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Mini Review

Cutaneous Manifestation and Vasculitis of COVID-19 in Dermatology

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Abstract

The emerging coronavirus disease 2019 (COVID-19) by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide outbreak and still has spread relentlessly and recrudescence because the new mutants begin to occur. The respiratory failure from acute respiratory distress syndrome (ARDS) presents the major cause of mortality and multi-organ failure represents other causes of mortality in patients with COVID-19. It has been revealed that SARS-CoV-2 infection induces the protean clinical manifestations from head to toe, affecting the multiple organ systems including the lungs, heart, brain, kidney, skin, and vasculature. In this article, the cutaneous features and vasculitis in COVID-19 in dermatological field were reviewed. Based on the evidences, it is suggested that the common cutaneous manifestation caused by SARS-CoV-2 infection is chilblains. The direct-induced skin damage and/or a systemic inflammatory reaction by the indirect injury may be considered as the pathophysiological mechanisms in vasculitis of COVID-19. The author suggests that COVID-19 represents an endothelial disease and may be a systemic disease or a multiorgan disease based on the vasculitis in the microvasculature.

Keywords: Vasculitis; Chilblains; Endothelial Disease; SARS-CoV-2; COVID-19

Introduction

The emerging COVID-19 still has spread relentlessly and recrudescence because the new mutants begin to occur. The author previously described a link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19 [1] and also emphasized that COVID-19 may be an endothelial disease and a systemic disease especially in the severe stage. In this article, the current knowledge of cutaneous manifestation and vasculitis in COVID-19 in dermatological field were reviewed.

Endothelial dysfunction and damage in COVID-19

The expression of angiotensin-converting enzyme 2 (ACE2) which serves as an essential role in renin-angiotensin system (RAS) was recognized in the respiratory epithelium, vascular endothelium, and other cell types. It has been also regarded as a primary mechanism of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry and infection processes. The study by Hoffmann., *et al.* [2] suggested that SARS-CoV-2 infection depends on ACE2 and type 2 transmembrane serine protease (TMPRSS2) as host cell factors. The author previously described a link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19 [1]. Pre-exiting endothelial dysfunction in patients with atherosclerosis status combined with vascular damage because SARS-coV-2 infection contribute to severe morbidity and mortality. It has been demonstrated that flow-mediated vasodilation (FMD) and nitroglycerin-mediated vasodilation (NMD) in the brachial artery is a potential procedure for evaluating vascular endothelial and vascular smooth muscle cell (VSMC) function in atheroscle-

rosis status [3]. The author has described several reports on the diseases of migraine, cardiovascular disease (CVD), chronic kidney disease (CKD), dyslipidemia, and aging liver [4-14] using FMD and NMD test. It is also well known that the endothelium regulates the control of haemostasis, fibrinolysis, vascular tone or vasomotion, inflammation, oxidative stress, vascular permeability, and structure. Libby., *et al*. [15] described that SARS-CoV-2 induces the protean clinical manifestations from head to toe, affecting the multiple organ systems including the lungs, heart, brain, kidney, and vasculature. With respect to the clinical course in COVID-19, in the initial phase, the type I and II pneumocytes and alveolar macrophages participates in the initiation of infection. In severe stage, it has been suggested that SARS-CoV-2 serve as a destructive actions beyond the lung organ, showing that predispose to thrombosis in the pulmonary circulation, cerebral circulation, and all arterial beds within the microvasculature [15].

Hypercoagulability in COVID-19

As a result of SARS-CoV-2 infection, the host cell loses ACE2 activity leads to decreased conversion to angiotensin. Raised angiotensin II stimulate vascular constriction and reduced angiotensin suppresses nitric oxide (NO) production which causes increased thrombogenicity and vasoconstriction [16]. As a result of the infected monocyte/macrophage due to coagulation cascade and the infected vascular endothelial cell due to the release of factor VIII and von Willebrand Factor (VWF), the typical coagulopathy in COVID-19 can demonstrate increased D-dimer, raised fibrinogen and VWF levels with relatively normal prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count [16].

