



Perspective

Significance of cutaneous manifestations of COVID-19

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ABSTRACT

The COVID-19 pandemic has brought the whole world to a grinding halt. With the pandemic still ongoing, it is worthwhile to recapitulate the cutaneous manifestations for dermatologists, their significance, and spectrum of COVID-19 disease. COVID-19 is a highly contagious respiratory tract disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported on December 1, 2019, from Wuhan, China and was declared a pandemic by the World Health Organization on March 11, 2020. COVID-19 indirectly involves the skin just like any other viral infection and is independent of the disease stage or severity. Cutaneous manifestations of COVID-19 may present a few days before or after the first general symptoms of the disease. The appearance of cutaneous manifestations before early respiratory symptoms can promote early recognition of COVID-19 in such cases. The pathophysiology of cutaneous lesions in COVID-19 is still unclear. It is attributed to immune dysregulation, vasculitis, vessel thrombosis, neogenesis, hypercoagulable states, or simple hypersensitivity in COVID-19. Endothelial swelling with the presence of SARS-CoV-2 viral particles in the endothelial cells has also been seen on electron microscopy. Thus, the clinical features indicative of viral exanthems/enanthems which can be found in other diseases therefore fail to provide specific clues for diagnosis and prognosis of COVID-19. On the other hand, vasculopathy-related skin manifestations may provide prognostic values by indicating severe complications due to COVID-19 and may help in monitoring disease severity. Early detection of cutaneous signs associated with severe disease is crucial to improve patient outcomes.

Keywords: COVID-19, Cutaneous manifestations, Pathomechanism, Significance

The COVID-19 pandemic has brought the whole world to a grinding halt. With the availability of the vaccine to a fraction of the population, the majority being health workers and above the age of 45 years in India, the pandemic is raising its head in its second wave, with fatalities running in thousands per day in April 2021 in India. People continue to wonder which way they should go; wear the mask outdoor as well as indoor, whether to expect lockdown or not in the second wave. With the pandemic still ongoing, it is worthwhile to recapitulate the cutaneous manifestations for dermatologists, their significance, and spectrum of COVID-19 disease.^[1] Several reports have described the association of urticaria, erythema multiforme, Kawasaki, Grover's, morbilliform-like, vasculitis-like, vasculopathy, livedo, retiform, and hemorrhage, as well as others with COVID-19 and their significance in COVID-19.^[1]

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WHAT IS COVID-19, FROM WHERE IT CAME FROM, SOURCES OF INFECTION? WHY IS IT LETHAL?

COVID-19 is a highly contagious respiratory tract disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported on December 1, 2019, from Wuhan, China and was declared a pandemic by the World Health Organization on March 11, 2020.^[2]

Coronaviruses are RNA viruses of the family of coronaviridae.^[3] On electron microscopy, their envelope shows large spikes (S protein) which resembles the “crown,” hence the name “Corona” was coined for these viruses. They have been found in cats, dogs, rats, mice, chickens, swine, turkeys, rabbits, horses, cattle, and humans. Initial cases of COVID-19 had contact with live bats, poultry, or marmots at the Huanan Sea Food Market in China.^[3]

COVID-19 virus is transmitted through virus-containing droplets and contaminated objects.^[2] Currently, airborne transmission of COVID-19 is gaining importance. The incubation period of the infection is in the range of 2–14 days, with an average of 5 days. Common symptoms of COVID-19 are fever, cough, sore throat, shortness of breath, muscle pain, nausea, diarrhea, and loss of taste and smell. In addition, organ dysfunction, progressive respiratory failure, and coagulation disorders associated with high mortality are also reported. This occurs owing to the unchecked release of pro-inflammatory cytokines and chemokines. Severe disease is characterized by breathlessness, blood oxygen desaturation, respiratory failure symptoms, and thromboembolic phenomena.^[2]

Complications known to occur are acute respiratory distress syndrome, cardiac injury, pulmonary injury, secondary bacterial infection, renal injury, septic shock, ventilator-associated pneumonia, and multiorgan failure.^[3] Various hematological and biochemical parameters such as reduced lymphocyte count, monocyte count, platelet counts, CD4+/CD8+ T cells and elevated D dimer, prothrombin time, serum urea, and creatinine levels are thought to be predictive markers of fatal outcomes in COVID-19.^[3]

