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REVIEW ARTICLE

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Cutaneous manifestations of COVID-19: A review of the published literature

Ömer Faruk Elmas[1] | Abdullah Demirbaş[2] | Kemal Özyurt[1] | Mustafa Atasoy[3] | Ümit Türsen[4]

[1]Department of Dermatology, Kırşehir Ahi Evran University, Kırşehir, Turkey

[2]Department of Dermatology, Konya Numune State Hospital, Konya, Turkey

[3]Department of Dermatology, Health Science University, Kayseri City Hospital, Kayseri, Turkey

[4]Department of Dermatology, Mersin University, Mersin, Turkey

Correspondence
Kemal Özyurt, Department of Dermatology, Kırşehir Ahi Evran University, Kırşehir, Turkey.
Email: drkozyurt@gmail.com

Abstract

COVID-19 is a highly contagious respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2. COVID-19 outbreak, which caused thousands of deaths, has been declared a pandemic by the World Health Organization in March 2020. The infection has been reported to demonstrate different types of cutaneous manifestations including urticarial, maculopapular, papulovesicular, purpuric, livedoid, and thrombotic-ischemic lesions. Given the high mortality rate of the infection, timely and accurate identification of relevant cutaneous manifestations may play a key role in the early diagnosis and management. In this study, we provide a review with a focus on the reported cutaneous manifestations of COVID-19.

KEYWORDS

coronavirus, COVID-19, cutaneous manifestations, skin

1 | INTRODUCTION

COVID-19 is a highly contagious respiratory tract disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), which was first reported on December 1, 2019 from Wuhan, China.[1] COVID-19 outbreak has been declared a pandemic by the World Health Organization on March 11, 2020 and as of April 26, 2020, approximately 3 million cases were identified worldwide and more than 200 thousand deaths occurred.[1,2] SARS-CoV-2 is transmitted through virus-containing droplets and contaminated objects. The incubation period of the infection is ranging between 2 and 14 days, with an average of 5 days.[3] Fever, cough, sore throat, shortness of breath, muscle pain, nausea, diarrhea, and loss of taste and smell have been reported as common symptoms of COVID-19.[4] In addition, organ dysfunction, progressive respiratory failure, and coagulation disorders, which are associated with high mortality, are also reported.[5]

Infectious diseases that have serious effects on public health may primarily or secondarily involve the skin. Therefore, timely and accurate identification of skin lesions in patients with fever and rash may significantly increase diagnostic accuracy.

Viral infections are common both in children and adults and may cause a wide variety of mucocutaneous manifestations. In the current literature, COVID-19 has also been reported to demonstrate different types of cutaneous manifestations including urticarial, maculopapular, varicella-like, purpuric, livedoid, and thrombotic-ischemic rashes. In this study, we aimed to review the cutaneous findings that have been associated with COVID-19.

2 | URTICARIAL LESIONS

Infections are one of the common causes of urticaria. Bacterial (Streptococcus, Mycoplasma, etc.), parasitic (Schistosomiasis, Strongyloidiasis, Filariasis, etc.), fungal and viral infections (Epstein-Barr virus, enterovirus, adenovirus, hepatitis B, hepatitis C, etc.) can cause urticarial eruptions.[6]

In the most comprehensive study focused on the cutaneous manifestations of COVID-19, Casas Galvan et al[7] reported that 19% of the 375 patients showed urticarial eruption mostly distributed in the trunk or disperse. Only a few cases were limited to the palmar region. Recalcati et al reported that 18 (20.4%) out of 88 patients with COVID-19 had skin findings and three of these showed urticarial lesions. The lesions predominantly distributed over the trunk, and the urticarial eruption was not related to disease severity.[8] Hedou et al

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observed urticarial eruption in two out of 103 patients with COVID-19. In one of these patients, the eruption occurred in the prodromal stage of the infection.[9] Henry et al identified urticarial lesions limited to the face and acral regions in a 27-year-old COVID-19 positive female patient who did not have a high fever.[10] In contrast, C van Damme et al reported two patients with widespread urticarial lesions with fever as the initial signs of COVID-19.[11]

It is obvious that urticaria may be a cutaneous manifestation of a viral infection. In this context, during the pandemic, patients with urticarial lesions should be carefully evaluated for the possibility of COVID-19.

