Vascular skin symptoms in COVID-19: a french observational study

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Coronavirus 19 (COVID-19) was declared as a pandemic viral infection by the World Health organization on March 11th 2020. Usual clinical manifestations of COVID-19 infection include fever, fatigue, myalgia, headache, diarrhea, dry cough, dyspnea that may lead to acute respiratory distress syndrome and death (1). Skin symptoms of COVID-19 have been poorly described but may include erythematous rash, urticaria and chicken pox like lesions (2-7). Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for COVID-19. This peculiar mode of entry of COVID-19 in human cells induces angiotensin II accumulation. Angiotensin II excess may contribute to acute lung injury and vessel dysfunction such as vasoconstriction, vascular permeability and abnormal myocardial remodeling (8). Vascular skin lesions during COVID-19 infection have never been described to date. We performed a retrospective observational nationwide study of skin lesions encountered during COVID-19 epidemy in France from march 18th to april 6th 2020 in an ambulatory setting of French dermatologists (national union of French dermatologists and venereologists, *SNDV*) and in 2 hospitals (Saint Louis hospital, Paris and René Dubos hospital, Pontoise, France). All 14 patients reported had formerly proved COVID-19 infection using PCR on samples collected using nasopharyngeal swabs. Skin symptoms started a few days after first COVID-19 general symptoms unless specified in the Figure legend. All patients gave their informed consent for publication of their clinical pictures. Inflammatory lesions were reported in 7 patients: exanthema (n=4), chicken pox like vesicles (n=2), cold urticaria (n=1) as already reported (2-7). Vascular lesions were reported in 7 patients: violaceous macules with "porcelain-like" appearance (n=1, Figure 1A), livedo (n= 1, Figure 1B), non-necrotic purpura (n=1, Figure 1 C), necrotic purpura (n=1, Figure 1D), chilblain appearance with Raynaud's phenomenon (n=1, Figure 1E), chilblain (n=1, Figure 1F), eruptive cherry angioma (n=1, Figure 1G). Forty other patients with chilblain lesions were reported by the *SNDV* but their PCR for COVID-19 detection was either negative (n=6) or not performed (n=34). The pathophysiology of these lesions is

unclear but may include immune dysregulation, vasculitis, vessel thrombosis or neoangiogenesis. Infected COVID-19 patients with severe respiratory distress have an increased risk of pulmonary embolism (9) suggesting a hypercoagulable state of these patients. Seven patients with acro-ischemia (toe cyanosis, skin bulla and gangrene) and frequent disseminated intravascular coagulation (4 patients) have been reported during COVID-19 epidemy in Wuhan (China)(10). A well-described case of antiphospholipid syndrome has been recently published (11). Chilblain "like lesions" in our study had clinical similarities with digital changes observed in type 1 interferonopathies such as Aicardi-Goutières syndrome and STING-associated vasculopathy with onset in infancy that includes skin and pulmonary manifestations.Importantly, French dermatologists belonging to the *SNDV* reported numerous chilblain lesions in persons in close contact with COVID-19+ patients without COVID-19 PCR confirmation and without general symptoms of COVID-19 infections which raises 3 hypotheses: these chilblain lesions may: i/ be due to another confounding factor than COVID-19, ii/ be due to a post viral immunological reaction in asymptomatic forms of COVID-19, iii/ represent a skin presentation of COVID-19 infection in a subgroup of patients with peculiar immune anti-viral response. As isolated sudden onset anosmia was recently described as a symptom highly suggesting COVID-19 infection (12), eruptive chilblain lesions during spring and containment may be a new symptom revealing a pauci-symptomatic COVID 19 infection. The inclusion of our patients was declarative which did not allow us to analyze the frequency of vascular skin lesions in COVID-19 affected patients. Nonetheless, clinicians should be aware of these skin symptoms to optimize COVID-19 detection and quarantine procedures. Prospective study with skin biopsies, serological and PCR analysis of COVID-19 suspected patients with vascular skin symptoms are warranted in order to understand the pathophysiology and the prognosis of such vascular skin lesions.

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Figure Legend

Figure 1. Clinical features of COVID-19+ patients with skin vascular symptoms A: violaceous macules with porcelain appearance in a patient in intensive care unit for respiratory distress. B: livedo of the trunk with chest pain and cough. C: violaceous macule and Raynaud's phenomenom 10 days after fever and cough. D: necrotic purpura in a patient treated with leflunomide and systemic steroids for rheumatoid arthritis. E: chilblain appearance and Raynaud's phenomenom in a patient with anosmia, fever and cough. F: chilblains in a patient with cough. G: eruptive cherry angioma 21 days after COVID-19 healing of clinical symptoms

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