COVID-19 indirectly involves the skin just like any other viral infection and is independent of the disease stage or severity.^[3] Cutaneous manifestations of COVID-19 may present a few days before or after the first general symptoms of the disease. The appearance of cutaneous manifestations before early respiratory symptoms can promote early recognition of COVID-19 in such cases. The pathophysiology of cutaneous lesions in COVID-19 is still unclear. It is attributed to immune dysregulation, vasculitis, vessel thrombosis, neogenesis, hypercoagulable states, or simple hypersensitivity in COVID-19. Endothelial swelling with the presence of SARS-CoV-2 viral particles in the endothelial cells has also been seen on electron microscopy.^[3]

Identification of skin lesions in patients with fever and rash may significantly increase the diagnostic accuracy by all physicians.^[2] Viral infections are common both in children and adults and may cause a wide variety of mucocutaneous manifestations in the setting of COVID-19.^[2]

SETTING FOR THE COVID-19 PANDEMIC

Recently, the COVID-19 pandemic has stimulated the interest of multiple nations on “One Health,” interconnectedness of health of animal, humans and environment.^[4] Studies indicate that more than two thirds of existing and emerging infectious diseases are zoonotic or can be transferred between animals and humans, and vice versa, when the pathogen in question originates in any life form but circumvents the species barrier. China informed WHO about an outbreak of 27 cases of “pneumonia of unknown cause” in Wuhan city of Hubei Province on December 31, 2019, linked to a seafood market. The origin of the causative coronavirus from bats was indicated, and pangolin was suggested to be acting as the intermediate host before human beings contracted the infection.^[4]

Many of the respiratory viruses have pandemic potential unless stopped early in their tracks. In the past few decades, some zoonotic viruses have posed a pandemic threat.^[5] But the devastating effect of a prolonged global public health emergency with COVID-19 has only now been experienced after the influenza pandemic of 1918–1920. The whole world had become more familiar with pandemic origins since December 2019, when the SARS-CoV-2 virus announced its arrival to an unprepared world. The stage was well set for the pandemic due to an increase in the world population (from 2.58 billion in 1951 to 6.1 billion in 2000, and further to 7.8 billion in 2020), a rapidly growing urban segment (which expanded from 46.7% in 2000 to 56.2% in 2020), greater urbanization and greater contact between humans and wildlife, thereby increasing chances of new virus outbreaks globally. The unprecedented scale of mobility of persons, within and between countries, which resulted in the integration of the global economy through trade and travel, also led to the spread of COVID-19. Most recently, the COVID-19 pandemic has been responsible for 2.55 million deaths by early 2021. Unless, there is timely detection, world risks facing many more pandemics in times to come. Now as we battle yet another wave of a deadly zoonotic disease (COVID-19), awareness generation and increased investment towards meeting “One Health” targets is the need of the hour.^[5]

ROLE OF DERMATOLOGISTS IN COVID-19 PANDEMIC

Dermatologists could play an important role in the early recognition of skin lesions suggestive of COVID-19.^[6] The prevalence of cutaneous lesions reported in patients

with COVID-19 infection ranges from 0.2% to 20.4%. They appear at different times in the disease course and are associated with different duration, severity, and prognosis.

Five types of clinical patterns of COVID-19 cutaneous manifestations have been identified, and they are: (a) acral areas of erythema with vesicles or pustules (pseudochilblain); (b) other vesicular eruptions; (c) urticarial lesions; (d) maculopapular eruptions; and (e) livedo or necrosis.^[7] Two significant forms of pathomechanisms seem to be involved: (a) clinical features that indicate viral exanthems/enanthems and (b) vasculopathy-related skin lesions, especially vasculitis and thrombotic vasculopathy. Both clinical and pathophysiologic classifications may elucidate the diagnostic and prognostic values of cutaneous eruptions in patients with COVID-19.^[7]

Exanthematous/enanthematous eruptions are considered to be a hypersensitivity response to viral nucleotides.^[7] Morbilliform eruptions, purpuric macules, petechial rash, urticaria, and varicella-like vesicles, paraviral exanthems, including digitate papulosquamous eruption and pityriasis rosea, are examples of this. Among exanthema patterns, varicella-like type is an early and quite specific skin manifestation of COVID-19 infection and it may be a helpful clue in asymptomatic or mildly symptomatic patients. Urticarial and maculopapular exanthema may not be very helpful for diagnosis, as these are common and may have many different causes. Drug reactions may be an essential and challenging differential diagnosis.

