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COVID-19: Important Updates and Developments
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Cutaneous leukocytoclastic vasculitis secondary to COVID-19 infection leading to extensive skin necrosis

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Abstract A wide range of extrapulmonary manifestations in patients with COVID-19 has been reported during the ongoing pandemic, thus making the clinical spectrum of this new disease very heterogeneous. While COVID-19-associated vasculitis and vasculopathy have been described, cutaneous leukocytoclastic vasculitis (cLcV) due to SARS-CoV-2 has rarely been reported, and if it has, with relatively mild courses. We present the case of a 93-year-old man who, after having survived classic COVID-19 infection, developed a fulminant cLcV leading to extensive skin necrosis and tissue damage that resulted in his death. Considering the negative workup for other triggers of vasculitis, we find that cLcV is a secondary manifestation of COVID-19, even though SARS-CoV-2 polymerase chain reaction in the skin biopsy was not present in the tissue. We hypothesize this by providing a pathophysiologic rationale (eg, SARS-CoV-2-induced endotheliitis, complement activation, and interleukin 6 dominant intra- and perivascular inflammation).

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Introduction

COVID-19 is mainly known for its pulmonary manifestations, but with time, it has become evident that COVID-19 can affect nearly any organ, thereby exhibiting a broad clinical spectrum of signs and symptoms. Cutaneous manifestations of COVID-19 have been recently reviewed and classi-

fied.^{1,2} Whereas COVID-19-associated vasculitis and vasculopathy have repeatedly been described,^{3,4} cutaneous leukocytoclastic vasculitis (cLcV) due to SARS-CoV-2 has rarely been reported, and if it has, with relatively mild courses.⁵⁻⁹ We present a patient with initially mild COVID-19 infection who developed a fulminant cLcV that led to extensive skin necrosis and tissue damage contributing to his death.

Our patient

A 93-year-old man with a history of peripheral artery disease, chronic renal failure, and arterial hypertension presented to our emergency department with extremely

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Fig. 1 Evolution of cutaneous findings on the legs and feet. (A) Confluent palpable purpuric papules. (B) Demarcating, hemorrhagic, partly necrotic lesions. (C) Dry gangrene.

painful and itchy skin lesions on the left foot. These lesions had appeared the previous day and quickly spread to his legs in the next few days. He had tested positive for SARS-CoV-2 eight days prior. He had slight weakness. He had taken sartan, thiazide, aspirin, pravastatin, and trazodone for some time.

On physical examination, he presented with livid-erythematous, partly purpuric macules and papules on the legs, hands, and periumbilical area. This progressed within the next few days to having sharply demarcated, hemorrhagic papules with interspersed blisters (Fig. 1A, B). There was no mucosal involvement. His legs, feet, and hands were swollen, and the popliteal pulses were palpable in contrast to both pedal pulses. He was afebrile but quite weak. A nasopharyngeal swab for SARS-CoV-2 polymerase chain reaction (PCR) (1,340 c/mL) was slightly positive but became negative two days later.

Our initial differential diagnoses included stasis/congestive purpura, small vessel vasculitis, progressive pigmented purpura, acetaminophen-induced cutaneous drug eruption, and a paravirtual exanthema in the context of COVID-19.

Laboratory tests were remarkable for a neutrophilic leukocytosis with lymphopenia, elevated C-reactive protein (276 mg/L), impaired renal function with a creatinine of 225 $\mu\text{mol/L}$ (patient baseline 150 $\mu\text{mol/L}$), high lactate dehydrogenase (392 U/L), increased interleukin 6 (IL-6) level (107 ng/L) and positive IgG and IgM Nucleocapsid antibodies

to SARS-CoV-2 (66.500 COI, quantified with Immunoassay Elecsys [Roche Diagnostics, Indianapolis, IN]). The quantitative determination of SARS-CoV-2 by PCR in the plasma remained negative.

A vasculitis workup included ANA, ENA, ANCA, anti-Cardiolipin, anti-beta2 GP I antibodies, anti-streptococcal antibodies, and cryoglobulins CH50, complement C3, C4, and serology for syphilis, HIV, HBV, and HCV were non-reactive. A highly elevated D-dimer (13.64 $\mu\text{g/mL}$) without changes in the other coagulation markers suggested COVID-19-associated coagulopathy.¹⁰ An urinalysis revealed minimal, non-glomerular proteinuria and signs of tubular injury.

A chest CT scan exhibited typical patterns of COVID-19 pneumonia in only a small part of the lung parenchyma (9%), most likely reflecting the residual disease after documented COVID-19. Doppler ultrasonography of the lower extremity showed preserved microperfusion and no evidence for venous thrombosis.

