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Review Article

Cutaneous manifestations of COVID-19

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Abstract The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes, termed coronavirus disease 2019 (COVID-19), has rapidly swept across the world since its first known human manifestation on December 8, 2019. Confirmed cases are present in over 160 countries. Patients of COVID-19 infection present with diverse cutaneous manifestations seen in 0.2% to 20% of patients. This article summarizes different dermatological manifestations in patients with COVID-19 through literature review using Google Scholar, Sci Hub, PubMed and other online review articles. Case reports, case series and other studies which mentioned cutaneous manifestations in the patients with COVID-19 infection were added. The most common cutaneous manifestation of COVID-19 was found to be maculopapular (morbilliform) exanthem. Papulovesicular rash, urticaria, painful acral red purple papules (COVID toes), livedo reticularis and petechiae were other presentations. Majority of lesions were localized on the trunk; however, involvement of the hands and feet was also noted. Cutaneous involvement usually followed the respiratory symptoms; nonetheless, in a minority, it preceded systemic features. Majority of the studies failed to report any correlation between COVID-19 severity and skin lesions. Cutaneous manifestations may help in early diagnosis of disease and prompt treatment of COVID-19.

Key words
COVID-19, Cutaneous manifestations.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus of Coronaviridae family, was first isolated from Wuhan China in December, 2019 and due to rapid spread of disease across the globe, coronavirus disease 2019 (COVID-19) was declared as pandemic condition by WHO in March, 2020. Till date, more than 6,573,540 cases of COVID-19, with 388,041 deaths and 3,170,505 recoveries have been reported worldwide.[1]

The virus enters the respiratory system and attaches to angiotensin converting enzyme 2 ACE2 receptors on the cell surfaces.[2] The presenting symptoms of COVID-19 are flu-like including fever, dry cough, dyspnea, anorexia, ageusia and anosmia which later on progresses to pneumonia and acute respiratory distress syndrome in some patients. In most of the cases it is asymptomatic.[2]

During the viremic stage of disease, the virus particles reach the integument also and subsequent to direct viral exposure and indirect immune dysregulation, skin is expected to be involved in COVID-19, like other common systemic viral infections. Scanty data, international and national, exist about the cutaneous manifestations of this new disease; however, a variety of dermatological findings have been reported (discussed later) and this spectrum is likely to expand in future. The frequency varies from 0.2% from China to 20% from Italy.

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As this a novel virus so new signs and symptoms are also discovered with the passage of time. Many cutaneous findings have also been reported in international literature. The cutaneous manifestations of COVID -19 include erythematous lesions, petechiae, urticaria, vesicular eruption and chilblain of toes.[3]

Pathogenesis[2,4,5]

SARS-2 virus can affect skin by direct and indirect pathways (**Figure 1**).

1. Virus particles reach endothelial cells of cutaneous vasculature by hematogenous route directly or carried by inflammatory cells.
2. SARS-CoV-2, like other viral infections is suggested to induce autoimmunity; different underlying mechanisms may be molecular mimicry, release of self-antigens and epitope spreading.
3. Hypoxic injury to skin enhances the anaerobic metabolism and subsequent lactic acid accumulation further reduces cutaneous blood flow.
4. Virus uses ACE2 receptors, expressed in cutaneous tissues, to enter the host cell, followed by down regulation of ACE2 receptors. ACE-2 is a negative regulator of the renin-angiotensin system (RAS). Interference of ACE2-RAS underlies different vascular pathologies.

Hypercoagulable state is a feature of sever COVID-19 infection. Different underlying mechanisms may be activation of cogulation pathway and suppression of fibrinolytic pathways by IL-6 and other cytokines; direct activation of cogulation system by virus particles; and production of antiphospholipid antibodies.

Cutaneous manifestations

Cutaneous manifestations can be grouped into three types depending on the pathogenesis.[6,7]

1. Dermatoses due to immune response of the body.
2. Dermatoses due to systemic involvement.
3. Dermatoses due to complications of treatment or personal protective equipment (PPE).

Dermatosis due to immune response of the body

1. Morbilliform Rash/Maculopapular Rash

Morbilliform rash consists of macular lesions that are red and usually 2-10mm in diameter but may be confluent in places.

