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A clinical review: Covid-19 and dermatology

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Abstract

On March 11, 2020, the World Health Organization (WHO) declared Corona Virus Disease-2019(COVID-19) as a pandemic disease caused by SARS-CoV-2. During the COVID-19 pandemic, the importance of dermatology practice in patient management has emerged. Skin involvement was rarely documented in the first reported case series. The reason for this has been shown to be that a complete dermatological examination can not be performed in cases. Over time, significantly higher rates of skin findings have been reported.The mechanism of skin lesions associated with COVID-19 is not yet clear. The most common view is that lymphocytic vasculitis caused by vascularly located viral particles and langerhans cell activation is caused by an immune response to infection leading to vasodilation and spongiosis.Keratinocytes are thought to be secondary targets.It has been emphasized that skin findings are encountered at rates varying between 2-20% in COVID-19 patients. Casas et al. performed the first prospective study to classify the skin manifestations of COVID-19 into five major groups, including pseudo-chilblains (19%), other vesicular eruptions (9%), maculopapuler eruption (47%), livedo or necrosis (6%) and urticarial lesions (19%).

Keywords: COVID-19, dermatology, cutaneous manifestations, histopatology

1. Introduction

Coronaviruses (CoV) are RNA viruses belonging to the Orthocoronavirinae subgroup of the Coronaviridae family. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is in the beta subclass of this enveloped, positive-polar, single-stranded virus family (1).

SARS-CoV-2 was reported as a newly identified viral pneumonia agent in Wuhan, China in December 2019. SARS-CoV-2 belongs to the coronavirus family and the clinical condition it causes has been named COVID-19 disease (2). On March 11, 2020, the World Health Organization (WHO) declared Corona Virus Disease-2019 (COVID-19) as a pandemic disease caused by SARS-CoV-2. The COVID-19 pandemic represents the most serious health crisis faced by the modern world and being able to control this pandemic and its consequences cause a great effort all over the world (3,4).

During the COVID-19 pandemic, the importance of dermatology practice in patient management has emerged. Skin involvement was rarely documented in the first reported case series. The reason for this has been shown to be that a complete dermatological examination can not be performed in cases. Over time, significantly higher rates of skin findings have been reported (5).

2. Cutaneous Manifestations of COVID-19

The mechanism of skin lesions associated with COVID-19 is not yet clear. The most common view is that lymphocytic vasculitis caused by vascularly located viral particles and langerhans cell activation is caused by an immune response to infection leading to vasodilation and spongiosis. Keratinocytes are thought to be secondary targets (6). It has been emphasized that skin findings are encountered at rates varying between 2-20% in COVID-19 patients (7). Casas et al. (5) performed the first prospective study to classify the skin manifestations of COVID-19 into five major groups, including pseudo-chilblains (19%), other vesicular eruptions (9%), maculopapuler eruption (47%), livedo or necrosis (6%) and urticarial lesions (19%). In the pediatric COVID-19 patient group, signs such as petechiae, ecchymosis and vasculitic skin symptoms were also observed. These vascular changes are thought to be related to COVID-19's retention of porphyrin by affecting the p chain of hemoglobin and blocking heme synthesis (8).

2.1. Pseudo-chilblains

Itchy or painful acral lesions that become evident with exposure to cold are defined as pernio. Pernio may be idiopathic (primary)or may develop secondary to some systemic diseases. Mostly can manifest as erythematous-to-violaceous papular, nodular, or vesiculobullous, ulcerating skin symptoms (9).

Pseudochilblains, known as COVID toes, are painful, pernio-like acral lesions that can be encountered in patients of all age groups (10,11). These lesions resembling chilblains can be in the appearance of purpura and affect the hands and feet (5). Foot involvement alone is present in most of the cases (85.7%). It has seen that the hands and feet were involved in a lower rate (7%) or only the hands (6%) (10,11). Magro et al.

