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Cutaneous Manifestations of COVID-19: Review Article

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ABSTRACT

Background: In December 2019, a new infectious pathogen known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, China. The infection that caused the 2019 Coronavirus (COVID-19) disease was SARS-COV-2 distributed by respiratory drops. This novel COVID-19 infection is known to mostly induce respiratory failure and interstitial pneumonia; however, it is also frequently linked to cutaneous symptoms.

Objective: This review article aimed to throw the light on cutaneous manifestations associated with COVID-19 infection.

Material and methods: In our search for information on cutaneous manifestations associated with COVID-19, we used Google Scholar, Science Direct, PubMed, and other internet databases for COVID- 19 and Cutaneous manifestations. Additionally, the writers combed through relevant literature for references; however, they only included research that were either very recent or thorough, covering the years from 2010 to 2023. Due of lack of translation-related sources, documents in languages other than English were excluded. Excluded from consideration were works in progress, unpublished publications, abstracts from conferences, and dissertations that did not form part of broader scientific investigations.

Conclusion: These COVID-19 symptoms fall into seven different categories: Alopecia and herpes zoster are among the following: (1) A skin rash resembling frostbite (similar to the toes of COVID-19), (2) A skin rash resembling hives, (3) A maculopapular rash, (4) A vesicular rash, (5) Purpura, (6) Reticular and necrotic lesions and (7) urticarial vasculitis. Vasculitic and inflammatory skin manifestations are the two main categories into which the pathophysiology of skin eruptions can be separated. Numerous skin conditions linked to COVID-19 have been documented, and the underlying mechanism has been partially clarified. For example, although it was formerly referred to as COVID-toe and was thought to be a cutaneous eruption connected with COVID-19, several articles have declared that it is irrelevant to COVID-19 infection. Certain skin reactions linked to COVID-19 can actually be mistaken for drug outbreaks. The mechanisms of skin reactions linked to COVID-19 must be clarified in the future, and causal linkages must be confirmed.

Keywords: COVID-19, Cutaneous manifestations, Chilblain-like.

INRODUCTION

In December 2019, Wuhan, China, discovered a new infectious agent called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [(1)]. This virus, which is mostly spread by respiratory droplets, is the cause of coronavirus illness 2019 (COVID-19). Although COVID-19 primarily causes respiratory failure and interstitial pneumonia, it is also commonly linked to a number of cutaneous symptoms. After invading the nasopharyngeal airway epithelium, the virus replicates in the alveoli and expresses the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2) [(2)]. Remarkably, healthy skin's dermis, subcutaneous capillaries, and veins all express ACE2 [(3)].

Cutaneous manifestations of COVID-19

Skin manifestations were reported in 0.19% to 20.45% of COVID-19-infected persons. Seven different kinds can be used to classify these symptoms: vesicular eruptions, purpura, necrotic lesions, maculopapular lesions, urticaria-like rashes, chilblain-like eruptions, urticaria-like rashes, and livedo reticularis. These skin lesions vary in intensity; mild cases are more likely to have chilblain-like eruptions, while severe cases are more likely to have livedo reticularis **[(4)]**.

Erythematous lesions accounted for 44% of verified COVID-19 cases in Europe and America, followed by urticaria-like lesions (16%) and chilblain-like eruptions (20%) [(5)].

The timing of skin lesion appearance also varied: 46% of patients developed lesions concurrently with systemic COVID-19 symptoms (e.g., fever, cough), while 44% experienced skin symptoms later. Notably, in 9.6% of cases, skin lesions manifested before any systemic signs of COVID-19 [(6)].

The prevalence of cutaneous symptoms tends to differ across regions; Europe reported a 6.6% incidence compared to only 0.2% in Asia. In Asian countries, maculopapular lesions were observed in 34% of cases, while chilblain-like eruptions accounted for 5.3% [(7)].

Furthermore, **Giavedoni *et al.*** **[(8)]** proposed categorizing the cutaneous lesions into six patterns, encapsulated by the acronym "GROUCH": Grover's disease and other papulovesicular eruptions, livedo reticularis, urticarial lesions, chilblain-like eruptions, and generalized maculopapular lesions.

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1. Chilblain-like skin eruptions:
Also referred to as "COVID toes [9]," these eruptions are characterized by painful, itchy, edematous purple lesions. They are primarily observed in younger individuals without previous episodes of COVID-19 and manifested cyanosis and a sensation of coldness. A recent study suggests that "COVID toes" may not be directly associated with COVID-19; about one-third of individuals reported prior exposure to an infected person, and another third experienced symptoms preceding the skin lesions. Interestingly, lockdowns may have contributed to increased instances of "COVID toes," as individuals often went barefoot at home. The lower incidence of "COVID toes" reported in Japan might relate to cultural practices of removing shoes indoors. The heightened awareness and media attention on this symptom may have encouraged more individuals to seek medical advice for such lesions [9].

2 . Urticaria-like skin eruptions:
This type of eruption resembles those typically caused by viral infections, lasting up to a week and commonly seen in moderate cases. It often appears alongside general symptoms and tends to respond well to oral steroids and antihistamines.

3 . Maculopapular lesions:
These lesions are the most frequently reported cutaneous manifestation and can sometimes mimic drug eruptions. They typically develop on the trunk, with an average onset occurring 27.6–28.5 days after infection and lasting 8.6–11.6 days. Treatment options include oral compounds such as steroids and antihistamines.