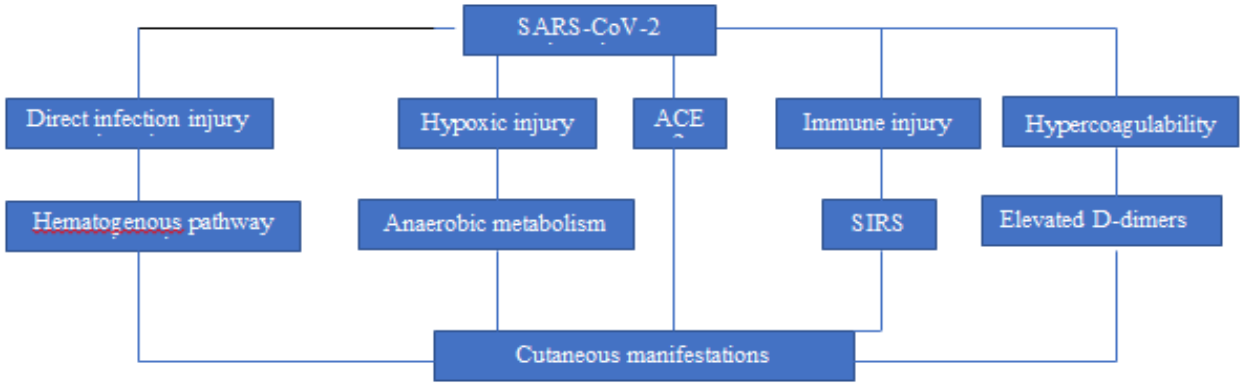

Figure 1 Pathogenesis of cutaneous manifestations in COVID-19 (Adopted and modified from Wu *et al* []).
ACE2 = Angiotensin converting enzyme 2, SIRS = Systemic inflammatory storm syndrome

Table 1 Classification of cutaneous manifestations due to COVID-19

Sr. No.	*Dermatoses due to immune response of the body*	*Dermatoses due to systemic involvement (Vasculopathy)*	*Dermatoses due to complications of treatment or PPE*
1.	Morbilliform rash	Peripheral cyanosis with bullae and dry gangrene	Drug reactions
2	Vesicular rash (Varicelliform rash)	Livedo reticularis	PPE (face masks, gloves etc) induced injuries
3.	Urticaria and Angioedema	Chilblains and Pseudo chilblains	
4.	Erythematous and violaceus patches and papules	Urticarial vasculitis	
5.	Pityriasis rosea	Vasculitis with oral ulcers	
6.	Erythema Multiforme	Cutaneous vasculitis with petechial rash	
7.		Kawaski disease	

It has been observed that a generalized macular or maculopapular exanthem (morbilliform) appeared to be the most common cutaneous manifestation in COVID-19, with 36.1% of patients presenting such lesions on their skin.

A 71-year-old Caucasian woman presented with fever, productive cough and worsening shortness of breath which started 10 days before in the emergency department in Milan. Over the following days a maculopapular itchy rash appeared on the trunk resembling a Grover disease. In another similar case, a 77-year-old Caucasian woman presented with neck lymphonodal enlargement, fever, cough and diffuse maculopapular exanthem (morbilliform) on the trunk in Milan hospital.[4]

Recalcati reported 14 patients of COVID-19 with maculopapular erythematous rash.[8] Hunt reported diffuse, morbilliform, maculopapular, and nonpruritic rash on the trunk and extremities sparing the face along with fever in the patients of COVID-19 in New York.[9] Mahe reported erythematous macular rash which first appeared on the antecubital fossa and later spread to the trunk and axillary folds in COVID-19 patient in France. Skin rash appeared four days after fever.[10] Najarian reported erythematous macules with islands of normal appearing skin between them, arranged in a morbilliform pattern on the legs, thighs, forearms, arms, shoulders, back, chest and abdomen 1 day after onset of respiratory symptoms in the patients of COVID-19.[11]

2. Vesicular Rash (Varicelliform Rash)

A papulovesicular rash (vesicles) was seen in 34.7% of COVID-19 patients in Italy. Monomorphic disseminated vesicular lesions and acral vesiculo-pustular lesions are quite specific. A 72-year-old Caucasian woman, otherwise healthy, presented to the Emergency Department in Milan with headache, arthralgia, myalgia and fever. Four days later, a papular-vesicular, pruritic eruption appeared on sub-mammary folds, trunk and hips.[4]

Vesicular eruption has also been seen as an early presentation of COVID-19, in 15% of cases before other symptoms. Marzano reported Varicella-like itchy papulovesicular exanthem on the trunk and limbs in 22 COVID-19 patients.[12] Recalcati reported one patient with chickenpox-like vesicles on the trunk with little to no itching. They healed within a few days No correlation was seen with disease severity.[8]

3. Urticaria

Urticaria occurred in 9.7% of reported patients of COVID-19 in Italy. Recalcati reported 3 patients of COVID-19 with widespread urticaria.

