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Cutaneous Manifestations in COVID-19 "Long Haulers": Is This A Part of the Multisystem Inflammatory Syndrome?

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Abstract The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a multisystem inflammatory syndrome that affects many different organs of the body. Extrapulmonary cutaneous manifestations are now being reported in greater frequency as occurring before or after onset of clinical symptoms. To the authors knowledge, there are few, if any published study that has documented the persistent cutaneous manifestations in patients who have recovered from COVID-19. In this report, we describe some of the cutaneous manifestations in patients known as COVID-19 "long haulers".

Keywords: *COVID-19, long haulers, persistent symptoms, Cutaneous manifestations*

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1. Introduction

"Long Haulers" has been coined to describe patients that continue to experience persistent symptoms weeks to months after they have recovered from Covid-19. [1] The prevalence of persistent symptoms remains unclear. [2] It is estimated that even after 12 weeks, patients continue to experience symptoms related to the coronavirus. [3,4] The most reported post-COVID-19 symptoms include dyspnea and fatigue. Extrapulmonary symptoms reported include myalgia, arthralgia, chest pain, cognitive deficits, neurological symptoms, fever, diarrhea, and skin rashes. [5,6,7,8,9] Reports of decreased oxygen saturations as low as 88% have also been reported. [10]

2. Cutaneous Manifestations

Whether cutaneous manifestations are part of the clinical spectrum of COVID-19 remains unclear as they are observed in other viral infections. But, as the number of COVID-19 cases increase reporting cutaneous symptoms, our understanding will continue in terms of how the coronavirus affects the skin. Six morphologic cutaneous findings have been described: urticarial rash, confluent erythematous/maculo-papular/morbilliform rash, papulovesicular eruptions, purpuric vasculitic rash; livedo reticularis and chilblain-like acral rash. [11,12]

The incidence of cutaneous manifestations in patients infected with the coronavirus is estimated between 0.2 to 20%. [13,14] Although most skin lesions occurred simultaneously or after other COVID-19 symptoms, reports of skin lesions occurring before other COVID-19 symptoms have been reported. [9,15,16]

Persistent dermatological manifestations have been reported with increasing frequency in patients that have recovered from COVID-19. Persistent cutaneous manifestations in long haulers can be defined as lasting more than 60 days. [5] Morbilliform, urticarial and macular-erythema type lesions were frequently observed with laboratory confirmed polymerase chain reaction (PCR) testing. Further, polymorphic skin lesions have been reported. [9,17,18]

As COVID-19 is a multisystem disorder that can affect many different organ systems, we hypothesize that the cutaneous manifestations are part of the newly identified multisystem inflammatory syndrome. Although the pathogenesis for development of rashes in patients infected with the coronavirus is yet to be elucidated, one hypothesis is a direct effect of the virus on the skin due to high concentrations of lymphocytes, lymphohistiocytic infiltrates and papillary dermal edema. [19,20] A second theory is activation of the complement system resulting in a diffuse microvascular vasculitis. [21] Vascular injury leads to increased circulating angiotensin 2 levels that result in vasoconstriction, thrombosis and endothelial dysfunction. [22]

In one of our patients, edematous pruritic plaques occur at various times on the palmar surface of the hands and fingers (Figure 5). To the authors knowledge, there is only one case report documenting cutaneous manifestations on the surface of the hand. [23] However, in a study by Estebanez et al [24] they reported confluent erythematous plaques on the heels of their patient. Such clinical findings of extremity involvement may be due to increased bradykinin production that results in increased vasodilation and vascular permeability. Increased bradykinin levels may result in the observed edematous urticarial plaques due to its host exuberant inflammatory response. [25,26,27]

