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COVID-19 skin lesions are rarely positive at RT-PCR test: the macrophage activation with vascular impact and SARS-CoV-2-induced cytokine storm

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Abstract

Background Several skin manifestations have been reported since the start of the COVID-19 pandemic: chilblains-like, livedoid lesions, urticaria-like, pseudo-Kawasaki disease, and others. Histopathologic images of these lesions most often show aspects of endothelitis, images similar to autoimmune vasculitis. Cutaneous lesions are often negative at RT-PCR for SARS-CoV-2 virus.

Method and Results We reviewed recent articles on the mechanisms of COVID-19 and we synthesized main pathways of inflammatory cascade. After the penetration into the cells of the respiratory epithelium, SARS-CoV-2 virus initiates a "cytokine storm" well described in previous publications: the expression of interferon type I (IFN-I) is one of the key elements of the antiviral response in COVID-19 patients, IFN-I expression seems to play an important role in the induction of interleukin 6 (IL-6), chemotactic factors such as Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) and the consequent activation of monocyte-macrophage system followed by the expression of TNF-alpha, and finally by the induction of coagulation factors by both extrinsic and intrinsic pathways.

Conclusions The simplified synthesis of the main pathophysiological mechanisms of COVID-19 could help us to understand at least partially the importance of macrophage activation and its vascular involvement in many skin lesions that remain often negative at *in situ* tests for SARS-CoV-2.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for the epidemic of coronavirus disease-19 (COVID-19), which began at the end of 2019 in Wuhan, China, declared a pandemic by the World Health Organization on March 11, 2020. An important part of patients positive at the RT-PCR nasal test for SARS-CoV-2 is being asymptomatic.[1] Symptomatic COVID-19 patients most frequently present general symptoms (fever, fatigue, and anorexia), dysgeusia, anosmia, and respiratory signs (cough, dyspnea, pneumonia, and in the most severe cases, a severe acute respiratory syndrome). Dermatological manifestations of COVID-19 described in case-series published over the past 12 months were most often (according to the prevalence of these manifestations[1–11]): chilblains-like lesions (toes 88%, fingers 24%[11]), diffuse erythematous rash, erythema multiforme-like, punctiform purpura lesions, urticaria-like, varicella-like, and ischemic acrosyndromes.[11] In a large series of chilblains observed in France during the COVID-19 pandemic, most cases of skin lesions were negative to RT-PCR and serological tests.[11] Skin RT-PCR tests were made in most reports some days after their onset, which was the reason for consulting a dermatologist, with or without other symptoms.[8–11] The histopathology, immunofluorescence, and immunohistochemistry examination of chilblains in symptomatic COVID-19 patients showed an aspect of endothelitis similar to that of autoimmune vasculitis, with negative results for *in situ* test for SARS-CoV-2.[12] RT-PCR results for SARS-CoV-2 were also negative in papulosquamous lesions in severe cases of COVID-19.[13] In patients with more ischemic and/or more necrotic acrosyndromes, SARS-CoV-2 was detected by immunohistochemistry, and the presence of viral particles was seen in electron microscopy.[14]

Simplified physiopathology of vascular lesions induced by SARS-CoV-2

SARSC-CoV-2 uses two receptors to enter host cells[15]: angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) expressed by human epithelial