A skin biopsy showed the classic features of cLcV with diffuse leukocytosis, fibrin deposition, obliteration of vessels, and extravasated red blood cells (Fig. 2). Direct immunofluorescence tests for IgA, IgG, IgM, and C3 were negative, as was SARS-CoV-2 PCR in the skin biopsy.

There was diffusely severe pain in the legs and a rapid rise of creatine kinase up to 2831 U/L. The MRI of the lower extremity demonstrated muscle edema pronounced in the distal region. A muscle biopsy did not show vasculitis, myositis,

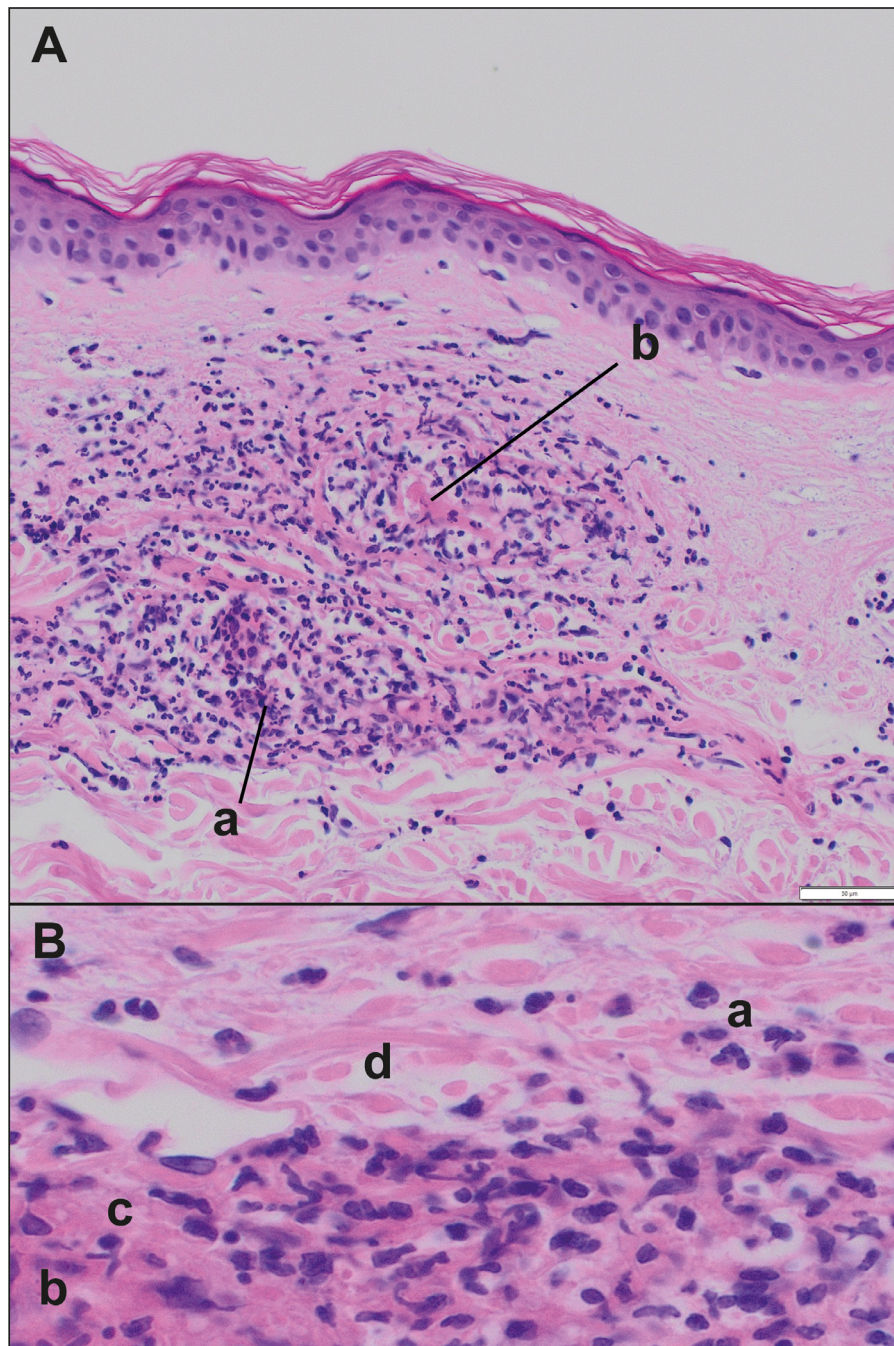


Fig. 2 Histopathologic findings. Skin biopsy showed cutaneous leukocytoclastic vasculitis with diffuse leucocytoclasia (**a**), obliteration of small cutaneous vessels (**b**), fibrin deposits (**c**), and extravasation of erythrocytes (**d**). Hematoxylin-eosin staining at 100 × (**A**) and 400 × (**B**) magnification.

or the presence of SARS-CoV-2 (negative PCR). There were no signs or symptoms suggesting the involvement of other organs due to the vasculitis were present. Acute, chronic kidney failure was interpreted to be pre-renal with consecutive tubular necrosis.