Immune response or cytokine storm in COVID-19

While, it is well known that immune response to SARS-CoV-2 infection is also considered as a crucial role. The inflammatory response induced by PAMP sensors is fundamental and natural killer cells (NK), macrophages (M), dendritic cells (DC), CD8 T cells, and cytokines like interferons (IFNs), TNF-α, monocytic chemoattractant protein 1 (MCP1), and macrophage inflammatory protein (MIP) serve as a role of the first barrier. In advanced stage, viral elimination brought on by a systemic inflammatory response syndrome (SIRS) subsequently produced immune hyperactivation or cytokine storm leading to an activation of coagulation cascade and multiorgan failure and death [17].

Cutaneous manifestation and vasculitis in COVID-19

In this article, the cutaneous manifestation and vasculitis in COVID-19 in dermatological field have been reviewed. Recalcati., *et al*. [18] firstly described that cutaneous manifestations were erythematous rash, widespread ulticaria and chickenpox-like vesicles involved in trunk region, while they also mentioned acral cutaneous lesions including acral eruption of erythemato-violaceous papules and macules [19]. Cappel., *et al*. [20] mentioned the renin-angiotensin-aldosterone system (RAAS) resides in the skin and included angiotensin II. It has been suggested that chilblains which is previously associated with vasospasm and a type 1 interferon response is one of the most common cutaneous presentation related COVID-19 [20]. It is well known that vasculitis is defined as inflammation directed at vessels which leads to hemorrhagic and ischemic phenomenon [21]. The variable spectrum of vascular response to injury are observed [21]. Gianotti., *et al*. [22] reported the cutaneous clinico-pahological findings in patients with COVID-19 indicating vasculitis with a small thrombus and superficial perivascular dermatitis with lymphocytic vasculitis. Larenas-Linnemann., *et al*. [17] reviewed cutaneous manifestations related to COVID-19 immune dysregulation in the pediatric cases and mentioned skin features including purpuric such as pseudo-chilblain, morbilliform/maculopapular, erythema multiforme, urticarial, vesicular, Kawasaki-like, and miscellaneous. They supported that pathophysiological mechanisms may be vasculitis-like reactions caused by the direct virus-induced skin damage and/or a consequence of a systemic inflammatory reaction due to the indirect injury [17]. With respect to other reports of vasculitis, severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic [23] and Type 3 hypersensitivity in COVID-19 vasculitis, indicating that interleikin 6 is the key myokine [24] have been reported. Maiuolo., *et al*. [25] noted several reports of SARS-CoV-2 related vasculitis and another study [26] indicated that COVID-19 associated vasculitis and vasculopathy is regarded as an appearance of a virus-induced systemic disease in dermatologic field [27-29]. While, Verga., *et al*. [30] described the direct SARS-CoV-2 viral invasion of vascular endothelial cell and diffuse endothelial inflammation, suggesting that the virus can invade into human vascular and induce vasculitis. Colmenero., *et al*. [29] indicated that lymphocytic vascular damage was the appearance in patients with COVID-19-associated

chilblains. They described that SARS-CoV-2 endothelial infection causes COVID-19 chilblains based on the histopathological, immunohistochemical and ultrstructual study, indicating lymphatic vasculitis in pediatric cases [29].

Conclusion

- It is suggested that common cutaneous manifestation caused by SARS-CoV-2 infection is chilblains based on the reports.
- As the pathophysiological mechanism, the direct-induced skin damage and/or a systemic inflammatory reaction by the indirect injury may contribute to the vasculitis in COVID-19.
- The author also suggests that COVID-19 represents an endothelial disease and may be a systemic disease or a multiorgan disease based on the vasculitis in microvasculature.

Conflict of Interest

Author declares that I have no conflicts of interest.

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