Vasculopathy-related skin manifestations have a range of severity of COVID-19 manifestations, which are due to the multiple cytokines released that induce vasculitis, microangiopathy, and a variety of coagulation disorder-associated skin manifestations. Vascular forms of dermatological lesions associated with COVID-19 are (a) Chilblain-like lesions on the toes; (b) purpuric lesions on the lower limbs; and (c) livedoid/purpuric plaques on the leg. Chilblain-like (acro-ischemic, perniosis-like, pseudochilblain) lesions in most cases are asymptomatic or have mild clinical features. The presence of chilblain-like lesions might help diagnose asymptomatic patients and might indicate a good prognosis. Whereas livedo racemosa, retiform purpura, acrocyanosis, and dry gangrene occur in critically ill patients with a systemic hypercoagulable state that may predict a poor prognosis. The degree of thromboembolism may correlate with the disease severity.^[7] Among vascular forms, pseudo-chilblain appears late in the disease course. Livedoid and purpuric lesions are uncommon and mainly occur in elderly and severe cases with COVID-19. Necrotic lesions occur late in the COVID-19 patient and are therefore unlikely to be helpful for diagnosis.

The limbs seem to be more frequently involved than trunk and face.^[8] Male-to-female ratio of 1 : 9 has been found in several studies. Chilblains are typical feature of COVID-19,

very common amongst the skin lesions and are seen in almost half of all cases with skin lesions. In three-fourth of cases with cutaneous manifestations, the skin lesions appeared before the other characteristic clinical manifestations of COVID-19. Vasculitis or thrombosis was suspected in almost two-third of patients who suffered from skin manifestations. This suggests that a correlation between cutaneous manifestations and systemic vascular damage is possible in COVID-19. COVID-19 seems to be less severe during childhood. Recently cases of Kawasaki disease in children are increasingly being reported.^[8]

Recently it has been suggested that cryofibrinogenemia might be an important pathogenic factor for the development of chilblains related to COVID-19.^[9] Chilblains, purpuric lesions, livedo reticularis, cyanosis, Raynaud's phenomenon, acral blisters, and ulceration are common clinical manifestations of cryofibrinogenemia as such.^[9]

The retiform-like purpuric lesions that occur in the setting of an advanced form of the coagulopathies with thrombi in larger vessels could lead to strokes, pulmonary emboli, and an elevated D-Dimer associated with a poorer prognosis.^[11]

Overall, pseudo-chilblain and vesicular lesions may represent the most common and characteristic skin manifestations of COVID-19. Whether these dermatological manifestations in COVID-19 have any impact on the prognosis and consequent treatment of the disease remain unanswered. Finally, other skin manifestations to be considered are the adverse cutaneous drug reactions to the drugs prescribed for the treatment of COVID-19.^[6]

COVID 19 infects the host using the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in several tissues, including endothelial cells.^[6] The spectrum of the vascular lesions may be due to different overlapping mechanisms, including a direct action of the virus on endothelial cells, an indirect effect involving the triggering of immune or autoimmune reactions as in the case of the immune thrombocytopenic purpura, or to an exaggerated and uncontrolled host response accompanying the well-known "cytokine storm." Whatever the starting mechanism, the consequent microvascular dysfunction can lead to increased vasoconstriction and organ ischemia, inflammation, and a further pro-coagulation state. Whether skin lesions such as chilblain-like lesions correlate with the involvement of internal organs remains to be defined. Very recently, an association between COVID-19 and Kawasaki syndrome, an acute vasculitis of childhood has been reported, which can complicate with heart disease, mostly in developed countries.^[6]

Thus, the clinical features indicative of viral exanthems/enanthems which can be found in other diseases are seen in COVID-19 infections and therefore fail to provide specific

clues for diagnosis and prognosis of COVID-19.^[7] On the other hand, vasculopathy-related skin manifestations may provide prognostic values by indicating severe complications due to COVID-19 and may help in monitoring disease severity. Early detection of cutaneous signs associated with severe disease is crucial to improve patient outcomes.^[7]

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Dr. Devinder Mohan Thappa is the Editor-In-Chief; and Malathi M is on the editorial board of this journal.

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