The clot thickens with COVID-19 and cryofibrinogenemia: A thought-provoking association

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INTRODUCTION

Cryofibrinogenemia (CF) is a rare condition of the plasma characterized by cryoprecipitation of abnormal protein complexes, sometimes resulting in thrombotic vasculopathy.[1] CF may be essential (primary) or secondary to neoplastic, autoimmune, or infectious diseases.[1] We present a case of livedoid vasculopathy (LV) due to secondary CF associated with COVID-19 and recrudescence in the setting of a non–SARS-CoV-2 infection.

Abbreviations used:

CF: cryofibrinogenemia
Ig: immunoglobulin
LR: livedo reticularis
LV: livedoid vasculopathy

CASE REPORT

A 65-year-old woman with a history of trochanteric osteoarthritis and COVID-19 presented to a tertiary care facility with painful purpura. She had been diagnosed with COVID-19 7 months prior to presentation using nasopharyngeal polymerase chain reaction for SARS-CoV-2. Within 3 days of testing positive, she had manifested myalgias and purpuric macules on the nose, fingers, and legs, which resolved after steroid taper (Fig 1).

Seven months after the COVID-19 diagnosis, she was admitted to an outside hospital with 4 days of burning, pruritic purpura, and edema of her fingers, arms, and legs associated with chills, myalgias, and fever (up to 38.7 °C). She was given intravenous glucocorticoids because of the concern for IgA vasculitis and discharged the next day on a corticosteroid taper. Despite the administration of glucocorticoids, the pruritus and pain worsened, prompting her current presentation to a tertiary care hospital.

Examination revealed symmetric hemorrhagic bullae of both distal fingers, racemose purpura of both forearms, and dusky purpuric patches involving the nasal tip and both helices (Fig 2). Confluent erythemato-violaceous petechiae and livedoid purpura were present on the abdomen, chest, and extremities (Fig 2), notably sparing the intertriginous areas. Sublingual violaceous macules were evident.

A 4-mm punch biopsy revealed noninflammatory intravascular thrombosis of papillary dermal capillaries (Fig 3). Pertinent laboratory findings are detailed in Table I. Specifically, a nasopharyngeal polymerase chain reaction test for SARS-CoV-2 was negative; however, serum IgG antibodies were detected. Serum cryoglobulins were negative and plasma cryofibrinogens were positive after 48 hours of incubation. A repeat cryofibrinogen assay 8 days later was positive after 24 hours of incubation, confirming the diagnosis of CF.[1] An autoimmune process causing secondary CF was considered owing

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Fig 1. Livedoid vasculopathy and nasal purpura associated with COVID-19. Erythematous and purpuric patches with overlying petechiae of the dorsal aspect of the hand, fingers (**A**), and upper parts of the lower extremities (**B**) with areas of confluence. Purpuric patch along the nasal dorsum with incidental background erythematotelangiectatic rosacea (**C**). Source: Anonymous. 2020. *Patient documented livedoid vasculopathy and nasal purpura associated with SARS-CoV-2 infection*. Georgia, USA.

to an elevation in the antinuclear antibody titer and rheumatoid factor. However, these results lack diagnostic specificity, and no further laboratory, radiography, or clinical findings supported a definitive autoimmune or neoplastic diagnosis. Due to the strikingly similar clinical presentation with COVID-19 7 months previously and absence of other etiologies on diagnostic studies, CF was thought to be provoked by a non–SARS-CoV-2 viral infection. It was suspected, but not confirmed, that CF was etiologic of the initial racemose purpura during COVID-19 7 months previously.

The patient was anticoagulated with a high-standard heparin infusion, resulting in rapid improvement in pain, purpura, and petechiae. The patient was treated with gabapentin for a right ulnar sensory mononeuritis. She was discharged on hospital day 8 with apixaban and, incidentally, continued the prednisone taper that antedated her admission.

Nine days later, she developed recurrence of painless petechiae while on apixaban and tapering to lower steroid doses. However, there was no evidence of deep-tissue ischemia or digital necrosis on examination (Fig 4). The patient was readmitted, administered glucocorticoids, and continued apixaban, which improved the petechiae. She was discharged on hospital day 3 with apixaban and prednisone taper. Follow-up laboratory tests and visits extending 7 months post-CF diagnosis did not demonstrate any signs or symptoms of connective tissue disease or cytopenia to suggest myeloid dyscrasia.