Urticarial lesions healed without medication.[8] Fernandez reported one female COVID-19 patient with urticarial rash 6 days after the onset of symptoms in Spain.[13] Zhang in Wuhan, China reported two COVID-19 patients with Urticaria.[14]

Henry reported one female patient of COVID-19 with pruritic urticarial eruption on the face, hands and feet (acral involvement) 48 hours before onset of respiratory symptoms in France.[15]

Urticarial exanthem has also been seen as an early diagnostic clue for COVID-19 infection. A 61-year-old Spanish medical doctor presented with progressive cutaneous rash for the last 4 days. He was treating patients with coronavirus infection for three weeks. On presentation, his temperature was 37.3ºC. He did not complain of respiratory symptoms (as cough or dyspnoea), headache, malaise, sore throat or nasal congestion. Physical examination showed an urticarial rash consisting of confluent, edematous and erythematous papules on his thighs, arms, and forearms. Palms and soles were spared. Cutaneous lesions were mildly itchy.[16]

4. Erythematous and Violaceous patches and papules

Kolivras found violaceous, infiltrated plaques on an erythematous background on the dorsal aspect of toes and lateral sides of feet 3 days after onset of respiratory symptoms. These were painful also.[17] Mazzotta (Italy) reported one COVID-19 patient with erythemato-violet, rounded lesions of 5-15 mm in diameter, with blurred limits on the plantar surface of 1st right toe and dorsal surface of the 2nd toe on both feet. It was associated with intense itching and burning.[18] Alramthan (Qatar) reported two cases with acral ischemic lesions presenting as red purple papules on the dorsal aspect of fingers.[19]

5. Pityriasis Rosea

Ehsani *et al* reported pityriasis rosea in a patient with COVID-19. A scaly annular eruption over arms and trunk was observed in the 27-year old man. The lesions were pruritic and disseminated over 5 days. The lesions resolved after topical steroids and oral antihistamine therapy.[20]

6. Erythema multiforme

It is an immune mediated skin reaction to viruses or drugs. It appears as macule, papule and typical target-like lesion on acral parts. Histologically apoptotic individual keratinocytes in epidermis and perivascular lymphohistiocytic infilteration is seen in dermis. In a study by Janah *et al*, two cases have been reported with erythema multiforme in patients with COVID-19 who were on treatment and the lesions resolved despite continuation of treatment.[21]

Dermatoses due to systemic involvement (Vasculopathy)

1. Peripheral cyanosis with bullae and dry gangrene

Recalcati *et al* reported cases with associated cutaneous peripheral cyanosis with bullae and dry gangrene.[8] Zhang *et al* reported seven cases with acral cyanosis, bullae and dry gangrene.[14] Ma *et al* also reported acral dry gangrene in patients with COVID-19.[22] Young *et al* and Suerez *et al* also reported cases with acral purpura, cyanosis and acral ischemia in their study.[23,24]

2. Livedo reticularis

A network pattern of erythematous to dusky cutaneous vessels due to microvascular occlusion or injury is commonly seen on lower legs around the malleoli. This pattern has been reported in patients with COVID-19. In the study by Magro *et al* significant deposition of terminal complement components C5b-9, C4d mannose binding lectin (MBL) associated serine protease (MASP)2 was observed in the microvasculature of skin biopsy samples of the COVID-19 patients with livedo reticularis and purpuric lesions. This study suggests that microvascular injury is mediated by complement activation and associated procoagulant state.[5] De Masson *et al* also reported a case of livedo in their study.[3] Manalo *et al* studied two cases with unilateral livedo which was transient in nature in patients with COVID-19.[25]

