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Relapsing symmetric livedo reticularis in a patient with COVID-19 infection

Editor

During the Coronavirus 2019 (COVID-19) pandemic, several associated skin conditions were reported in infected patients, including, urticaria,¹ exanthema,¹ erythema multiforme,² chickenpox-like vesicles,¹ pityriasis rosea,³ erythema nodosum like Sweet's syndrome,⁴ symmetrical drug-related intertriginous and flexural exanthema,⁵ petechial rash,⁶ vasculitic purpura,⁷ acro-ischaemia/necrosis,⁶ Kawasaki disease² and chilblain lesions.⁶

We present a 57-year-old man with cough, dyspnoea, headache, myalgia arthralgia, fever up to 38.7 °C and abdominal pain worsening over 8 days. Extensive, symmetric livedo reticularis (LR) was present on trunk and thighs (Figs 1,2). Laboratory testing showed elevated C-reactive protein, ferritin, D-dimers and lymphopenia. Nasopharyngeal PCR detected SARS-CoV-2, and chest CT showed multifocal ground glass opacities, suggestive for COVID-19. Because of the unusual sudden onset of symmetric LR in a middle-aged man, an additional workup for underlying conditions was performed. While antineutrophilic cytoplasmic antibodies, platelets, INR/APTT, rheumatoid factor, cryoglobulins and antiphospholipid antibodies were negative, antinuclear factor (ANA) was positive with nuclear pattern (titre 1/320, but without ENA-blot specificity). The patient's previous ANA titre was unknown, and so far, it has not been investigated whether COVID-19 can induce such antibodies (as described in other viral disease⁸). Infectious causes of livedo including HIV, mycoplasma pneumonia, syphilis, Legionella pneumophila, influenza A/B, RSV and hepatitis B/C were negative. During 8 days, oxygen, acetaminophen, hydroxychloroquine and low-molecular weight heparin in preventive dosing were administered. After discharge, livedo fluctuated, but progressively weaned. At 3 weeks follow-up, inflammatory parameters were normal (besides insignificantly elevated ferritin), while the patient still experienced slight dyspnoea on exertion.

Livedo reticularis describes a regular, lace-like network of non-fixed, dusky patches forming complete rings surrounding a

pale centre.⁹ This clinical picture is caused by constriction of central arterioles and subsequent peripheral venodilation.⁹ LR is rarely associated with underlying diseases. It is mostly seen in healthy young woman as a physiological reaction triggered by cold-induced vasospasms and is then named cutis marmorata.⁹ When LR is not influenced by cold exposure, it is called primary LR.⁹ A congenital form is referred to as cutis marmorata telangiectatica congenita.⁹ When livedo presents as a non-symmetric, localized, mostly unilateral and irregular network with broken rings, it is named livedo racemosa (LRC).⁹ LRC is associated with more significant reduction in blood flow caused by protracted arteriolar vasospasm, thrombosis and/or hyperviscosity.