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(12), reported that the lung and skin of 5 cases diagnosed with severe COVID-19 evaluated the tissues. In 3 cases, they described skin purpura and livedo racemosa, microvascular thrombotic disorder and D-dimer elevation. In the lung and skin tissues of the cases complement accumulation, complement activation and microvascular thrombosis has been detected. They stated that complement-mediated microvascular damage and thrombosis may be an important pathogenetic mechanism in COVID19. Therefore, it was stated that anticoagulant and anticomplement therapies were might be important in early intervention in severe cases. Freeman et al. (13) examined 505 cases of COVID19 with dermatological findings. In 318 (63%) of cases pernio-like lesions were present. Patients with pernio-like lesions had milder signs of COVID-19. They were also generally young and healthy. In this study, pernio-like lesions were the only symptom in 55% of the patients. Other COVID-19 symptoms were present in 45% of patients with pernio-like lesions. The most common symptoms were cough (21%), headache (15%), sore throat (12%) and fever (12%). In patients with other COVID-19 symptoms, pernio-like lesions appeared after other symptoms. Osorio et al. (14) studied 14 cases with pseudo-chilblain lesions. The mean age of the cases was 13.2 years. COVID19 was detected in 2 of the cases. It has been emphasized that pseudo-chilblain in lesions is a late manifestation of COVID-19, mostly observed in young patients with mild symptoms (5,13,14).

Histopathological Findings

In the pathology of a case with PCR positive for COVID 19 and pernio-like lesions, intense superficial and deep lymphocytic inflammation and mild vacuolar interface dermatitis consistent with pernio and connective tissue disease were observed. No thrombus was observed (13). Several other reported pathology reports showed findings consistent with pernio-like changes: Spongiosis, vacuolar interface change, apoptotic epidermal keratinocytes. Some cases showed superficial and deep perivascular lymphocytic or lymphohistiocytic infiltrate, without evidence of vasculitis. Small vessel lymphocytic vasculitis without microthrombus, a subepidermal bleb and rarely lymphocytic vasculitis with microthrombus and underlying epidermal necrosis have been reported in a smaller number of cases (13,14).

2.2. Vesicular Eruptions

Vesicular eruptions associated with COVID-19 occur in two forms as diffuse and localized forms. The diffuse type is polymorphic and has a widespread distribution, while the local type is monomorphic and localized only on the trunk. Although vesicular eruption often occurs after the onset of typical COVID-19 symptoms, it can sometimes occur before symptoms begin (15). Some authors have noted an increase in the frequency of herpesvirus in COVID-19 patients, with some of the vesicular lesions associated with it. In the presence of herpesvirus accompanying COVID-19 disease, the formation of hemorrhagic vesicles and bullae with sizes ranging from 2-3 mm to 1 cm has been demonstrated (16). In a multicenter study conducted in Italy, 18.2% of COVID-related skin manifestations were papulovesicular rash. In addition, although papulovesicular exanthema occurs more frequently in the adult population, In the study of Marzano et al. (17) the median age was 60 years.

Histopathological Findings

Significant acantholysis and dyskeratosis were observed in the histopathology of three cases with papulovesicular rash associated with COVID-19. Because of these histopathological findings, the authors do not use the term “chickenpox-like rash”. They used the term “COVID-19 associated acantholytic rash” to group these cases. In the report of another papulovesicular case there was extensive epidermal necrosis with bursting, ac antholysis and swelling of keratinocytes, ballooning of keratinocytes, and signs of endothelitis (18,19).

2.3. Maculopapuler Eruption

Maculopapular rash is a common skin finding. It occurs in bacterial and viral infections like scarlet fever, measles, rubella, erythrovirus (parvovirus B19, smallpox, varicella. It is also seen as heat rash and hypersensitivity reactions (exanthematous drug reactions) (20). The skin findings of 88 COVID-19 patients were examined in a study. Skin findings occurred in one-fifth of the patients. Skin findings were present in 8 patients at the time of admission. The majority of rashes that occurred during follow-up in 10 patients were erythematous maculopapular rash. There was no correlation between the severity of the disease and skin findings (21,22). Maculopapular rash, which is mostly located on the trunk, is reported as the most common dermatological finding associated with COVID-19. Extremities and face are often seen to be protected. The maculopapular rash associated with severe COVID-19 usually resolves within 10 days (23). Atypical maculopapular eruptions may occur in patients with COVID-19. In some patients, scaly rash with perifollicular location was observed. In addition, pityriasis rosacea-like lesions, purpuric lesions, erythema elevatum diutinum-like pseudovesicles and erythema multiforme were also observed (5). In some cases, symptoms of COVID-19 mimics the rash found in other viral infections. A case diagnosed as a Denga fever due to skin rash, petechiae on initial examination, low platelet count and fever. When respiratory problems begin within a few days definitive diagnosis of COVID-19 infection by excluding other common viral infections confirmed by RT-PCR (22) There is a suspicion that COVID19 may be a trigger for maculopapular rash. However, the role of SARS-CoV-2 in inducing skin lesions is unclear and needs to be clarified by further observations.

