Prevalence of Cutaneous Manifestations in COVID-19 Patients and Their Relationship With Disease Severity

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Background

In December 2019, COVID-19 caused by a beta coronavirus called SARS-CoV-2 was initially identified in Wuhan, China as a global public health emergency.1 The clinical features of COVID-19 are often different and non-specific. The main clinical presentations were fever, dry cough, fatigue, sputum production, difficulty breathing, sore throat, and chills.2,3 Although this novel coronavirus (nCoV) is known to mainly cause hypoxemic respiratory failure, various investigations all over the world have revealed that COVID-19 may be linked with specific skin manifestations.4 The skin is an organ where commonly present lesions are caused by various viral infections.5,6 In COVID-19 infection, various cutaneous symptoms, including chilblains, petechial and purpuric rash, urticaria, erythema-multiforme-like eruptions, pityriasis-rosea-like eruptions, pruritus, and vesicular eruptions, might be due to two mechanisms. The first one is virus-skin interaction through the angiotensin-converting enzyme 2 receptor present in the basal epidermal layer of the skin, and the second one is overactive or impaired immune responses to COVID-19 by complement pathway activation or microvascular dysfunction.7 In the early months of the COVID-19 spread, the incidence of skin disorders was 0.2%, but the types of skin lesions were not explained because it was challenging.8 As the nCoV outbreak progressed, the range of the represented skin manifestations varied between 5% and 20%.9 Hence, the frequency of COVID-19-related cutaneous lesions has continuously grown, simultaneous with the global spread of COVID-19. Cutaneous findings are different, heterogeneous, and frequent, and their diagnosis can be used in the early distinction of COVID-19 from other infections in asymptomatic patients. It would otherwise go undetected to spread the disease.10

Keywords: COVID-19, SARS-CoV-2, Cutaneous manifestations, Skin, Disease severity

Abstract

At the beginning of COVID-19 pandemic, highly accurate information about the clinical manifestations of the disease was not available, and the reported symptoms were non-specific and more related to respiratory symptoms such as fever, dry cough, fatigue, and sputum production. As time has passed, skin manifestations have been proposed as one of the clinical manifestations of COVID-19 in some patients. Among all reported lesions, livedoid lesions appeared simultaneously with the symptoms of SARS-CoV-2, mainly in elderly people with severe infections, and were associated with the highest risk of the mortality of all skin lesions. Knowledge of the skin manifestations that may be the only symptoms of COVID-19 may help in early diagnosis and specific treatment. In the current review, the skin findings of patients in association with COVID-19 were summarized into the categories of maculopapular or purpuric lesions, urticarial lesions, chilblain-like lesions, vesicular lesions, petechiae or purpura lesions, and livedoid lesions.
**Cutaneous Findings of COVID-19 and Disease Severity**

Disease severity varies in confirmed COVID-19 patients with cutaneous manifestations. Cutaneous findings during the COVID-19 pandemic are summarized in Table 1. Extremity ischemia with varying severity was reported in the confirmed cases of COVID-19 with acute symptoms. The dermatological findings of COVID-19 cases were highly non-specific, uncommon, and identical to skin disorders caused by other viruses, including herpes simplex virus type 1 and 2, poxviruses, varicella-zoster virus, and Steven Johnson syndrome. Based on a study from Spain, skin manifestations (pseudo-chilblain, urticarial, vesicular, maculopapular, livedoid, and necrotic lesions) in COVID-19 patients were correlated with gradually increasing severity of the disease.

**Cutaneous Manifestations**

**Maculopapular/Morbilliform Lesions**

These rose-red flat or slightly elevated eruptions are commonly the consequence of adverse drug reactions (typically in adults) or nCoV infection (mainly in children). These rashes are linked to more severe COVID-19 infections, with a 2% mortality rate. The frequency of maculopapular lesions varied among studies, ranging from 5% to 70%, and they were mainly identified in older patients with a mean duration ranging from 8.6 to 11.6 days. The prevalence of these skin manifestations was almost equal in men and women. Anatomically, most morbilliform lesions were found on the trunk. Histopathological findings vary and depend on the onset time. The potential side effects of drugs prescribed anti-COVID-19 (including ribavirin, colchicine, intravenous immunoglobulin (IVIG) treatments, lopinavir, and ritonavir) are similar to maculopapular and morbilliform rashes.

**Urticarial Lesions**

Urticaria (hives) is a common skin disorder that often presents with highly pruritic angioedema (itchy). Acute urticarial eruptions have been mentioned in various nCoV investigations and are associated with the severity of disease. The prevalence of urticaria, among other dermatological disorders, varied from 7-40% and was mainly observed in females. Urticarial lesions were frequently observed among middle-aged patients. These eruptions are mainly affected by limbs or trunks. These lesions’ onset coincides with the other systemic symptoms of SARS-CoV-2 infection, with a median duration of 6.8 days. Urticarial lesions have been observed in dermatological adverse effects in various anti-COVID-19 drugs, excessive activation of immune cells consequently leading to cytokine storm, and skin injury associated with personal protective equipment. Urticarial lesions should be considered as an early marker for nCoV infection regardless of whether patients are symptomatic or asymptomatic.

**Chilblain-Like Lesions (Coronavirus Disease Toes)**

Chilblain lesions (pernio) are inflammatory skin disorders of the hands or feet caused by prolonged cold and damp (humid) exposure. Anatomically, these lesions involve the acral surface of fingers and/or toes. These eruptions are sometimes associated with itching (22% of cases) or pain (11% of cases), and the meantime of the eruption’s onset is about ten days. According to reports, they typically last for about 1-2 weak on average. Chilblain lesions are commonly reported in COVID-19 patients presenting with a mild infection, especially in children and young adults, tending to disappear without scarring after recovering from infection. According to various studies, the frequency of these skin lesions in COVID-19 cases varied from 14.3% to 72% and was higher in females than in men. The current findings have not been able to associate these lesions with confirmed SARS-CoV-2 infections; consequently, chilblain-like lesions should not be considered a specific indicator for diagnosing SARS-CoV-2 infection.