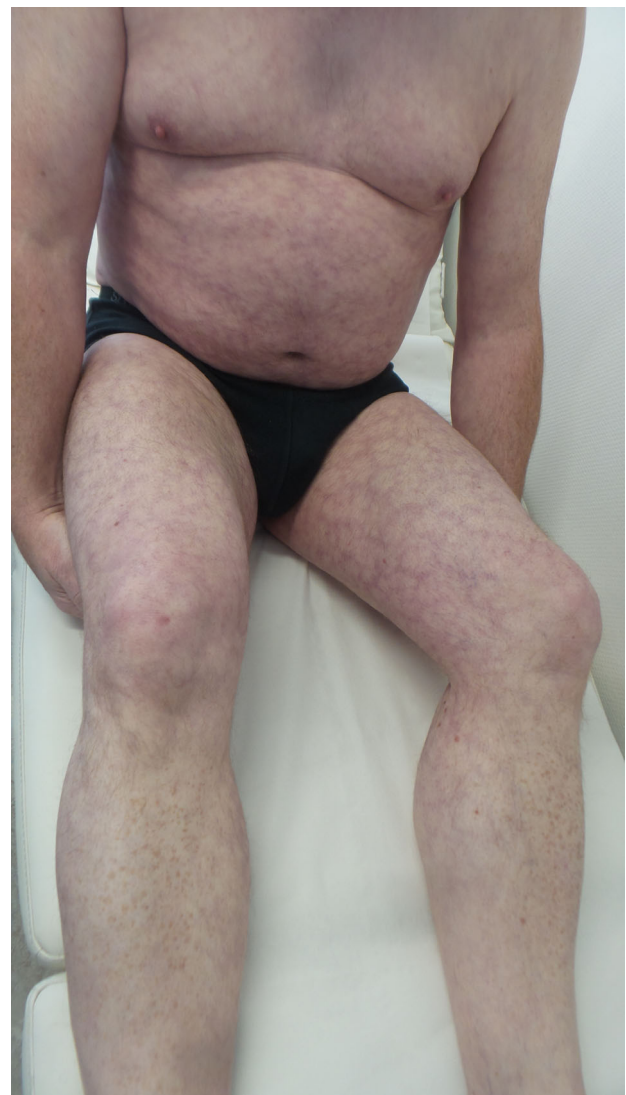


Figure 1 Symmetric regular lace-like network on the legs and trunk.

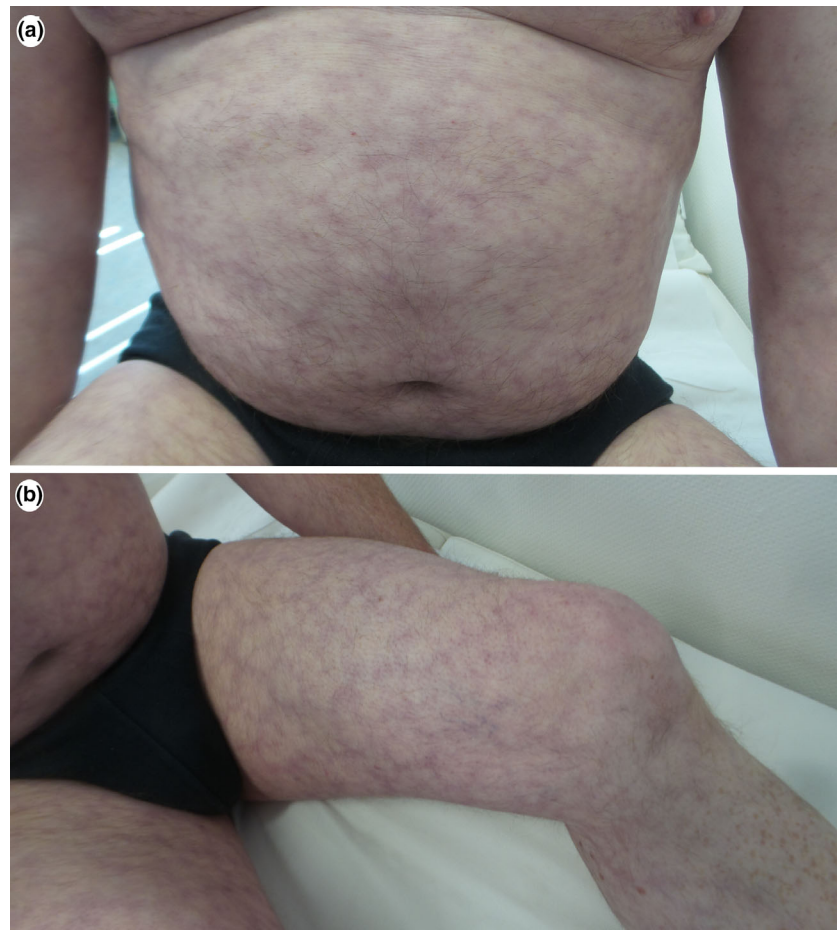


Figure 2 (a) Symmetric regular lace-like network on the trunk. (b) Symmetric regular lace-like network on the left leg.

LRC is always a red flag for an underlying pathology, such as vasculitis, autoimmune disease, infection, systemic disorders and neoplasia.⁹

Our patient had a first occurrence of a symmetric, fluctuating, unsuspecting-looking LR in the context of COVID-19, without other causes. Livedo was not blanching on pressure and typical clinical signs of vasculitis, like purpura, (asymmetric) LRC or skin necrosis were absent. COVID-19 can cause a procoagulant state,⁶ with small blood vessel occlusion. However, the absence of purpura and skin necrosis together with normal coagulation parameters makes thrombi unlikely as cause of the observed LR. This suggests the presence of low-grade vascular inflammation and vasodilation caused by direct SARS-CoV-2-infection of endothelial cells or vessel-associated smooth muscle cells. Both cell types express angiotensin-converting enzyme 2-receptor on their surface, the target of SARS-CoV-2-spike protein.⁶

In addition to previously reported two cases of asymmetric/unilateral and transient livedo,¹⁰ our case identifies a symmetric, fluctuating, relapsing, non-blanching LR as a warning sign for COVID-19. If symmetric LR occurs for the first time in patients

without any risk factors, it warrants the search for underlying pathology, including COVID-19.