3 | MACULOPAPULAR LESIONS

Maculopapular eruption is a common cutaneous condition that can be caused by drugs, and bacterial and viral infections. It is often associated with a viral or bacterial infection when accompanied by symptoms such as fever, headache, muscle pain, and respiratory distress. Infectious mononucleosis, measles, scarlet fever, hand-foot-mouth disease, herpes, hepatitis B, hepatitis C, Zika virus, Ebola, and HIV are viral conditions that can cause maculopapular eruptions.[12]

Casas Galvan et al[7] reported that 47% of 375 patients with COVID-19 had a maculopapular eruption. Some of them showed perifollicular distribution and scaling, while some were similar to pityriasis rosea. The authors also reported that a few cases showed infiltrated papular lesions, resembling erythema elevatum diutinum or erythema multiforme.

Recalcati et al[8] identified maculopapular eruptions in 14 out of 18 patients with COVID-19, while Hedou et al[9] reported similar eruptions in two patients. Mahe et al,[13] Hunt et al,[14] Estebanez et al,[15] Alramthan et al,[16] and Ahouache[17] reported single cases of maculopapular eruptions in patients with COVID-19.

Jones et al[18] reported a case of Kawasaki disease in a COVID-19 positive 6-month-old female patient who fulfilled the criteria for Kawasaki disease with fever, conjunctivitis, prominent tongue papilla, dry cracked lips, polymorphous maculopapular rash, and swelling of the hands and lower extremities. The authors pointed out the necessity of further studies to clarify the potential association of COVID-19 and Kawasaki disease.

4 | PAPULOVESICULAR ERUPTIONS

In addition to the primary cutaneous diseases and drug eruptions, many bacterial (staphylococcal skin infections, gonococcal bacteremia, and vibrio vulnificus) and viral infections (enteroviral infections, herpes simplex, herpes zoster, varicella zoster, HIV, and parvovirus B19) can be manifested with vesiculobullous and papulovesicular eruptions. Infection-related vesicular lesions can be localized or widespread. While herpes simplex and herpes zoster are usually presented with limited lesions, chickenpox often shows widespread papulovesicular eruption.[12]

Recalcati et al,[8] who conducted the first study regarding the cutaneous findings of COVID-19, reported varicella-like lesions in one of 18 patients. Marzona et al[19] also identified varicella-like eruption in 12 out of 22 patients with COVID-19 and they concluded that this type of eruption may be a specific manifestation of COVID-19. Casas Galvan et al[7] described small monomorphic vesicles located on the trunk in 9% of 375 patients with COVID-19. The authors reported that the vesicular eruptions identified were unlike polymorphic vesicles of chickenpox.

On the other hand, Hedou et al[9] described oral herpes reactivation in an intubated patient, while Tammaro et al[20] reported herpes-related vesicular lesions localized on the trunk in three patients.

5 | PURPURIC ERUPTIONS

Infection-related purpuric eruptions may occur due to vascular invasion of the infectious agent or disseminated intravascular coagulation caused by toxic vascular effects of the infection. Early diagnosis and treatment of purpuric eruptions are crucial due to high rates of morbidity and mortality.

Coxsackievirus A9, Echovirus, Epstein-Barr virus, Cytomegalovirus, Measles virus, Arbovirus, and Arenavirus are the known viral causes of purpuric eruptions.[12] Jimenez-Couche et al[21] reported a purpuric macular eruption distributed over the flexural areas, appearing on the third day of hydroxychloroquine and lopinavir/ritonavir treatments in an 84-year-old female patient.

Magro et al[22] observed purpuric lesions in three patients with severe COVID-19. Histopathological examination of the lesions showed pauci-inflammatory thrombogenic vasculopathy, and C5b-9 and C4d accumulation both in the normal and lesional skin. These interesting findings suggest that, in addition to hypercoagulation, complement activation may contribute to the pathogenesis of COVID-19.