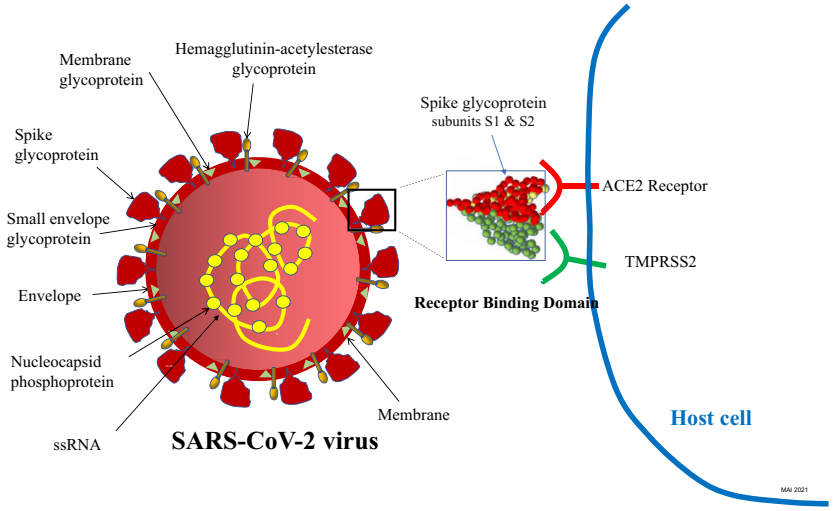

Figure 1 SARS-CoV-2 structure and its receptor binding domain (RBD) using human angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) for cellular entry; mRNA, messenger ribonucleic acid

cells (Fig. 1). SARS-CoV-2 then enters cells (endocytosis), its RNA is lysed into nonstructural proteins, and then RNA polymerase initiates RNA synthesis and assembly of new viruses[16] (Fig. 2a).

Pericytes (Rouget's cells)[17] that envelop the endothelial cells of small blood vessels express high levels of ACE2 receptors and by consequence facilitate SARS-CoV-2 entrance[18] (Fig. 2b). The distribution and density of ACE2 receptor expression underline the important role of endothelitis and endothelial cells' damage and the consequent microvascular dysfunction in the pathophysiology of COVID-19.[19] Significant expression of the ACE2 receptor has also been found in monocytes, macrophages, T-cells, myocytes, and neuronal cells.[18]

The activation of interferon type I (IFN-I) expression in COVID-19 can be compared to the "IFN-I signature" in *systemic lupus erythematosus* (SLE).[20,21] The IFN signature in SLE is because of the activation of several types of IFN-producing cells, endogenous inducers of IFN-I, and autoimmune mechanisms.[22,23] The clinical and histopathological similarities between COVID-19 chilblains-like lesions with those seen in SLE could be related to the antiviral and immunostimulatory properties of IFN-I and its role in SLE microangiopathy.[24,25]

SARS-CoV-2 initiates the expression of IFN-inducible genes as an antiviral response. The activation of these genes in COVID-19 patients exacerbates the "cytokine storm," especially linked to the induction of IFN-I and GM-CSF, followed by the T-cell and NK responses[26,27] (Fig. 2c,d).

Molecular factors, such as pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), interluekin-6 (IL-6), and chemotactic factors such as granulocyte-macrophage stimulating factor (GM-CSF), activate the monocyte-macrophage system.[1] Activated pericytes and endothelial cells express chemotactic factors and adhesion molecules leading to the recruitment of monocytes and neutrophils. Monocytes activate the extrinsic coagulation pathway inducing (via IL-6-stimulated tissue factor coagulation factor III) deposits of fibrinogen and the appearance of thrombi (Fig. 2e). Extracellular neutrophil traps (NETs) activate the intrinsic coagulation pathway activating platelets that adhere and aggregate forming thrombi (Fig. 2f).[28]

The activation of macrophages is mainly linked to the expression of IL-6 and GM-CSF. The IFN-I expression has already been shown to be one of the most important mechanisms in the induction of skin vascular lesions in COVID-19.[1,5,26,29]

IFN type I expression and tissue macrophage's activation (Fig. 2g) aggravate the "cytokine storm"[26] which worsens vascular impact (Fig. 2h).

On the contrary, in SARS-CoV-2-induced pulmonary distress, the suppression of first-line interferon responses and abrogation of NK and T-cells' responses suggest a role for type 2 pneumocyte gp130 receptor expression and important IL-6 release.[27]

In most COVID-19 cases, the skin signs as chilblains appear several weeks after SARS-CoV-2 infection, explaining partially the negative nasal and skin RT-PCR tests, underlining again that these skin lesions are rather induced by the SARS-CoV-2 "cytokine storm" and less by a direct virus-induced cytopathic effect.