For the suspected small vessel vasculitis and a possible severe drug eruption, systemic corticosteroids were immediately started on admission with intravenous methylpred-

nisolone (250 mg for one day), followed by oral prednisone (1 mg/kg/d), after the histologic confirmation of vasculitis.

Due to clinical worsening with confluent livid-necrotic macules and hemorrhagic bullae, with extension to the proximal aspect of the extremities, resulting in extensive necrosis on the legs, we escalated the therapy after five days again to intravenous methylprednisolone (125 mg daily for three days). Additionally, in consideration of this rapid de-

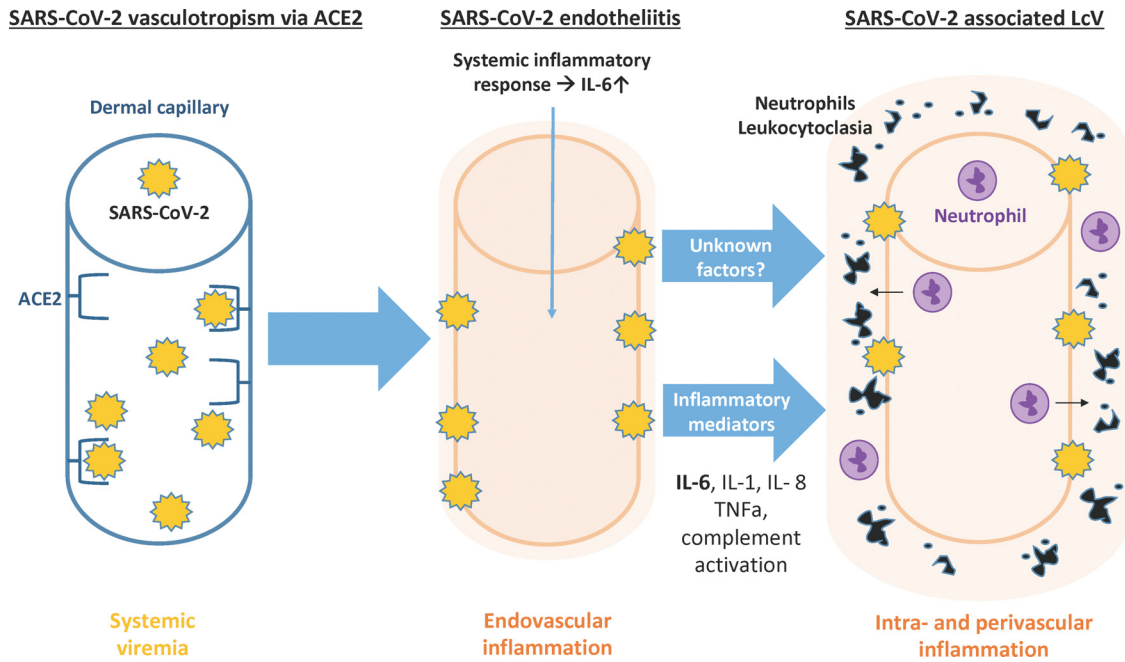


Fig. 3 Hypothetical pathophysiological mechanism of SARS-CoV-2-associated cutaneous leukocytoclastic vasculitis (cLcV).

terioration with wide necrosis, we postulated an excessive formation of "microthrombi" in the skin's microcirculation.

Screening for thrombophilia yielded a heterozygous Factor V Leiden mutation. Subsequently, we intensified the treatment with dalteparin in a subtherapeutic range, followed by apixaban (2.5 mg twice daily). The antiplatelet therapy with aspirin was continued. He had used clobetasol propionate cream since admission.

His overall condition stabilized (Fig. 1C) so that the systemic corticosteroids could be slowly tapered over ten weeks; however, he developed extensive dry gangrene of his legs and feet, but he declined amputation. He was discharged to a rehabilitation facility in a lessened physical condition one month later. Unfortunately, his decline continued with increasing gangrene and renal failure. Following palliative care, he died seven weeks after the initial diagnosis of COVID-19 infection.

