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A New Dermatological Research Focus in the Era of COVID-19 Pandemic

Hsuan-Hsiang Chen^{1*}

¹Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

***Corresponding Author:** Hsuan-Hsiang Chen, Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; Tel: +886-2-2356-2141; Email: beauty101@gmail.com

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Editorial

In the era of COVID-19 pandemic, the significance of skin manifestations is more important than we think. Dermatologists have a unique opportunity to adequately describe skin manifestations of COVID-19, and make our contribution during this pandemic.

Various Clinical Manifestations

Cutaneous manifestations, a well-known phenomenon of viral infections, are beginning to be reported in patients with COVID-19 disease. These manifestations mostly are morbilliform rash, urticaria, vesicular eruptions, acral lesions, and livedoid eruptions [1].

If there are specific COVID-19 cutaneous manifestations, it will be important to determine whether any of them have clinical value. Especially, the cutaneous manifestations may help us to predict a more severe course and potentially mandate early aggressive intervention.

Recently, Sachdeva M et al., described the most common cutaneous manifestation of COVID-19. They found maculopapular exanthem (morbilliform) was presenting in 36.1% of patients. The other cutaneous findings included a papulovesicular rash (34.7%), urticaria (9.7%), painful acral red purple papules (15.3%), livedo reticularis lesions (2.8%) and petechiae (1.4%) [2]. The majority of these lesions were localized on the trunk (66.7%). Only 19.4% of patients

developed skin lesions in the hands and feet. Most skin lesion occurred after the onset of respiratory symptoms or COVID-19 diagnosis.

Although, the majority reported no correlation between COVID-19 severity and skin lesions, the clinical presentation of COVID-19 associated cutaneous manifestations may be classified as two categories: (1) mild and early stage; (2) severe and late stage.

Mild and Early Stage: Urticaria, Maculopapular Rash, and Reactive Viral Exanthema

Recalcati S described a total of 88 patients evaluated by dermatologists. Among them, 18 developed skin involvement including erythematous rash, widespread urticaria and chickenpox-like vesicles [3]. Trunk was the main involved region with low or absence of itching. There was not any correlation with disease's severity, either. However, no clinical images or biopsy results were available in this article. It was speculated that skin manifestations were similar to cutaneous involvement occurring during common viral infections.

Fernandez-Nieto D et al., reported another example of an urticariform rash in a 32-years-old woman with COVID-19. The histologic examination of skin biopsy revealed a perivascular infiltrate of lymphocytes, some eosinophils and upper dermal edema [4]. The pathological findings were compatible with common viral exanthema without other unique histological changes.

Estébanez A et al., reported a case of confluent erythematous-yellowish papules in both heels, without any lesions on the rest of the skin. The lesions persisted and became erythematous plaques that were both hardened and pruritic later [5]. However, a biopsy was not performed.

Rarely, some of COVID-19 infection may develop herpetiform varicella-like rash. Tammaro A et al., reported 2 (1.5%) cases presented with isolated herpetiform lesions on their trunk, with numerous vesicular isolated lesions on her back, suggestive of the infections caused by the Herpes viridae family [6]. It is not clear whether this infection is due to concurrent infection or reactivation of herpes viridae or a unique presentation of SARS-CoV-2 infection. More studies should be performed to investigate the nature of the relationship between the appearance of chickenpox-like manifestation and COVID-19.

All of the cases described above showed that the early and mild skin manifestations may include variable morbilliform rash, urticaria, vesicular eruptions and acral lesions with no clinical severity correlation.

Severe Late Stage: Purpura, Petechia, Livedoid Eruptions, and COVID toes

Previously, acute hemorrhagic edema of infancy associated with coronavirus NL63 infection was reported [7]. A similar skin rash with petechiae has also been described as a possible presentation of COVID-19 disease [8]. The clinical appearance of the rash might be recurrent and "target-like purpuric plaques".

Bouaziz JD et al., described vascular lesions with various clinical presentations including violaceous macules with “porcelain-like” appearance, livedo pattern, necrotic or non-necrotic purpura, chilblain appearance with or without Raynaud’s phenomenon, and eruptive cherry angioma [9]. The pathophysiology of these lesions is unclear but may include immune dysregulation, vasculitis, vessel thrombosis or neoangiogenesis. Whether these phenomena are caused by a virus induced peculiar immunological reaction in patients of COVID-19 or represent a true direct viral cytopathic damage on the endothelial walls of vasculature is not clear right now.

Recently, Magro C et al., examined cutaneous tissues from 5 patients with SARS-CoV-2 infection with severe respiratory failure, 3 of whom had features including retiform purpura or livedo racemosa, and markedly elevated d-dimers [10]. The skin lesions are generally considered a prominent dermatologic signs of a generalized microvascular thrombotic disorder. They found the purpuric skin lesions showed a pauci-inflammatory thrombogenic vasculopathy, with deposition of C5b-9 and C4d in both grossly involved and normally-appearing skin. In addition, there was co-localization of COVID-19 spike glycoproteins with C4d and C5b-9 in the cutaneous microvasculature. It is believed that sustained, severe COVID-19 may trigger a catastrophic microvascular injury syndrome mediated by activation of complement pathways and resulted in a procoagulant state and poor prognosis of the disease.

The Differences between Adult and Children

Although vascular lesions with pauci-inflammatory thrombogenic vasculopathy are thought to be an indicator of severe infection of COVID-19, acute chilblains were observed as a mildly symptomatic condition with an excellent prognosis during COVID-19 pandemic in children and teenagers [11]. The differences of immune response and microvascular injury between children and adult should be further investigated.

Prognostic Values of Skin Manifestations

In conclusion, although the actual pathophysiology of SARS-CoV-2 infection is not completely understood, the skin manifestation can still give the clinicians some clues and help the decision making of treatment. Most lesions with urticaria, maculopapular rash, and reactive viral exanthema may not need aggressive treatment. On the contrary, if the patient develops purpuric vascular skin lesions such as purpura, petechia, or livedoid eruptions, a catastrophic microvascular injury syndrome with a procoagulant state mediated by activation of complement pathways should be highly suspected and vigorous early aggressive intervention may be warranted.

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