TO THE EDITOR

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes mucocutaneous manifestations, including maculopapular eruptions, urticaria, and unusual acral vasculopathic rashes (pseudochilblains, pernio-like lesions) referred to as COVID toe. Cutaneous manifestations can occur in asymptomatic individuals, sometimes preceding COVID-19 symptoms, concurrent with COVID-19, or commonly after other COVID-19 symptoms (Freeman et al., 2020a; Seirafianpour et al., 2020). In a case series of 505 patients, 55% of the patients’ only symptoms were pernio-like lesions lasting a median of 14 days (Freeman et al., 2020b). The most common cutaneous rash morphologies in a registry of 716 patients associated with COVID-19 with dermatological manifestations were morbilliform (22%), pernio-like lesions (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%), and retiform purpura (6.4%) (Freeman et al., 2020a). Pernio-like lesions were common in patients with mild disease, and retiform purpura presented exclusively in hospitalized patients (Freeman et al., 2020a); these different manifestations are directly related to patient disease severity. Coronavirus particles were found in the cytoplasm of endothelial cells of the capillary and postcapillary venules of the upper dermis and secretory portion of eccrine units (Colmenero et al., 2020); this establishes SARS-CoV-2 infection in the affected tissues. The pathogenesis of COVID-19–associated cutaneous manifestations remains unknown. Other cutaneous lesions can result from SARS-CoV-2 infections reactivating latent viruses (Brambilla et al., 2020; Elsaie and Nada, 2020; Elsaie et al., 2020; Ferreira et al., 2020; Le Balc’h et al., 2020; Tartari et al., 2020; Xu et al., 2020). The majority of the observed mucocutaneous manifestations (maculopapular eruptions, urticaria, acral vasculopathic rashes, retiform purpura [late disease with likely wider dispersion], etc.) may have etiology associated with SARS-CoV-2–hyperactivated mast cells releasing histamine and other inflammatory molecules. With collaborators, I have previously proposed that mast cell hyperactivation contributes to COVID-19 symptoms and disease progression (Malone et al., 2021). As an alternative to the lesions representing a coagulation disorder or a hypersensitivity reaction, I propose that SARS-CoV-2 infection of endothelial cells and likely pericytes results in capillary vasoconstriction followed by vascular ischemia; this is followed by infiltrating lymphocytes and localized hyperactivation of mast cells releasing histamine and other inflammatory molecules. I propose that vascular ischemia and the released histamine are the most likely major initial components in the development of COVID-19–associated cutaneous manifestations. Released local histamine is also the likely major source of the itching associated with COVID-19 cutaneous manifestations (Shim and Oh, 2008). This hypothesis concerning cutaneous manifestations of vascular ischemia and the histamine released from activated mast cells likely extends to most viral-associated cutaneous manifestations, including Kawasaki disease and multisystem inflammatory syndrome in children and multisystem inflammatory syndrome in adults (Ricke et al., 2020). Mast cells can be activated by Fc receptor–bound antibodies binding to virions or possibly viral proteins. The SARS-CoV-2 nucleocapsid protein has been predicted to bind to the cyclooxygenase 2 (COX-2) promoter upregulating PTGS2/COX-2, resulting in elevated prostaglandin E2 levels (Yan et al., 2006). Elevated levels of prostaglandin E2 can cause the hyperactivation of mast cells (Morimoto et al., 2014). Another potential pathway for upregulating COX-2 includes the SARS-CoV-2 spike protein interacting with TNF-α–converting enzyme inducing TNF-α production such as observed for the SARS-CoV-1 spike protein (Haga et al., 2008); the NF-κB pathway is activated by inducing Iκβζ degradation (Wang et al., 2007). TNF-α stimulates COX-2 expression (Kim et al., 2018). COVID-19–associated cutaneous manifestations resolve after the immune system eliminates localized SARS-CoV-2–infected cells. Persistent infections can result in localized anoxia and possibly gangrene (Adekgibe et al., 2020; Novara et al., 2020).

Treatments are consistent with the mast cell hypothesis associated with preliminary reports of clinical efficacy in patients with COVID-19. On the basis of initial responses of patients with COVID-19 to famotidine, we proposed the mast cell hypothesis (Malone et al., 2021). Independently, montelukast (leukotriene receptor antagonist) (Khan et al., 2021), dexchlorpheniramine (HRH1 antagonist) (Morán Blanco et al., 2021), and cetirizine (HRH1) (Morán Blanco et al., 2021) were discovered to exhibit efficacy in patients with COVID-19 consistent with the proposed mast cell hypothesis. Combining COX-2 inhibition with celecoxib (Hong et al., 2020) with famotidine is demonstrating efficacy in patients with COVID-19 (Tomera et al., 2020a, 2020b). Aspirin, with possible roles in anticoagulation, mast cell stabilization, and COX-2 inhibition, also exhibits efficacy in patients with COVID-19 (Chow et al.,

Abbreviations: COX-2, cyclooxygenase 2; SARS-CoV, severe acute respiratory syndrome coronavirus
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2021; Osborne et al., 2021). Note that combining celecoxib with either dexamethasone or aspirin is contraindicated. It is possible that the observed efficacy from these treatments may be from alternative mechanism(s), including modulating neutrophil responses as an alternative to the proposed mast cell hypothesis. Case reports and/or case series evaluating responses of patients with COVID-19 with cutaneous manifestations receiving current standard of care compared with responses of matched patients receiving standard of care plus adjunctive therapy evaluating exemplar(s) from these proposed treatments (e.g., cetirizine and/or famotidine plus celecoxib) will inform follow-up studies if warranted.

Distribution statement
Data presented in this study are approved for public release. Distribution is unlimited.

Data availability statement
No datasets were generated or analyzed during this study.

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CONFLICT OF INTEREST
The author states no conflict of interest.

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