Perniolike lesions and coagulopathy in a patient with COVID-19 infection

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INTRODUCTION

Perniolike lesions of the toes that are caused by coronavirus disease 2019 (COVID-19), known as COVID toes, have recently been reported around the world.[1-3] The etiology and optimal management remain largely unknown. We present the case of a patient with COVID toes in association with acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, in whom a comprehensive hematologic evaluation revealed a striking elevation of factor VIII activity and von Willebrand factor level, suggesting that endothelial dysfunction may be associated with this cutaneous manifestation of coronavirus infection.

Abbreviations used:

COVID-19:	coronavirus disease 2019
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2

CASE REPORT

A 77-year-old woman with history of hypertension, Alzheimer dementia, and adrenal insufficiency was admitted to the hospital for lethargy and acute kidney injury in the setting of a urinary tract infection with *Enterococcus faecalis*. At admission, a polymerase chain reaction test result for SARS-CoV-2 was negative. She was afebrile and vital signs were normal on room air. She was treated with appropriate antibiotics and intravenous fluids, with restoration of baseline kidney function and mental status, and was preparing for hospital discharge when a repeated polymerase chain reaction test was positive for SARS-CoV-2. She did not exhibit any respiratory symptoms and a chest radiograph showed no focal findings. At that time, inflammatory markers were notable for elevated levels of C-reactive protein (10.6 mg/L, normal <3 mg/L), ferritin (587 ng/mL, normal <150 ng/mL), D-dimer (1.49 mg/L, normal <0.77 mg/L), and fibrinogen (501 mg/dL, normal 136-464 mg/dL). Electrolyte levels, complete blood cell count, prothrombin levels, partial thromboplastin time, and international normalized ratio were within normal limits. A cytokine panel result including interleukin 2, 4, 5, 8, 12, 13, and 17; interferon γ; tumor necrosis factor α; and interleukin 2R was unremarkable. She did not meet institutional criteria for hydroxychloroquine or tocilizumab treatment. Six days after the positive polymerase chain reaction test, she developed violaceous patches, some retiform, involving the bilateral aspect of the plantar and dorsal toes and feet (Fig 1). The rash was nontender and there was no involvement of skin elsewhere. The differential diagnosis included perniolike lesions and early/evolving retiform purpura associated with COVID-19.

Laboratory evaluation results, including antinuclear antibody, C3, C4, cryofibrinogen, and total complement, were negative. Repeated cytokine panel result was notable for elevation of interleukin 2R level (1565 pg/mL, normal <1033 pg/mL). A

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Fig 1. Appearance of perniolike rash on dorsal and plantar aspects of the feet.

hypercoagulability evaluation was consistent with a prothrombotic state, with elevated levels of thrombin-antithrombin complexes (11.3 μg/L, normal <4 μg/L), factor VIII activity (430.8%, normal 66%-143%), von Willebrand factor antigen (612%, normal 62%-175%), von Willebrand factor activity (>390%, normal 58%-163%), and plasminogen activator inhibitor 1 activity (96 ng/mL, normal 4-43 ng/mL). There was no evidence of lupus anticoagulant. The magnitude of elevation in von Willebrand factor and factor VIII was much greater than that in other patients with mild SARS-CoV-2 in our hospital and more similar to that observed in patients with severe SARS-CoV-2 at our hospital who were receiving mechanical ventilation because of acute respiratory distress syndrome (data not shown).

Therapeutic anticoagulation was considered, but the patient continued to receive prophylactic low-molecular-weight heparin, which had been started at hospital admission. The rash resolved during the subsequent 72 hours, and no thromboembolic events were reported at 1-month follow-up.

DISCUSSION

Perniolike lesions, or COVID toes, are emerging as a relatively common observation in association with the COVID-19 pandemic.[1-3] The etiology, timeline, and optimal management remain poorly understood. Recent articles by Manalo et al[3] and Parodi et al[4] appropriately discuss potential hematologic abnormalities that may be underlying cutaneous findings observed in COVID-19. Parodi et al[4] posed the important question of whether coagulopathy in COVID-19 patients is a manifestation of mild or severe antiphospholipid syndrome. Herein, in collaboration with hematology colleagues, we report a case of COVID toes with a benign clinical course, but with striking elevation in factor VIII activity and von Willebrand factor levels. SARS-CoV-2 has been detected in endothelial cells of COVID-19 patients and has been proposed to cause endothelial dysfunction and increased risk of thromboembolic disease.[5] Elevation of plasma von Willebrand factor level is an established marker of endothelial activation and injury, and is significantly associated with death in acute lung injury.[6] Our findings suggest that perniolike lesions may be associated with endothelial dysfunction, typically observed in critical illness and similar to that believed to occur in acute respiratory distress syndrome. However, the juxtaposition of a hypercoagulability profile typically observed in critical illness and a benign clinical course presented here highlights the complexity of the pathobiology of this disease manifestation. The factors that contribute to a benign course (eg, perniolike lesions) versus a severe coagulopathy[7,8] such as disseminated intravascular coagulation or pulmonary embolism are presently unknown. Although our report is limited by lack of histopathology, others have reported lymphohistiocytic perivascular inflammation and cutaneous microthrombi in association with COVID-19 infection.[9,10] We hope that this report, together with others, will inform larger studies and additional collaboration of dermatologists and hematologists to further elucidate the diagnosis, prognosis, and pathophysiology of cutaneous and systemic manifestations of COVID-19.

CONCLUSION

Herein, we describe a case of COVID toes in association with striking elevations in factor VIII

activity and von Willebrand factor level. Our findings suggest that endothelial dysfunction may be associated with perniolike lesions reported in cases of novel coronavirus infection. Further collaboration between dermatologists and hematologists may be critically important to advance our understanding of cutaneous manifestation of novel coronavirus infection and improve patient care.

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