DISCUSSION

We describe secondary CF-induced LV associated with COVID-19 and recrudescence, likely from a non–SARS-CoV-2 viral infection. Other cases of recrudescent CF related to infectious diseases include a case of LV in the setting of hepatitis C with recurrence of skin lesions[2] and a case of giardiasis with relapse of CF, without skin lesions, after cessation of metronidazole.[3] Our literature review revealed no other infectious disease-associated cases of CF with recurrence. CF recrudescence is primarily reported in essential CF associated with subsequent development of lymphoma.[4]

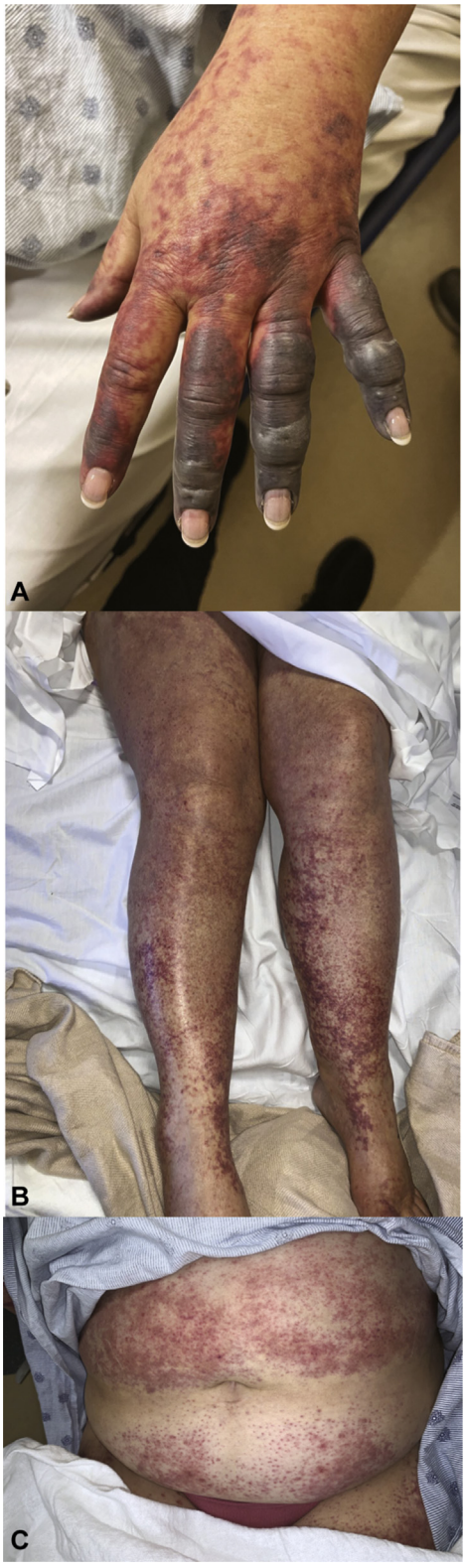

Fig 2. Severe recrudescent livedoid vasculopathy with hemorrhagic bullae of the digits during a non-SARS-CoV-2 viral infection. **A,** Dusky purpura of the left hand with distal hemorrhagic bullae. **B** and **C,** Both extremities and abdomen with confluent erythemato-violaceous macules and petechiae, notably sparing the skinfolds. Source: Salame, Nicole; Cheeley, Justin T. 2021. *Severe recrudescent livedoid vasculopathy with hemorrhagic bullae during a non-SARS-CoV-2 viral infection*. Georgia, USA.