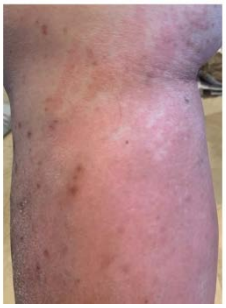

Figure 1. Confluent erythematous maculopapular rash on right lower extremity

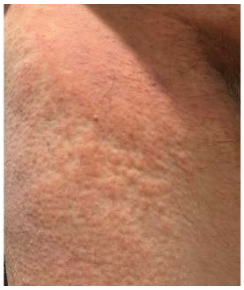

Figure 2. Erythematous pruritic maculopapular rash on right lower extremity. Note the cutaneous wheals

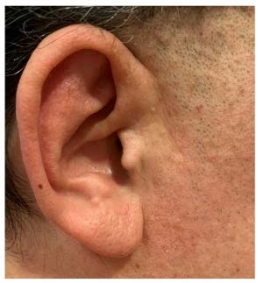

Figure 3. Pseudovesicular rash on right preauricular region of face

Polymorphic cutaneous lesions (Figure 4A and Figure 4B) in the same host are being reported in greater frequency and may be due to infection from multiple variants because of viral mutation. [11,28] However, such polymorphous manifestations could also represent the entire effect of the coronavirus on the immune system. One of our patients experienced three different skin variants-urticarial, maculopapular and pseudovesicular over a period of 120 days (Figure 1, Figure 2, and Figure 3). Angioedema of the lips have also been reported (Figure 6). Angiotensin-converting enzyme 2 (ACE2) is the primary functional host receptor for SARS-CoV-2 and plays a key role in the pathogenesis of Covid-19 infections. It is expressed in many different organs, including the mucosa of the oral and nasal cavities. [29] ACE2 cleaves bradykinin and down-regulation leads to increased bradykinin production and angioedema.

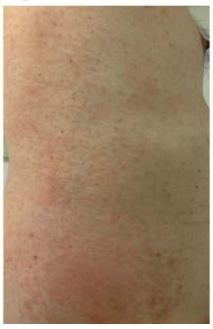

Figure 4A. Polymorphic rash. Scarlatiniform eruptions on the upper half of the trunk and the confluent erythematous rash on the lower half of the patient

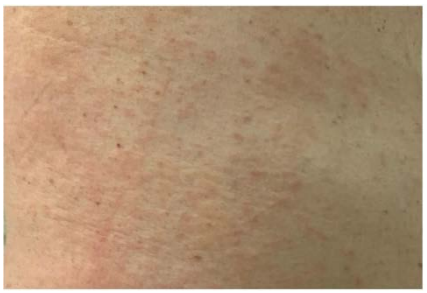

Figure 4B. Close up view of patient in Figure 4A. Note the scarlatiniform eruptions

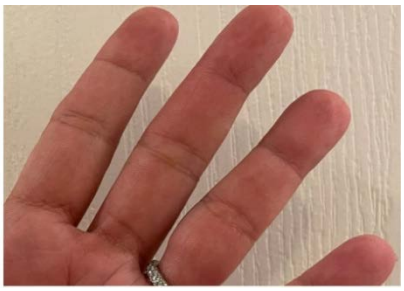

Figure 5. Palmar erythema. Note the erythematous edematous plaques on the palm and fingers

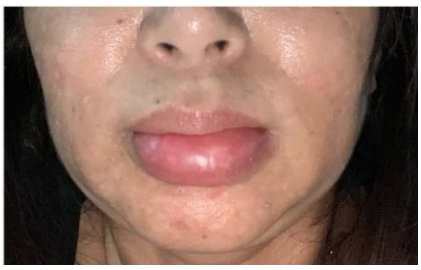

Figure 6. Angioedema of lips

3. Conclusion

Such post-viral cutaneous manifestations are present with other COVID-19 symptoms and may be correlated with immune or inflammatory mechanisms in the

pathogenesis of coronavirus infection. The presence of cutaneous manifestations after COVID-19 recovery needs to more fully understood and may suggest that viral infection may not be completely resolved and is part of the multisystem inflammatory syndrome.

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