Histopathological Findings

Histologically, maculopapular lesions have different features. Maculopapular lesion biopsies mostly contains superficial perivascular dermatitis with lymphocytic infiltrate, neutrophils, eosinophils, nuclear debris, and dilated vessels in the papillary and middle dermis. Hydropic changes in the epidermis with minimal acanthosis, subcorneal pustules, mild

spongiosis, basal cell vacuolation and parakeratosis foci are found (24). Rosell-Diaz et al. (25) presented a lichenoid model with the presence of eosinophils in the biopsy of maculopapular lesions. In one study, the histopathology of maculopapular eruptions was classified according to lesion onset as follows: In early-onset lesions, perivascular lymphocytic infiltrate and spongiosis with moderate epidermal and dermal eosinophils were observed. However, in late-onset lesions, histiocytes were found in collagen fibers with perivascular lymphocyte infiltration. These late-onset lesions do not contain mucin deposits (26).

2.4. Livedo Reticularis/Racemosa-Like Skin Findings

Livedo reticularis (LR) is a cutaneous physical finding characterized by a transient or permanent, red-blue or purple, net-like cyanotic pattern. LR can occur in a variety of physiological and pathological conditions. It may indicate cutaneous blood flow disturbance (27). The pathophysiology of these lesions is unclear. Bouaziz et al (28) stated that immune dysregulation, vasculitis, vessel thrombosis, or neoangiogenesis may produce this clinical picture. In a study conducted in France with 277 patients with suspected COVID-19, livedo reticularis was found in 4 patients (1%) (29). In another study investigating vascular skin manifestations associated with COVID-19, livedo was observed in 1 out of 7 patients (28). These differences in rates may be due to cases with unclear diagnosis of COVID19 (29). Tusheva et al. (30) reported a case of unilateral LR in a patient, with a fatal outcome. They observed patchy bilateral lung opacities on the chest radiograph of a 59-year-old female patient with a history of dry cough, mild shortness of breath, and low-grade fever. The diagnosis of COVID-19 was confirmed by polymerase chain reaction. There was no whitening or tenderness in the dermatological examination. Red to purple reticular discoloration was present for 8 hours in the distal right lower extremity. Coagulation disorders may be seen in patients infected with COVID-19. In this case they detected thrombocytopenia, increased D-dimer level and prolongation of prothrombin time. Thus, they stated that macro and micro thrombosis attacks formed livedo reticularis. Various mechanisms exist to explain this clinical picture and livedo reticularis seen with COVID 19. Disseminated intravascular coagulation, antiphospholipid syndrome, features of COVID19, activation of complement cascade, and drug interactions may be responsible for the development of livedo and necrosis (31,32). Additional clinical trials may determine whether anticoagulants can improve overall outcomes in the treatment of such liveoid manifestations (33).

Histopathological Findings

The histopathology of LR varies according to the underlying cause. There are no histopathological changes in physiological forms. In secondary causes, a number of changes may occur, such as vasculitis, calcium deposition in vessel walls (calciphylaxis), intravascular eosinophilic occlusion (monoclonal cryoglobulinemia), intraluminal thrombosis (hypercoagulation states), cholesterol cleavage (cholesterol embolism), and crystal deposition (27). Khalil et al. (34) presented a 34-year-old female patient with livedo reticularis that developed with COVID19. Histopathologically, perivascular lymphocytic infiltration, superficial dermal mucin increase, and necrotic keratinocytes indicating viral exantemia were observed. The observation of mucin on this biopsy may be directly related to the exanthem or may indicate a subclinical condition masked by infection.

