Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Reply to: "A dermatologic manifestation of COVID-19: Transient livedo reticularis"

To the Editor: I enthusiastically read the article by Manalo et al, "A dermatologic manifestation of COVID-19: Transient livedo reticularis."[1] The authors should be commended for quickly recognizing and reporting possible cutaneous findings of COVID-19.

With any emerging disease, we must integrate a rapidly evolving evidence base into our understanding of the illness. Although Manalo et al[1] postulate a potential etiology of livedo reticularis in COVID-19 involving low-grade disseminated intravascular coagulation, recent data suggest other mechanisms for vaso-occlusive findings in nonsevere infection. Disseminated intravascular coagulation is much less common in those with mild COVID-19 infection, affecting only 0.6% of survivors as opposed to 71.4% of nonsurvivors in one study.[2] Similarly, most reports of large-vessel thromboses and microemboli in COVID-19 are in those with severe illness. Supporting this observation is a retrospective study demonstrating that thromboprophylaxis has a mortality benefit in only patients severely ill with COVID-19 with a high sepsis-induced coagulopathy score.[3]

Although studies in mild disease are limited, these combined data suggest that disseminated intravascular coagulation and macrothromboses may be restricted to severe COVID-19 infections. This is not unexpected, given that severe infection is accompanied by features of the Virchow triad, including venous stasis in the setting of immobility, hypercoagulability as a result of cytokine storm, and endothelial cell dysfunction due to sepsis and inflammation. With this in mind, what then accounts for the vaso-occlusive phenomena that preferentially affect cutaneous small vessels in mild cases of COVID-19? Emerging data show several other potential factors may play a role in microthrombi formation in less severe disease.

Inflammation commonly predisposes patients to thrombosis. As demonstrated in a retrospective study, patients with severe COVID-19 have high levels of inflammatory cytokines, including interleukin 1β, 8, and 9, interferon-γ, and tumor necrosis factor-α, among others. Although less profoundly elevated than in severe illness, levels remain moderately elevated in nonsevere disease.[4] Many of these involved cytokines are thought to promote thrombogenesis, and even mild cytokine elevations in nonsevere disease could theoretically contribute to thrombosis.

Another potential reason for microthrombosis in nonsevere COVID-19 infection is due to the mechanism of viral entry into cells. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to bind angiotensin-converting enzyme 2 (ACE2), a transmembrane enzyme, allowing entry into the cell.[5] ACE2 binding results in decreased expression of ACE2, activation of the renin-angiotensin system, promotion of platelet aggregation, and thrombus formation. Because endothelial cells also express ACE2, SARS-CoV-2 may additionally cause direct endothelial dysfunction after binding to ACE2, leading to subsequent thrombosis.

In the setting of mild disease where profound coagulopathy is unlikely, mild elevations in prothrombotic cytokines and direct endothelial cell damage by SARS-COV-2 may theoretically contribute to the small-vessel occlusive phenomena noted in the skin. Other potential mechanisms include complement activation, antiphospholipid antibody production, and tissue factor expression on endothelial cells.

The balance between coagulation cascade activation and fibrinolysis in patients with COVID-19 is complex, and further studies may elucidate this delicate tug-of-war. Until further data are available, the skin appears to represent an innocent bystander in the prothrombotic milieu of SARS-CoV-2 infection.

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