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Conflicts of interest

There is no conflict of interest to disclose.

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Cutaneous manifestations in SARS-CoV-2 infection (COVID-19): a French experience and a systematic review of the literature

Editor

Skin manifestations have been increasingly reported in the setting of COVID-19. However, their incidence and presentation are debated, and the role, direct or indirect, of SARS-CoV-2 in their pathogenesis has yet to be determined.

In this work, we aimed to analyse our experience in a French referral centre and to perform a systematic review of the literature to evaluate the incidence and prognosis of cutaneous lesions observed in COVID-19 patients.

Cutaneous manifestations were assessed in COVID-19 patients admitted to Cochin Hospital (Paris, France) between 16 March and 27 April 2020. Seven hundred and fifty-nine confirmed moderate-to-severe COVID-19 cases were diagnosed in our institution. Eight patients (1%, six males, two females, mean age 55.6) presented with skin lesions, mainly disseminated maculopapular exanthema, but also digitate papulosquamous rash (reported in Ref.1), herpes recurrence, papulovesicular rash and

Grover's disease. The mean delay between respiratory/systemic and dermatological signs was 13 days.

Our systematic review of the literature identified 56 articles (including our series) evaluating 1020 patients (Table 1, WHOLE cohort) between 1 December 2019 and 9 of May 2020.^{2–10} Diagnosis of COVID-19 infection was confirmed in 47% of patients (Table 1, CONFIRMED cohort). The female-to-male ratio was 1.1 in both cohorts. Mean ages were 42 and 48 in the WHOLE and CONFIRMED cohorts, respectively. Rashes were the most frequent manifestations (54% and 70% in the WHOLE and CONFIRMED cohorts, respectively). These rashes were erythematous maculopapular/morbilliform, urticarial/annular, vesicular/varicelliform or petechial/purpuric by order of frequency. Trunk was the preferential localization of rashes. Other cutaneous manifestations included chilblains in 34% patients in the WHOLE cohort, but in only 11.5% cases in the CONFIRMED cohort. Digital necrosis was more frequently reported in the CONFIRMED cohort (11.5% vs. 5%). Transient livedo was uncommon (1%). About 70% of all patients experienced pruritus. Other symptoms were burning and pain.

The mean delay between the onset of respiratory/systemic symptoms and cutaneous manifestations was around 6.8 days in both cohorts. In some cases, rashes preceded the occurrence of systemic symptoms. When mentioned, chilblains appeared most frequently as a late manifestation. The mean duration of skin lesions was 9 days in both cohorts.

We retrieved six series, including ours, in which the numbers of both infected patients and patients with skin signs were available.^{4,6,7,9,10} Cutaneous lesions were observed in 38 patients over 2199 COVID-19 cases. Therefore, the mean incidence of cutaneous manifestations in COVID-19 patients was 1.7% (Fig. 1a).

Besides, we investigated whether cutaneous manifestations could correlate with COVID-19 severity. Therefore, we analysed severity criteria [hospital admission, pneumonia, transfer to Critical Care Unit (CCU), death] in patients of the WHOLE cohort with rashes or chilblains. In patients with rashes, severity was found in 64% of cases and death in 2%, while it was respectively found in 5% and 0% patients with chilblains. We found a statistically significant association between pneumonia, hospitalization, transfer to CCU or death and the occurrence of a rash as compared to chilblains (Fig. 1b).

The incidence of skin signs during COVID-19 is variable in the literature, ranging from 0.2% in China to 20% in North Italy. Our literature analysis indicated that the worldwide incidence is low, around 1–2%, as we observed in our hospital. Skin lesions were dominated by rashes and chilblains, that seem to present opposite prognosis. However, rashes could not always be discriminated with drug-induced exanthema. Likewise, chilblains pathogenesis in the setting of COVID-19 remains poorly understood and its relationship with SARS-CoV-2 is still unclear. Importantly, in our systematic review of the literature,