Discussion

COVID-19 has been associated with various cutaneous manifestations.^{1,2} Reports on cLcV secondary to COVID-19 infection are, however, scarce.⁵⁻⁹ In the reported cases, patients ranged from 29 years of age to 83, all developed cLcV in the course of the acute infection with fever or respiratory signs, and clinical improvement with gradual resolution of the skin lesions occurred 2-3 weeks after starting systemic or topical corticosteroids. Another severely ill patient with COVID-19 had developed generalized purpuric eruptions on day 35 postadmission.¹¹ Like our patient, his initial skin

lesions resembled a drug eruption rather than classic LcV, which was unexpectedly found by lesional biopsy. The authors hypothesized that COVID-19-related endothelial damage and vasculopathy changes might have contributed to LcV and the patient's skin lesions, respectively.¹¹

The skin lesions appeared when nasopharyngeal PCR for SARS-CoV2 was still positive in our patient. Considering the negative workup for other triggers of vasculitis, we considered the cLcV as a secondary manifestation of COVID-19, even though SARS-CoV-2 PCR in the skin biopsy was negative. One limitation of our qPCR assay that was applied to identify SARS-CoV-2 in the skin biopsy is that an RNA concentration of 15 ng is required. In our patient, the concentration of the isolated RNA may have been too low to achieve a positive test result (2 ng only).

The mechanisms by which SARS-CoV-2 induces cLcV are unclear. So far, in the other cases of cLcV secondary to COVID-19, the vasculitis might have been due to the immune response against viral antigen deposition with involvement of ACE2 or as a result of a cytokine storm with primarily IL-6 elevation. Based on previous assumptions and in consideration of the absence of immune complexes (negative direct immunofluorescence) in our case, we postulate that the recruitment of inflammatory cells such as neutrophils and their leukocytoclasia may be the consequence of the endothelial cell inflammation and dysfunction described in patients with COVID-19 (Fig. 3).³ It is known that SARS-CoV-2 targets the vascular endothelium of various organs, including the skin, primarily via the ACE2.¹² The resulting endotheliitis is in turn enhanced and sustained by complement activation and other immune mediators, including cytokines.³

Our patient had very high IL-6 levels at admission. This chemokine plays an essential role in the cytokine storm with ensuing hyper inflammation and, therefore, in the pathology of COVID-19, where elevated blood levels have been associated with poor outcomes¹³ and the need for mechanical ventilation.¹⁴ Blocking this inflammatory IL-6 pathway may prevent disease progression.¹⁵ A rise in IL-6 may have also been a determining factor for the onset of the cLcV; however, it remains unclear why a patient can be affected by a vasculitis limited to the skin after a mild COVID-19 and without previous or simultaneous pulmonary manifestations. Cutaneous vasculitis-like lesions, in addition to systemic venous and arterial thromboembolism and other vasculopathy features, mainly develop in adults with severe or critical COVID-19 pneumonia.⁴ Different mechanisms underlying the cutaneous disease are proposed for these patients, including a small vessel thromboembolic disease due to severe illness, hypoxemia and RNAemia, viral dissemination with direct systemic endothelial infiltration, and resulting endotheliitis, complement activation, and type I IFN disablement.⁴

Another interesting point of our case report is the severe course with progression to extensive skin necrosis, which might reflect an unusual and exceptional complication of COVID-19. Necrotic skin lesions are an example of the possible vascular damage due to SARS-CoV-2. They may occur in 6% of patients with cutaneous disease related to COVID-19 and are associated with older age and increased disease severity.² In our patient, the unfavorable evolution may be explained by the presence of additional risk factors, including older age, arterial hypertension, peripheral artery disease, and a heterozygous Factor V Leiden mutation. In the setting of a COVID-19-associated coagulopathy, this latter element has played a role in the aggravation of the skin manifestations, leading to an intensification of the small vessel thromboembolic disease. Consequently, we suggest performing screening for thrombophilia in the context of a COVID-19 infection if the enhanced coagulation activity is suspected.

Conclusions

cLcV may represent one of the several types of cutaneous manifestation of COVID-19 in patients of all ages. Our case highlights how a COVID-19 infection with an initially mild presentation without severe pneumonia then developed a critical illness resulting from non-pulmonary manifestations. Patients with risk factors for severe disease who present with

mild COVID-19 manifestations and without lung involvement should be monitored even after virus clearance.

Disclosures

No external funding sources were involved in this case report. The authors declare that the work was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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