Conclusion

The physiopathology of COVID-19 presented synthetically in this article supports the hypothesis concerning the mechanisms of the induction of skin lesions in which interferon type I response and immune response inducing a vascular

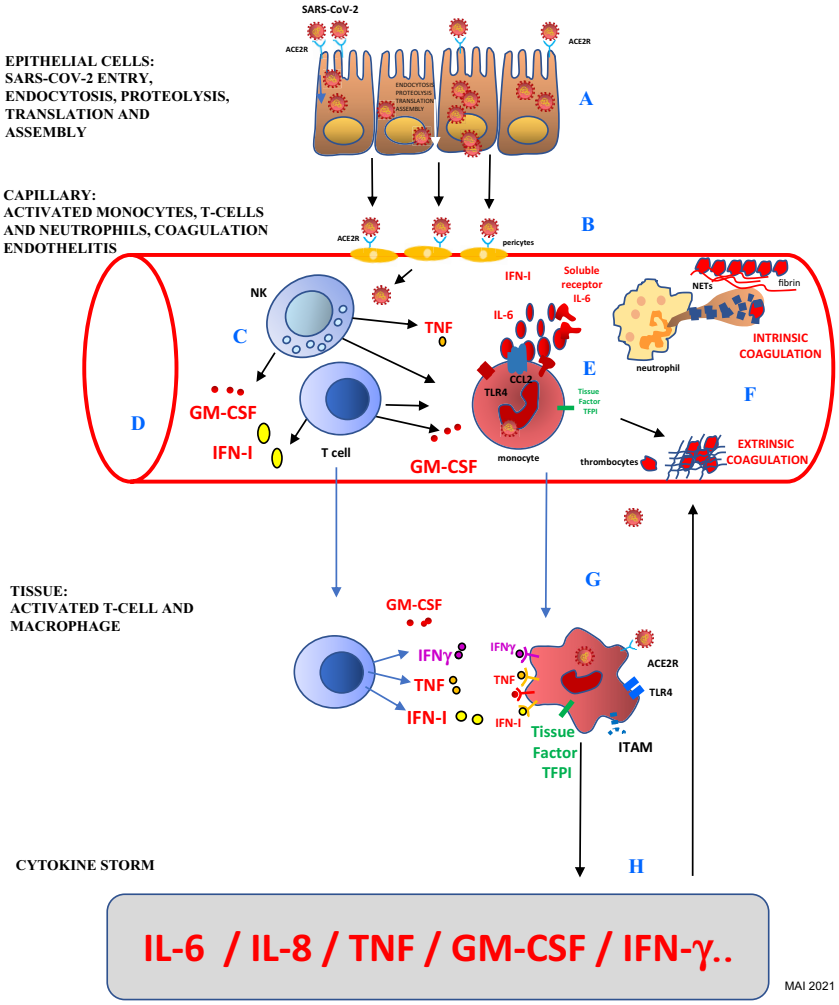

Figure 2 SARS-CoV-2 induced endothelitis and macrophage activation: (A) viral endocytosis, proteolysis, translation, assembly, and exocytosis; (B) capillaries' pericytes strongly express ACER2; (C) T-Cells and NK cells activation; (D) induction of IFN-I and GM-CSF; (E) monocytes activate intravascular coagulation; (F) extrinsic and intrinsic coagulation; (G) tissue macrophage activation; (H) cytokine storm aggravate endothelitis. ACE2R, angiotensin-converting enzyme 2 receptor; CCL2, chemokine ligand 2; GM-CSF, granulocyte-macrophage stimulating factor; IFNg, interferon gamma; IFN-I, interferon type I; IL-6, interleukin 6; ITAM, immunoreceptor tyrosine-based activation motif; NETs, neutrophil extracellular traps; PAMPs, pathogen-associated molecular patterns; P-s, P-selectin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TFPI, tissue factor pathway inhibitor; TLR, toll-like receptor; TLR4, toll-like receptor 4; TNF, tumor necrosis factor; vWF, von Willebrand factor

involvement play a central role in the induction of chilblains-like lesions, livedoid lesions, and urticaria-like lesions.[3,5,12,13] In recent reports, the presence of SARS-CoV-2 was seen by electron microscopy in lesions of endothelitis,[14] but in the majority of published articles, the skin lesions as chilblains are mostly negative being induced "at a distance" by the virus that is triggering an immune reaction responsible for the initiation of the "cytokine storm" and for the release of activators of the monocyte-macrophage system, explaining at least partially the endothelitis and chilblains-like lesions that are often negative at the screening by RT-PCR *in situ* test for SARS-CoV-2.

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