6 | LIVEDO RETICULARIS

Livedo reticularis is a cutaneous finding consisting of a mottled reticulated vascular pattern that appears as a lace-like purplish discoloration. It can be associated with progressive ischemia with or without any evidence of systemic diseases. The color change is caused by a decrease in the blood flow of the arterioles feeding the cutaneous capillaries, resulting in blue discoloration due to deoxygenated blood. Systemic diseases-related livedo reticularis is defined as secondary livedo reticularis. Hematological, rheumatic, and cardiovascular diseases and infections can cause secondary livedo reticularis.[23] Cytomegalovirus and parvovirus B19 are the reported causes of secondary livedo reticularis.[24]

Casas Galvan et al[7] reported that 6% of 375 patients with COVID-19 demonstrated cutaneous lesions indicating varying degrees of occlusive vascular disease. Manalo et al[25] identified livedo reticularis like lesions in two patients with COVID-19 and hypothesized that the lesions might be associated with microthrombosis.

TABLE 1 Key points of the articles reported cutaneous manifestations of COVID-19

Article	Country	Type of the article	Key points
Rodriguez-Jimenez et al[7]	Spain	Original article	- The study included a total of 375 patients showing cutaneous manifestations of COVID-19 - 47% showed maculopapular lesions - 19% of the patients showed urticarial lesions - 19% showed pseudo-chilblain - 9% showed small monomorphic vesicles - 6% showed livedo/necrosis
Recalcati[8]	Italy	Case series	- The study included 18 patients with COVID-19. - 20.4% (n = 18) of the patients showed cutaneous manifestations. (Erythematous rashes [n = 14], urticaria [n = 3], and Varicella-like vesicular lesions [n = 1]) - The lesions were usually located on the chest - There was no relationship between cutaneous manifestations and the severity of COVID-19
Hedou et al[9]	France	Case series	- The study included 103 patients. - 5 (4.9%) out of 103 patients had cutaneous manifestations. (Erythematous rash [n = 2], urticaria [n = 2], and oral herpes activation [n = 1]) - One of the patients had urticaria in prodromal stage. - The lesions disappeared with a median time of 48 h.
Henry et al[10]	France	Single case report	- 27-y-old female with urticarial lesions distributed over the face and acral areas. - The lesions started before fever and moderately responded to antihistamine treatment.
Mahe et al[13]	France	Single case report	- A 64-y-old female with type 2 diabetes with erythematous macular lesions distributed over the chest, axilla, and antecubital region. - The lesions appeared at the fourth day of the infection and disappeared on the following day.
Jimenez-Cauche et al[21]	Spain	Single case report	- A 84-y-old female with flexural erythematous purpuric macules. - The lesions appeared 3 d after the treatment of hydroxychloroquine, lopinavir/ritonavir.
Hunt et al[14]	United States	Single case report	- A 20-y-old male with widely distributed morbilliform rash sparing the face and mucosa.
Marzano et al[19]	Italy	Multicentric case series	- Varicella-like eruption in 22 patients. - Mean age of 60. - The time interval between the symptoms of COVID-19 and skin manifestations was 3 d. - Mean duration of the eruption was 8 d. - The most common location was chest. - There was no face and mucosa involvement. - The histopathological examination of the lesions was in keeping with viral exanthem.
Estebanez et al[15]	Spain	Single case report	- A 28-y-old female with itchy erythematous yellow papules on both heels at the 13th day of the infection. - The patient used paracetamol 10 d before the lesions started. - The lesions were unresponsive to topical corticosteroids.
Manalo et al[25]	United States	Two cases report	- The authors reported two patients with livedo reticularis like eruption. - Patient 1: 67-y-old male. The lesions appeared on the seventh day of the infection and disappeared after 19 h. Transient hematuria accompanied. - Patient 2: 47-y-old female. The lesions appeared following sun exposure on the 10th day of the infection and disappeared after 20 min. The patient had Hashimoto thyroiditis and portal vein thrombosis.
Mazzotta et al[28]	Italy	Single case report	- A 13-y-old boy with erythematous purple macules, ulceration, and crusts. - The lesions disappeared in a few days.
Alramthan et al[16]	Qatar	Two cases report	- Two female patients aged 27 and 35 y. - Erythematous purple maculopapular lesions on the dorsal hands, and subungual erythema.