4 .Vesicular eruptions:
Characterized by small blisters less than 1 cm in diameter, these eruptions are observed on the limbs and trunk, particularly in middle-aged patients suffering from moderate to severe illness. Histopathological examinations reveal intraepidermal vesicles with keratinocyte abnormalities and the presence of multinucleated giant cells.

5. Purpura:
More commonly found in older adults experiencing severe illness, purpura can manifest post-systemic symptoms and may result from conditions such as intravenous immunoglobulin (IVIG) therapy, arterial ischemia, or disseminated intravascular coagulation. Signs of vasculitis have also been reported in connection with this manifestation [10].

6 . Livedo reticularis and necrotic lesions:
These lesions are frequently observed in older patients, often presenting alongside systemic symptoms. Livedo reticularis is typically associated with severe cases of COVID-19 and is characterized by a significant mortality rate of around 10%. Histopathological evaluations reveal thrombi present in capillaries and veins, often showing inadequate inflammatory cell infiltration. In approximately half of the cases, thrombosis is found in small arteries and microvessels. Notably, the SARS-CoV-2 spike protein can be detected in subcutaneous adipose tissue and within deep dermal microvessels [11].

7 .Urticarial vasculitis:
Urticarial vasculitis is classified as a type III hypersensitivity reaction characterized by the deposition of immune complexes. This condition can be idiopathic, but it may also arise as a paraneoplastic syndrome, an autoimmune disease, or as a reaction to medication. Clinically, urticarial vasculitis is marked by wheal-like lesions that persist for more than 24 hours.

The precise mechanisms underlying the cutaneous symptoms associated with COVID-19 remain unclear. It is hypothesized that the spike protein of SARS-CoV-2 interacts with ACE2 in target cells, facilitating viral entry. The process is believed to be initiated by the priming of the spike protein via TMPRSS2 within target cells. Interestingly, even in the absence of TMPRSS2 expression, intracellularly replicated SARS-CoV-2 virions can potentially infect other organs expressing ACE2, indicating that the skin may function as a target organ as well [12].

The pathogenesis of skin rashes can be widely categorized into vasculitic and inflammatory processes. Vasculitic eruptions include chilblain-like lesions, purpura, and livedo reticularis with necrotic lesions, each exhibiting distinct pathophysiological mechanisms. Specifically, chilblain-like eruptions and livedo reticularis ensue from direct infection of vascular endothelial cells by SARS-CoV-2 via ACE2, which is expressed on these cells. Additionally, thrombotic vascular injuries resulting from elevated fibrinogen levels, mediated by complement activation and cytokines such as IL-6, contribute to these cutaneous phenomena [13].

The elevation of fibrinogen, along with other pro-inflammatory factors, can lead to thrombotic events that compromise blood flow to the skin and other organs. This thrombosis may contribute to the observed cutaneous manifestations, particularly in severe COVID-19 cases .

Conversely, mild or moderate patients with COVID -19 often experience chillbrane similar to skin that is considered to be caused by IFN type I. In addition, there is a single source T cell and the invasion of dendritic cells. In a study of 40 COVID-19 patients with frostbite-like skin rash, **Hubice *et al.*** [14] found that all cases were mild, whether diagnosed or not [14]. According to the in vitro stimulus test using the serum of the patient, patients who have received the egg bud eruption of the skin have a significantly higher IFN-α reaction ability than the patients hospitalized in COVID-19 in a lightweight or severe form. This means

that the virus can be destroyed before reaching the acquired immunity caused by IFN Type I.

Finally, urticaria, maculopapular lesions, and bullous rashes are examples of rashes caused by inflammation. These are thought to be caused by elevated levels of COVID-19 inflammatory cytokines that contribute to the development of inflammatory skin rashes, perivascular infiltration of inflammatory cells, vasodilation, and edema.

Moreover, direct viral infection of epidermal keratinocytes by SARS-CoV-2, facilitated by the ACE2 receptor, can result in damage to keratinocytes and the basal layer, leading to epidermal-predominant cutaneous manifestations such as blistering, spongiosis, and dyskeratosis. Although vascular damage and inflammation are recognized as key pathogenic mechanisms in COVID-19-related skin symptoms, the etiology of shingles and alopecia in the context of COVID-19 remains elusive."

In summary, the array of cutaneous symptoms associated with COVID-19 underscores the complex interaction between the virus and the immune system. While respiratory complications remain the hallmark of the disease, the significant incidence of skin manifestations highlights the need for clinicians to recognize and address these potential symptoms in affected patients. Enhanced recognition and understanding of these dermatological responses can inform management strategies and improve patient care during the pandemic moving forward. Further research is essential to explain the exact mechanisms behind these diverse cutaneous lesions and their clinical implications in the context of COVID-19.

CONCLUSION

COVID-19 can present with a variety of cutaneous manifestations, although some symptoms have been found to be more or less unique depending on the severity of the disease. With minimal infiltrating cells and vascular involvement, livedo reticularis and necrosis are the primary thromboembolic symptoms in severe instances. On the other hand, T- and B-cell-driven immune responses may be responsible for the cutaneous signs observed in mild or moderate cases, which could indicate an efficient immunological response to support viral elimination. Racial differences and SARS-CoV-2 mutations may cause variations in symptoms.

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