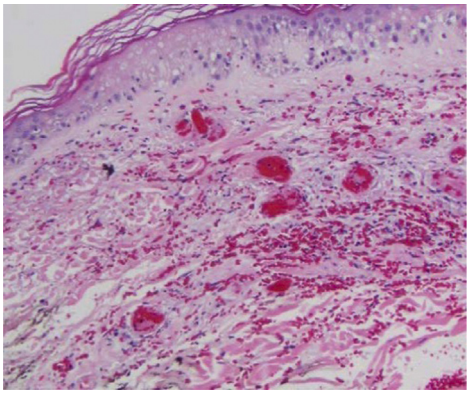

Fig 3. A 4-mm punch biopsy of the thigh to the level of the subcutis under hematoxylin and eosin stain. The epidermis exhibited mild spongiosis with adjacent necrosis. Within the subjacent dermis, there were microthrombi affecting small vascular channels with associated extravasated erythrocytes. Although a sparse, mixed inflammatory infiltrate was present, well-developed vasculitis was not identified. Source: Anonymous. 2021. *4 mm punch biopsy of a 65-year-old female with cryofibrinogenemia manifesting as a cutaneous racemose purpura*. Georgia, USA.

Individual dermatologic manifestations of CF and COVID-19 are well documented, and although not previously related, there is clinical overlap. Cutaneous findings in CF include urticaria, livedo reticularis (LR), purpura, and ulcerations.[1] Inflammatory dermatoses, such as urticarial or morbilliform exanthems, as well as vasculopathic features, including purpura and perniosis, are associated with COVID-19.[5] Both LR and LV have been described in association with COVID-19; eg, relapsing LR and worsening of previously controlled LV.[6,7] Neither patient in these case reports were tested for CF; thus, an association with CF cannot be confirmed or refuted.

A study from Spain was the first to associate skin findings in CF with SARS-CoV-2, showing a high prevalence of CF in patients presenting with chilblains during the peak of the initial COVID-19 outbreak.[8] That study and the current case, along with the evidence of similar cutaneous findings between COVID-19 and CF, support the possibility that cases of SARS-CoV-2 induced CF are being missed. The logistic challenges of obtaining and

Table I. Selected laboratory studies from patient evaluation—laboratory results (normal range)

Laboratory studies	Laboratory results (normal range)
White blood cell count	8.6 × $10^3/\mu$L (4.0 × $10^3/\mu$L - 10.0 × $10^3/\mu$L)
Hemoglobin	12.5 g/dL (11.4-14.4 g/dL)
Hematocrit	36.7% (33.3%-41.4%)
Platelets	374 × $10^3/\mu$L (150 × $10^3/\mu$L - 400 × $10^3/\mu$L)
Erythrocyte sedimentation rate	16 mm/h (1-30 mm/h)
Prothrombin time	11.3 s (9.4-12.5 s)
Activated partial thromboplastin time	22.5 s (25.1-36.5 s)
International normalized ratio	1.00 (>5.00)
Fibrinogen activity level	185 mg/dL (200-393 mg/dL)
D-dimer	9335 ng/mL (≤574 ng/mL)
DRVVT screen ratio	1.32 (≤1.30)
DRVVT screen/confirm ratio	1.20 (≤1.24)
Prothrombin fragment 1.2	609 pmol/L (65-288 pmol/L)
Thrombin antithrombin complexes	10.5 μg/L (≤5.5)
Fibrin monomer	33 μg/mL (≤6.0)
Anticardiolipin IgM	23.4 CU (≤20.0 CU)
Anticardiolipin IgG	<2.6 CU (≤20.0 CU)
Anti-β-2-glycoprotein 1 IgM	6.7 CU (≤20.0 CU)
Anti-β-2-glycoprotein 1 IgG	<6.4 CU (≤20.0 CU)
Antiphosphatidylserine IgM	13.9 MPS (≤21.9 MPS)
Antiphosphatidylserine IgG	3.7 GPS (≤15.9 GPS)
Serum protein electrophoresis	Normal without paraprotein
Immunofixation	Polyclonal immunoglobulins without paraprotein
C-reactive protein	6.1 mg/L (≤10.0 mg/L)
Cryofibrinogen	Positive after 48 h at 4 °C —abnormal
Cryoglobulin	Negative
Free K/Λ ratio	0.76 (0.26-1.65)
Urine protein electrophoresis	No paraproteins present
Urine immunofixation	No paraproteins present
Antinuclear antibody titer	1:640 - abnormal
Rheumatoid factor	31.0 IU/mL (0.0-3.5 IU/mL)
Cyclic citrullinated peptide IgG	<0.5 u/mL (0.0-2.9 u/mL)
Anti-neutrophil cytoplasmic IgG	<1:20 (<1:20)
Extractable nuclear antigen screen with reflex	Negative
C3 complement level	132 mg/dL (81-157 mg/dL)
C4 complement level	13 mg/dL (13-39 mg/dL)
Haptoglobin	160 mg/dL (32-197 mg/dL)
Lactate dehydrogenase	320 u/L (140-271 u/L)
SARS-CoV-2 by PCR	Negative
SARS-CoV-2 IgG	Positive