Table 1. Overview of clinical patterns in major studies on cutaneous manifestations associated with COVID-19

	Pseudo-chilblain	Vesicular	Urticarial	Maculopapuler	Livedo or necrosis
Galván Casas et al.(5)	19%	9%	19%	47%	6%
Nirenberg et al. (10)	Foot involvent				
Piccolo et al. (11)	Alone 85.7%				
Magro et al. (12)					Livedo racemosa(3cases)
Freeman et al. (13)	63%				
Marzano et al (17)		18.2% papulovesicular rash			
Recalcati et al. (21)				Maculopapuler rash(10 cases)	
de Masson etal.(29)					1%Livedo
reticularis(LR)					
Bouaziz et al. (28)				13%LR	
Tusheva et al. (30)					Unilateral LR
Damme et al. (37)			2 cases with acute urticaria		

2.5. Urticarial Lesions

Urticaria is characterized by itchy and edematous plaques called "urtica". Angioedema may develop along with urticaria when deep dermal and/or subcutaneous involvement occurs. Clinically, conditions lasting less than 6 weeks are classified as acute, and conditions lasting for 6 weeks or longer as chronic urticaria (35). There is limited data on the relationship between urticaria and COVID-19. It has been stated that there may be susceptibility to COVID-19 in patients with urticaria, and viral symptoms (cough, fever, shortness of breath, myalgia) should be questioned in cases with urticaria plaques (5). There are studies indicating that acute urticaria among dermatological

emergencies may be associated with COVID-19(36). Damme et al. (37). reported 2 cases, 71-year-old male and 39-year-old female, who were diagnosed with COVID-19. In both cases, weakness and fever were observed before the definitive diagnosis of COVID-19; In addition to these symptoms, they have been reported to have acute urticaria attacks. In a study conducted in Belgium, it was emphasized that there was a significant increase in the frequency of urticaria and urticarial vasculitis in patients presenting with dermatological complaints during the pandemic period. Despite this, no association was seen between COVID-19 and urticaria severity (38).

Histopathological Findings

The histopathological data available on urticaria cases associated with COVID19 are not sufficient (39). Amator et al (40) found in biopsy of a case of urticaria associated with COVID19 lichenoid and vacuolar interphase dermatitis, mild spongiosis, dyskeratotic basal keratinocytes and superficial perivascular lymphocytic infiltrate.

3. Dermatological findings associated with COVID19 prevention measures

The term "Maskne" was first defined during the (COVID-19) pandemic. It is a type of acne mechanic, previously described, associated with personal protective equipment. Maskne formation is caused by mechanical stress (pressure, congestion, friction), temperature increase, humidity and microbiome dysbiosis. Follicular occlusion triggers the picture. Mask wear time, tropical climatesand increased sweating are risk factors (41,42,43). However, the pathogenesis of mask-induced acne has not been fully clarified (44).

Suggested clinical criteria for maskne:

1.Acne formation or exacerbation of existing acne within the mask area within 6 weeks of the onset of regular surgical mask use

2. Involvement in a prominent pattern called the O-zone

3. Exclusion of differential diagnoses such as perioral dermatitis, seborrheic dermatitis, pityrosporum folliculitis and acne rosacea (41).

Maskne, can also increase the feeling of discomfort and itching on the face, increasing touching the face and thus the transmission of COVID19 (45). Some measures to prevent maskne are mentioned. In order to shorten the mask wearing time, it is necessary to take intermittent breaks and change the mask frequently (46). Han et al. (47) recommended changing the mask after 4 hours for the surgical mask and after 3 days for the N95 mask. Desai et al. (48) stated that after using the mask for 2 hours, a break of 15 minutes should be taken. There are also studies that recommend applying an oil-controlling moisturizer before wearing a mask to reduce sebum secretion (47,49,50). A literature series highlighted the importance of safety, tolerance and comfort in mask design. American Academy of Dermatology Association does not recommend the use of strong products such as retinoids, chemical peels, and exfoliants that can irritate the skin or increase maskne (51,52).

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