance of chilblain in these patients does not seem to be directly associated with COVID-19.[33]

Some studies reported that acrylic marker lesions could not be specifically used for COVID-19, and hence should not be considered as a COVID-19 symptom in asymptomatic patients, because most of the patients' tests were negative for COVID-19.[34] Therefore, regarding the relationship between COVID-19 and Pernews, the findings of the articles are heterogeneous.

In some studies, by observing COVID-19 particles in skin biopsy of patients with COVID-19 or by observing COVID-19 virus particles in endothelial cells under electron microscopy on skin biopsy and histological evidence of vascular injury, they supported the causal relationship of skin lesions with COVID-19 disease.[2,25] Therefore, it can be concluded that although pernicious is not a specific lesion for COVID-19, the occurrence of skin manifestations such as perniosis can be considered as a sign and predictor of COVID-19. Patients with pernio disease who are asymptomatic with COVID-19 should be isolated and tested to prevent the spread of the disease to immunosuppressed individuals with early diagnosis of the disease.[2]

Another complication of COVID-19 is hair loss in the form of telogen effluvium. Acute telogen effluvium is a type of acute hair loss that occurs during 2-3 months after events such as acute illness and fever, stress, surgery, childbirth, and sudden hemorrhage. In this model, hair loss is transferred from the activity phase to the rest phase and hair loss, and specific hair loss occurs in different places. The rate of hair loss increases from 100 hairs per day to over 1000 hairs. Accordingly, by igniting the inflammation, it will be eliminated and spontaneous hair regrowth will occur in three to six months. In these cases, reassuring the patient and using common scientific methods by dermatologists will be effective.[35]

Two patients with COVID-19 began with symptoms of herpes zoster.[36] A 44-year-old man also developed herpes zoster complications with a positive test.[37]

Also, four COVID-19 patients with epistemic lesions similar to erythema multiforme have been reported.[38] One of the patients had a positive COVID-19 test and the other 3 were negative. Skin biopsy of 2 patients had atypical manifestations of multiform erythema and infiltration around the arteries and sweat glands, lack of keratinocyte necrosis, immunohistochemistry of COVID-19 protein and granular appearance in endothelial cells and epithelial cells of the sweat glands of skin were seen, indicating a strong association between COVID-19 infection and erythema multiforme lesions.[37]

Two patients with urticarial vasculitis and coronary artery disease were also reported.[39]

An atypical cutaneous presentation of the cornea causes painful endodontic nodules on the cheek in a 61-year-old woman with urticaria and myalgia.[40]

Drug reactions in the skin of COVID-19 patients

Patients with COVID-19 receive multiple viral treatments, antibiotics, and various anti-inflammatory drugs. Receiving these drugs has led to cutaneous manifestations in some patients. For example, a 59-year-old man developed maculopapular purpuric exanthema on the 35th day of hospitalization.[41]

One of the drugs used to treat COVID-19 was the antimalarial drug hydroxychloroquine, which was used to reduce the duration of the disease and reduce the inflammatory response to infection. A report of itchy erythematous maculopapular rash in a 24-year-old man was published two days after receiving the drug.[42]

Traumatic skin conditions

The skin is the largest and first line of defense of the body against various infections and external factors.[43] Medical staffs are prone to various skin conditions due to the long-term use of personal protective equipment (Figure-2). These conditions include itching, redness, skin irritation, contact dermatitis, and worsening of underlying diseases such as seborrheic dermatitis and Vulgaris.[42]

Besides, pressure-related skin damage is caused by facial masks.[44] The most common iatrogenic skin damage in health workers is irritative and allergic contact dermatitis, which occurs following excessive hand washing and disinfection.[43]

Figure-2. Contact dermatitis in long term use of personal protective equipment

Although the prevalence of hand eczema is 14.9%, it has a prevalence of 90.4% among health workers.[45]

To investigate the severity and prevalence of pruritus associated with facial masks in the general population, 2315 people were analyzed during the COVID-19 pandemic, and finally, 2307 of them entered the final analysis. Among them, 1393 (60.4%) had used facial mask in the last weeks and 273 (19.6%) complained of itching. People with skin allergies and atopic predisposition and those with facial dermatoses (acne, atopic dermatitis, or seborrheic dermatitis) were at higher risk of itching. People who had used facial masks for a long time had more itching. Almost 30% of people experienced scratches on their faces.[46]

There have also been reports of dermatitis behind the ear caused by the mask strap that irritates the behind of the ear.[47]