CU, Cubic unit; *GPS,* phosphatidylserine IgG; *Ig,* immunoglobulin; *IU,* international unit; *MPS,* phosphatidylserine IgM; *PCR,* polymerase chain reaction; *U,* unit.

transporting warmed blood to a laboratory capable of measuring cryofibrinogens while donning and doffing personal protective equipment is one possible explanation.

There is mounting evidence of cytokine storm-provoked endothelial dysfunction and vascular thrombosis in the setting of COVID-19.[9] The pathogenesis of the cytokine storm induced by SARS-CoV-2 resulting in endothelial dysfunction may inform the immunologic stimulus for the development of secondary CF. For this reason, CF should not only be considered in patients who present with LR or LV but especially in association with COVID-19 or another viral illness. Further studies are needed to delineate any association between CF and SARS-CoV-2.

One case series suggested that secondary CF can be treated similarly to essential CF with immunosuppressants and anticoagulants.[4] This case further supports the role of anticoagulants in secondary

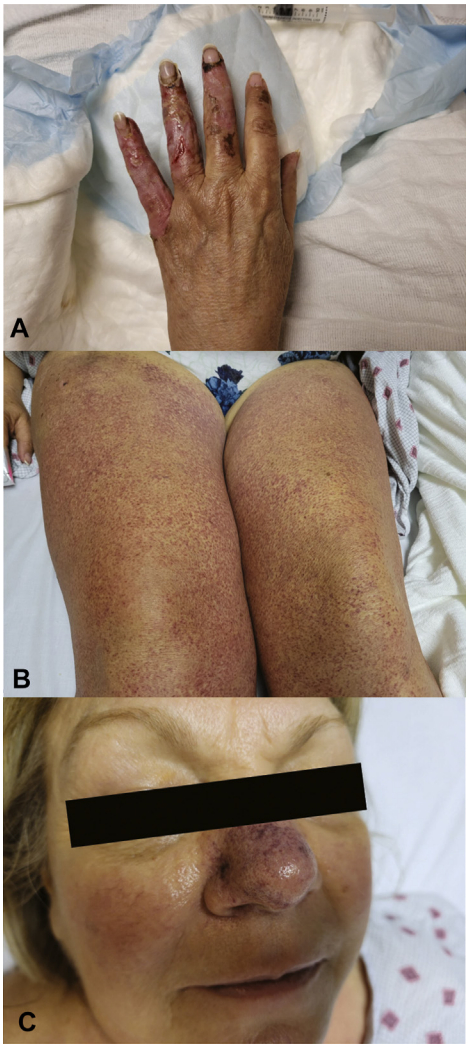

Fig 4. Mild livedoid vasculopathy and nasal purpura with convalescing desquamation of the digits in the setting of recrudescence after a non-SARS-CoV-2 viral infection while on anticoagulation. **A,** Digital erosions, yellow necrotic slough, and hemorrhagic crusts. **B,** Mild petechial rash on both lower extremities. **C,** Nose with a faded purpuric patch. Source: Cheeley, Justin T. 2021. *Secondary cryofibrinogenemia induced livedoid vasculopathy recrudescence after a non-SARS-CoV-2 viral infection while on anticoagulation*. Georgia, USA.

CF. Although our patient's petechiae more rapidly and durably cleared with heparin compared with apixaban, the tissue pain and infarction resolved. This patient outcome along with the convenience, tolerability, and lack of laboratory monitoring make direct oral anticoagulants an attractive and potential alternative treatment for LV due to CF. Further studies are needed to determine the role, timing, class, and duration of immunosuppressants and anticoagulants in the management of essential and secondary CF.

Conflicts of interest

None disclosed.

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