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Goran Micevic, MD, PhD, Jens a Morris, MD, Alfred Ian Lee, MD, PhD, Brett A. King, MD, PhD

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Pernio-like lesions and coagulopathy in a patient with COVID-19 infection

1 Goran Micevic, MD, PhD, 2 Jensa Morris, MD, 3 Alfred Ian Lee, MD, PhD, 1 Brett A. King, MD, PhD
2 1 Yale Department of Dermatology, New Haven, CT 06520
3 2 Yale Department of Internal Medicine, New Haven, CT 06520
4 3 Yale Department of Medicine, Division of Hematology, New Haven, CT 06520
5 1*corresponding author:
6 Brett King, MD, PhD, 333 Cedar St, LCI 501, PO Box 208059, New Haven, CT 06510
7 Email: brett.king@yale.edu
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19 Introduction
Pernio-like lesions, or ‘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 SARS-CoV-2 infection, in whom a comprehensive hematologic workup revealed a striking elevation of factor VIII activity and vWF level, suggesting that endothelial dysfunction may be associated with this cutaneous manifestation of coronavirus infection.

Case Report

A 77-year-old woman with history of hypertension, Alzheimer’s 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 the time of admission, a PCR test 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 repeat PCR test was positive for SARS-CoV-2. She did not exhibit any respiratory symptoms and a chest X-ray had no focal findings. At that time, inflammatory markers were notable for elevation of CRP (10.6 mg/L, normal < 3), ferritin (587 ng/mL, normal <150), D-dimer (1.49 mg/L, normal <0.77), and fibrinogen (501, normal 136-464). Electrolytes, complete blood count, PT, PTT and INR were within normal limits. A cytokine panel including IL-2,4,5,8,12,13,17, interferon-γ, TNF-α and IL-2R was unremarkable. She did not meet institutional criteria for hydroxychloroquine or tocilizumab treatment. Six days after the positive PCR test, she developed violaceous patches, some retiform, involving the bilateral plantar and dorsal toes and feet (Figure 1). The rash was non-tender and there was no involvement of skin elsewhere. The
differential diagnosis included pernio-like lesions and early/evolving retiform purpura associated with COVID-19.

Laboratory evaluation including ANA, C3, C4, cryofibrinogen and total complement was negative. Repeat cytokine panel was notable for elevation of IL-2R (1565 pg/ML, normal<1033). A hypercoagulability evaluation was consistent with a pro-thrombotic state, with elevated levels of thrombin-antithrombin complexes (11.3 mcg/L, normal<4), factor VIII activity (430.8%, normal 66-143%), von Willebrand factor (vWF) antigen (612%, normal 62-175%), vWF activity (>390%, normal 58-163%), and plasminogen activator inhibitor-1 (PAI-1) activity (96 ng/mL, normal 4-43). There was no evidence of lupus anticoagulant. Notably, the magnitude of elevation in vWF and factor VIII was much greater than other mild SARS-CoV-2 patients in our hospital and more similar to those observed in severe SARS-CoV-2 patients at our hospital on mechanical ventilation due to acute respiratory distress syndrome (data not shown).

Therapeutic anticoagulation was considered, but the patient remained on prophylactic low molecular weight heparin, which had been started at the time of her hospital admission. The rash resolved over the subsequent 72 hours, and no thromboembolic events were reported at 1-month follow-up.

Discussion

Pernio-like 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 seen in COVID-19. Parodi et al. (4) posed the important
question whether coagulopathy in COVID-19 patients is a manifestation of mild or severe APS. 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 vWF levels. SARS-CoV2 has been detected in endothelial cells of COVID-19 patients, and proposed to cause endothelial dysfunction, and increased risk of thromboembolic disease(5). Elevation of plasma vWF is an established marker of endothelial activation and injury, and is significantly associated with death in acute lung injury (6). Our findings suggest that pernio-like lesions may be associated with endothelial dysfunction, typically seen in critical illness, and similar to that believed to occur in acute respiratory distress syndrome (ARDS). However, the juxtaposition of a hypercoagulability profile typically seen in critical illness, and a benign clinical course presented here highlight the complexity of the pathobiology of this disease manifestation. The factors that contribute to a benign course (e.g. pernio-like lesions), versus a severe coagulopathy (7, 8), such as disseminated intravascular coagulation or pulmonary embolism are presently unknown. While our report is limited by lack of histopathology, others have reported lymphohystiocytic perivascular inflammation, and cutaneous microthrombi in association with COVID infection(9, 10). We hope that this report, together with others, will inform larger studies and further 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 a striking elevations in factor VIII activity and vWF level. Our findings suggest that endothelial dysfunction may
be associated with pernio-like 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.

References


Figure Legends

Figure 1. Appearance of pernio-like rash on dorsal and plantar feet.
Abbreviations and acronyms

COVID-Coronavirus disease 2019, SARS-severe acute respiratory syndrome, CRP – C-reactive protein, IL-interleukin, PCR-polymerase chain reaction, ANA-antinuclear antibody, PT-prothrombin, PTT, INR -international normalized ratio, TNF- tumor necrosis factor.
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None.

Footnotes

None.

Conflict of interest

BAK is an investigator for Concert Pharmaceuticals Inc, Eli Lilly and Company, and Pfizer Inc. BAK is a consultant to and/or has served on advisory boards for Aclaris Therapeutics, Arena Pharmaceuticals, Bristol-Meyers Squibb, Concert Pharmaceuticals Inc, Dermavant Sciences, Eli Lilly and Company, and Pfizer Inc; he is on speaker’s bureau for Pfizer Inc, Regeneron and Sanofi Genzyme.