(Continues)

TABLE 1 (Continued)

Article	Country	Type of the article	Key points
Magro et al[22]	United States	Case series	- A series of five patients with purpuric cutaneous lesions. - The lesions histologically demonstrated a pauci-inflammatory thrombogenic vasculopathy with deposition of C5b-9 and C4d in both involved and normally appearing skin.
Tammaro et al[20]	Italy	Case series	- Three patients with herpetiform lesions on the trunk. - The lesions were considered as suggestive of the infections caused by the members of the Herpesviridae family.
C van Damme et al[11]	Belgium	Two cases report	- Two patients (aged 39 and 71 y) with concomitant fever and extensive urticarial lesions as initial findings of COVID-19.
Ahouache et al[17]	France	Single case report	- A 57-year-old woman with fever lasting for 4 d. - Diffuse fixed erythematous maculopapular lesions over the limbs and trunk, with burning sensation over the palms that appeared 2 d before fever.
Kolivras et al[29]	Belgium	Single case report	- A 23-y-old male patient with acute-onset violaceous plaques on the toes and lateral feet. - The lesions appeared 3 d after a low-grade fever and cough. - The patient had a history of psoriasis, which was treated with secukinumab; however, the secukinumab was stopped 1 mo ago.
Jones et al[18]	United States	Single case report	- A 6-mo-old female with COVID-19 and concurrent Kawasaki disease. - The patient fulfilled the criteria for Kawasaki disease with fever, conjunctivitis, prominent tongue papilla, dry cracked lips, polymorphous maculopapular rash, and swelling of the hands and lower extremities. - The patient was free of respiratory symptom and the clinical course was mild.

7 | THROMBOTIC-ISCHEMIC LESIONS

Infection-related cutaneous thrombotic and ischemic lesions may occur due to direct vascular invasion of the infectious agent, vascular occlusion, or disseminated intravascular coagulation. These types of lesions are one of the important manifestations of serious infectious conditions with high morbidity and mortality such as meningococcemia, and staphylococcal and pneumococcal septicemias.[26,27]

Casas Galvan et al[7] identified asymmetrical acral erythema and edema with vesicles or pustules, which were described "pseudo-chilblain," in 19% of 375 patients with COVID-19. The lesions were also reported to have purpuric areas.

Mazzotta et al[28] reported erythematous purple-colored macular lesions developed on the toes of a 13-year-old boy with COVID-19. The lesions disappeared in a short time following the ulceration and subsequent crusting. The authors hypothesized that the lesions may be caused by acro-ischemia due to endothelial damage and micro-thrombi, induced by the virus.[28] Kolivras et al[29] presented a case of COVID-19 infection-induced chilblain in a patient with the previous history of psoriasis.

Purpuric lesions, livedo reticularis, and thrombotic-ischemic lesions reported in relation to the disease support the view that hypercoagulation may play an important role in the high mortality rate of the infection.

Key points of the articles reported that cutaneous manifestations of COVID-19 have been shown in Table 1.

8 | CONCLUSIONS

In the limited number of studies available to date, COVID-19 has been reported to be associated with different types of cutaneous manifestations. In this context, during the pandemic, the possibility of COVID-19 should be carefully evaluated, particularly in patients presenting with cutaneous findings reported. On the other hand, it should be kept in mind that the disease may also show the skin findings related to viral infections in general. Given the high mortality rate of the infection, timely and accurate identification of the relevant cutaneous manifestations may play a key role in the early diagnosis and management. It is obvious that more in-depth researches are needed to understand the relationship between COVID-19 and skin.

ORCID

Ömer Faruk Elmas https://orcid.org/0000-0002-5474-6508
Abdullah Demirbaş https://orcid.org/0000-0002-3419-9084
Kemal Özyurt https://orcid.org/0000-0002-6913-8310
Ümit Türsen https://orcid.org/0000-0002-5807-6759

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