*3.**Chilblains and Pseudo chilblains***

Acral eruption of erythematous or dusky papules and macules associated with swelling of the digits is called Perniosis or chilblains. These lesions have observed in the patients with COVID-19 in Italy and other countries.[22,3] Pseudo chilblain lesions have also been reported. Recalcati *et al* reported cases with Perniosis like lesions in their patients with COVID-19. The patient had acral eruption of erthemato-violaceous papules and macules with digital swelling.[26] Similar findings were seen in the study by Alramthan and Aldarajii.[19] De Masson *et al* in the retrospective study in France reported acral lesions as the most common finding with suspected or confirmed cases of COVID-19 (142/277 cases). Out of these 142 cases 106 patients (75%) had chilblain-like lesions.[3]

4.Urticarial Vasculitis

Estebanez reported a case presenting with erythematous yellowish papules on heels bilaterally which became confluent and developed into pruritic erythematous patches resembling urticarial vasculitis.[27,6]

5.Vasculitis with Oral ulcers

Chaux- Bodard *et al* reported a case of 45-year-old COVID-19 positive female patient with an irregular ulcer on the dorsal side of the tongue along with vasculitic lesions on the acral part.[28]

6.Kawasaki disease

It is an acute febrile illness characterized by vasculitis of the medium-sized arteries, including coronary arteries. An atypical Kawasaki disease has been reported in many countries including France (25 cases), United Kingdom (more than 12 cases) and United States of America (15 cases). Patients present with erythematous rash, conjunctivitis, glossitis and high grade fever. Systemic complications include abdominal pain and gastrointestinal symptoms and cardiac inflammation.[29,30]

7.Cutaneous vasculitis with petechial rash:

Bouaziz and Castelnovo in their studies reported cases presenting with signs of vasculitis and associated petechial rash along with acral ischemia and Raynaud's phenomenon.[31,32]

Dermatoses due to treatment

Various drugs are being tried for the treatment of COVID-19 all over the world with varied outcomes. The drugs used for the treatment are chloroquine/ hydroxychloroquine, azithromycin, lopinavir/ ritonavir, corticosteroids, tocilizumab and convalescent plasma. Possible Mucocutaneous side effects of these treatments have been reported which includes morbilliform rash almost with all the treatment options. Other adverse effects are erythroderma, exfoliative dermatitis, urticaria, acute generalized

Figure 2 Papulo-vesicular Eruption in a COVID -19 patient

Figure 3 Urticarial Eruption in COVID -19 patient

Figure 4 Cutaneous small vessel vasculitis involving legs, feet and arms of a COVID-19 patient

exanthematous pustulosis, acneiform eruption, Petechiae, leucocytoclastic vasculitis, hair loss and photosensitivity.[6] Sernicola *et al* reported incidents of toxic erythema and eosinophilia in patients being treated with tocilizumab.[33] Robustelli *et al* reported cases with acute generalized exanthematous pustulosis and erythema multiforme in patients on treatment for COVID-19.[34]

Figure 5 Scabies and Vasculitic lesions both seen in the same patient of COVID-19

Dermatoses due to PPE

Self protection of medical staff by wearing protective clothing, masks, goggles and gloves is mandatory in COVID wards. Prolong wearing of PPE is associated with multiple skin problems which can lead to break in the skin barrier function. The problems include pruritus, erythema, scratches, blisters, rhagades, papules, edema, exudation/crust and lichenification. These findings were observed in the study by Pei *et al* in China.[35] Pruritus ranged from mild to severe. Other cutaneous lesions were reported in 73.1% of the participants with 38.8% noticed erythema, scratch (22.9%), blister (13.8%), rahagades (13.6%), papule/edema (12.8%), exudation/crust (6.8%) and lichenification (5.6%). Majority of the lesions were reported on the face. Singh *et al* reported various dermatoses associated with donning of PPE. The most common was irritant contact dermatitis seen in 39.5% cases followed by friction dermatitis in 25.5% cases. The injuries were caused by goggles (51.9%), N95 masks (30.77%) and face shields (17.31%), pruritus and erythema were common symptoms. Nasal bridge, cheeks and chin were the common sites of lesions.[36] Reports of injuries have been reported in other studies as well.[37-40]

COVID-19 patients in our local population

In Pakistan COVID-19 infection is also spreading exponentially. As of 3rd June, 2020, there have been about 80,500 confirmed cases with 28,900 recoveries and 1,690 deaths in the country. Cutaneous manifestations have also been found in patients infected with this virus. Cutaneous presentations in few of the COVID-19 infected patients from Pakistani population are shown below **(Figure 2-5)**.

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