How to use biological drugs and immunosuppressants in inflammatory and chronic skin diseases

COVID-19 disease has a viral phase that is asymptomatic or mild in most cases (80%) and may be severe or critical in the remaining 20%. In most cases of this group, there is the second phase of the disease, which is in relation to an increase in the immune response to the virus. In the third phase of the disease, there is an increase in coagulation, and in the fourth phase, organ damage occurs.[48]

Also, due to reports of associated autoimmune diseases (antiphospholipid antibody syndrome, autoimmune cytopenia, Guillain-Barre syndrome, and Kawasaki disease), the phenomenon of autoimmune inflammation in COVID-19 has been reported.[47] Several drugs that are widely used in dermatology have antiviral properties.[49] Immunosuppressive and immunomodulatory drugs are also used to control the inflammatory phase (second phase of the disease) and to treat cytokine storms. These treatments are critical for the management of inflammatory and autoimmune conditions such as psoriasis and psoriatic arthritis. Several studies have been performed on whether patients treated with immunosuppressive and biological drugs are at a higher risk of developing COVID-19 or whether they need to discontinue the drug.[50] Patients with COVID-19 receiving apremilast experienced the fewest symptoms of COVID-19.[49] Apremilast (a small molecule of phosphodiesterase 4 inhibitors) led to a significant improvement in skin lesions in a study on 48 patients taking the drug for psoriasis and during the COVID-19 pandemic, this drug was not

discontinued in the patients of this group. This study was performed in Italy and confirmed the safety of this drug during the COVID-19 pandemic.[51] The patients receiving secukinumab also had a relatively good outcome, but patients with infliximab had a worse outcome.[49]

Many immunotherapies used in dermatology can be used safely during the COVID-19 pandemic, including biologic drugs that target immunoglobulin interleukin-3, interleukin-4, 13, 12, 17, and 23, and tumor necrosis factor.[52] Therefore, most current and biological immunotherapies do not appear to increase the susceptibility risk to the virus, and most are safe during the COVID-19 pandemic.[51] Besides, there is evidence that oral immunosuppressive drugs such as methotrexate and cyclosporine are not associated with an increased risk for patients.[51] There is also evidence that some biologics have antifibrotic activity in animal models.[53]

In some studies, it has been recommended to limit or stop the use of systemic and oral immunotherapy for skin diseases. Because, the use of these drugs during respiratory diseases is dangerous. For example, patients with biologic therapy for the treatment of chronic atopic dermatitis-rhinosinusitis with nasal polyps or chronic spontaneous urticaria who have developed biologically active infections while taking biologic drugs need to be discontinued and this biological treatment could be continued after recovery and negative COVID-19 test.[54]

In autoimmune connective tissue disease - neutrophilic dermatoses - vasculitis - Immunomodulatory drugs such as colchicine and antimalaria are used due to their beneficial effects on the COVID-19 virus and their wide range of functions and do not need to discontinue. Methotrexate, azathioprine, and mycophenolate mofetil increase the infection risk and should be used in low doses if necessary. However, the use of cyclosporine is not recommended in these patients due to the increased risk of hypertension during the COVID-19 pandemic and in the suspected COVID-19 people should be discontinued. COVID-19 individuals should also be tested before treatment. Tumor necrosis factor inhibitors are among the few biological drugs that pose an infection risk to people. However, studies showed that biological drugs, despite their susceptibility to infection, may reduce the cytokine storm.[55]

The question is whether discontinuation of systemic therapies in patients with chronic inflammatory diseases of the skin with COVID-19 aggravates skin lesions in these patients or not. To answer this question, in patients with chronic inflammatory diseases, the effect of discontinuation of biologic immunosuppressive and immunomodulatory were evaluated. In these people, mild to moderate exacerbation occurred in skin lesions, but with the recovery of COVID-19, previous treatments (biological, etc.) continued.[56]

Psoriasis and atopic dermatitis are chronic and common inflammatory skin conditions in which the immune system is disrupted. Therefore, their treatment is based on systemic immunomodulators. During the COVID-19 pandemic, their use is discussed.