**Vesicular Lesions**

Vesicular lesions are transparent fluid-filled blisters and less than 1 cm in size. Different studies have reported the prevalence of these lesions ranging from 3.77% to 15%. The prevalence of vesicular lesions was almost the same in males and females and was mainly observed in middle-aged adults; they are connected with intermittently severe disease and are frequently located on the trunk and extremities anatomically. These eruptions could be due to the overactivity of immune responses and

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**Table 1. Dermatological Findings Reported in COVID-19 Patients**

<table>
<thead>
<tr>
<th>Cutaneous Manifestations</th>
<th>Localization of Skin Lesions</th>
<th>Appearance</th>
<th>Mean Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular/morbilliform lesions</td>
<td>Trunk</td>
<td>Rose-red flat or slightly elevated eruptions</td>
<td>8.6-11.6 days</td>
<td>12,13</td>
</tr>
<tr>
<td>Urticarial lesions</td>
<td>Trunk</td>
<td>Smooth, slightly elevated papules, or plaques</td>
<td>6.8 days</td>
<td>15,16,17</td>
</tr>
<tr>
<td>Chilblain-like lesions (COVID toes)</td>
<td>The acral surface of fingers or toes/ lower limb</td>
<td>Red to purple swollen painful toes</td>
<td>1-2 week</td>
<td>18,26,27</td>
</tr>
<tr>
<td>Vesicular lesions</td>
<td>Trunk/limb</td>
<td>Fluid-filled sacs under the epidermal layer</td>
<td>9 days</td>
<td>19,21,26</td>
</tr>
<tr>
<td>Petechiae/purpura lesions</td>
<td>Trunk/limbs</td>
<td>Non-blanching red spots</td>
<td>-</td>
<td>22,23,29,30</td>
</tr>
<tr>
<td>Livedoid lesions</td>
<td>Trunk/hands/feet</td>
<td>A net-like cyanotic pattern/reddish-blue/blotchy</td>
<td>9.4 days</td>
<td>31,32</td>
</tr>
</tbody>
</table>
resulting cytokine storm, along with the cytopathic effect of COVID-19 on dermal endothelium vessels.\textsuperscript{24} Contrary to what has been mentioned about maculopapular rashes and urticarial eruptions, vesicular lesions etiologically are not connected to anti-COVID-19 drugs.\textsuperscript{28} These lesions have been reported as a specific cutaneous manifestation of nCoV infection; hence, their identification could help diagnose or verify SARS-CoV-2-infected individuals.\textsuperscript{9}

**Petechiae/Purpura Lesions**

Petechiae are small, non-blanching red spots on the skin that measure less than 2 mm in size.\textsuperscript{29} These rashes are less commonly mentioned cutaneous findings (3%) in the COVID-19 pandemic.\textsuperscript{9} The petechial purpuric rash was anatomically located on the trunk and limbs mainly at the distal extremities.\textsuperscript{8} These lesions appeared after SARS-CoV-2 symptoms, mainly in middle-aged cases recovering from severe SARS-CoV-2 infection.\textsuperscript{21,22,23} Proposed pathogenesis for these skin manifestations includes pauci-inflammatory thrombogenic vasculopathy with deposition of complement components (C5b-9 and C4d) within the cutaneous microvasculature, and sometimes with COVID-19 spike glycoproteins.\textsuperscript{41} An alternate etiology of petechiae/purpura rashes could consider the dermatological and adverse reactions of drugs used for COVID-19 treatment, including high-dose IVIG leading to petechia and camostat mesylate for representing purpura.\textsuperscript{23}

**Livedoid Lesions**

Livedoid reticularis can be either a transient or persistent dermatologic physical sign mainly observed with a net-like cyanotic pattern, reddish-blue, blotchy, and a net-like cyanotic pattern with a mean duration of 9.4 days.\textsuperscript{3,15} Livedoid eruptions are one of the minor frequent cutaneous findings reported during the nCoV outbreak. In a study conducted in Spain, only 6% of the confirmed COVID-19 patients had varying degrees of livedoid and necrotic skin lesions.\textsuperscript{15} These lesions are usually found on the trunk, hands, and feet.\textsuperscript{3,22} These skin symptoms coincided with the onset of other nCoV symptoms and mainly affected elderly individuals with severe nCoV infections and were associated with the highest rate of mortality (10%) of all skin lesions.\textsuperscript{15} Hypo-coagulability of COVID-19 leading to disseminated intravascular coagulation, microthrombi, and macrothrombosis formation are responsible for livedo reticularis-like skin manifestation.\textsuperscript{23}

**Conclusion**

Dermatological findings are mainly related to the severity of SARS-CoV-2 infection, and most of the manifestations are related to the adverse effects of anti-COVID-19 drugs or overactive immune response that can consequently generate cytokine storm. In terms of the time of appearance of lesions in the stages of the disease, it can be stated that maculopapular, urticarial, and livedoid lesions occur in severe stages. In addition, vesicular and chilblain-like lesions take place in severe intermediate and mild stages of COVID-19 infection, respectively, but petechiae or purpura lesions often occur in recovered people. Cutaneous manifestations may occur even before confirmed SARS-CoV-2 infection and may help in timely diagnosis and appropriate treatment of patients, as well as control and prevention of the infection.


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International Journal of Enteric Pathogens Volume 10, Issue 4, November 2022 | 143