In a previous study, it was reported that in patients with these skin conditions who develop COVID-19 and active infections, conventional systemic drugs, ginseng kinase inhibitors, and biologics should be temporarily discontinued and switched to safer drugs in non-COVID-19 individuals. In this study, it was found that interleukin 17, 12, and 23 inhibitors along with a low risk of COVID-19 infection and they are safer than tumor necrosis inhibitors. Apremilast-acitretin and dupilumab (interleukin-4 inhibitor) have good immunity, and therefore they can be used and continued in non-COVID-19 patients because of their safety.[57]

Psoriasis is a chronic inflammatory disease mediated by immune cells that require continuous treatment and continuous follow-up. There is considerable evidence that T lymphocytes play an important role in the formation of psoriasis plaques (especially T helper lymphocytes 1). Increased overexpression of T-helper cytokines such as tumor necrosis factor, gamma interferon, and interleukin-2 has been shown in psoriasis.[58] Inflammation caused by these cytokines increases the proliferation of keratinocytes and stimulates the psoriasis process. On the other hand, the resolution of psoriasis is accompanied by a decrease in T-cell infiltration, a decrease in neutrophils, and a decrease in tumor necrosis factor. Tumor necrosis factor is a protein produced by monocytes, macrophages, mast cells, fibroblasts, smooth muscle cells, endothelial cells, lymphocyte T cells, and NK cells. One of the effective treatments to reduce tumor necrosis factor is the use of biological drugs to inhibit this factor.[59] These drugs are monoclonal antibodies that bind to tumor necrosis factors and block the function of this factor on the receptors. Also, these monoclonal antibodies cause cell apoptosis by activating complement. One of the drugs in this class is

adalimumab.[60] Adalimumab has been extensively used in patients with COVID-19.[61]

In the COVID-19 pandemic, dermatologists need to adjust and adapt their treatment for these patients, especially psoriasis patients who receive systemic treatments. Therefore, a guideline should be provided for these patients.[62]

Another question is whether patients with psoriasis who take biologics have a higher risk of developing a severe type of COVID-19 and what is the clinical course of COVID-19 in these patients. According to the report of 8769 psoriasis patients, only 0.3% of patients had positive COVID-19 and their hospitalization rate was 0.1%. No death due to COVID-19 was observed among these patients.[63] Reports of psoriasis patients taking biologics also indicate that these individuals are not prone to COVID-19 and do not develop severe clinical cases .[62] In the reported articles, two psoriasis patients developed COVID-19, while receiving the biologic drug and had a fever and respiratory symptoms, but none were hospitalized and successfully recovered from COVID-19 infection.[60] Therefore, there is evidence that patients without psoriasis can continue their biological treatment.[64] In asymptomatic psoriatic arthritis, systemic treatments can be continued, but may not be shown during active infection and fever.[52,65]

In the case of vesicular autoimmune diseases such as bolus pemphigoid and pemphigus, Vulgaris destruction of the skin's defense barrier and immune dysregulation occurs.[52] For the treatment of moderate to severe cases, a monoclonal antibody against CD20 (rituximab) is used. To evaluate the prevalence of COVID-19 and associated symptoms in patients with pemphigus Vulgaris who received rituximab within 5 years of the onset of the pandemic. In the study, patients with Pemphigus Vulgaris enrolled between 2014 and 2020. The presence of COVID-19 symptoms or confirmed COVID-19 history was recorded. The number of registered patients was 167. Out of these, 45 patients received rituximab within one year of the current pandemic. Five cases (4 women) were confirmed by CT scan. The mean age was 41.8, none of whom had received rituximab for a year from the current pandemic. Among these five patients, four cases showed COVID-19's symptoms, one case was asymptomatic and was identified accidentally. They were not admitted and none of the patients experienced COVID-19 symptoms.[66]

The decision to initiate or continue immunosuppressive biological therapies in COVID-19 disease in any of the chronic inflammatory diseases of the skin should be made based on a case-by-case way by a dermatologist. Because the observations have demonstrated that immunosuppressive therapies may be effective in treating COVID-19 infection, and emphasizing safety and preservation, especially when there are no signs or symptoms of infection or the history of contact with a person with COVID-19.[67]

Conclusions

The skin system can be affected by COVID-19 like many other organs in the body. The skin traumas and damages are categorized in four ways including cutaneous manifestations of COVID-19, drug reactions after treatment, skin damages, and traumas of over-washing or rinsing with inappropriate detergents or inappropriate use of personal protective equipment (masks, gloves,…) and changes the duration of COVID-19 disease in patients with autoimmune, chronic and inflammatory underlying skin diseases. The effects of COVID-19 on the skin system can be serious and long-lasting, and adequate treatment and supportive therapy can prevent lasting consequences and disability of the patient.

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Authors' Contribution

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