Hyperactivated Mast Cells Pathogenesis Hypothesis for COVID-19 Cutaneous Manifestations

JID Innovations (2021);**1:**100052 doi:10.1016/j.xjidi.2021.100052

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 E_2 levels (Yan et al., 2006). Elevated levels of prostaglandin E_2 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 I-κBα 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 (Adekiigbe 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

Accepted manuscript published online 23 August 2021; corrected proof published online 2 December 2021

Cite this article as: JID Innovations 2021;1:100052

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.

ORCID

Darrell O. Ricke: http://orcid/org/0000-0002-2842-2809

AUTHOR CONTRIBUTIONS

Conceptualization: DOR; Writing - Original Draft Preparation: DOR; Writing - Review and Editing: DOR

ACKNOWLEDGMENTS

The author acknowledges the Department of Defense, Defense Threat Reduction Agency, and the Joint Science and Technology Office of the Chemical and Biological Defense Program for their support under the Discovery of Medical countermeasures Against Novel Entities initiative. This material is based on work supported under Air Force Contract number FA8702-15-D-0001.

Disclaimer

Any opinions, findings, conclusions, or recommendations expressed in this material are those of the author and do not necessarily reflect the views of the United States Air Force.

CONFLICT OF INTEREST

The author states no conflict of interest.

Darrell O. Ricke[1,*]

[1]*Lincoln Laboratory, Massachusetts Institute of Technology, Lexington, Massachusetts, USA*

[*]Corresponding author
e-mail: Darrell.Ricke@ll.mit.edu

REFERENCES

Adekiigbe R, Ugbode F, Seoparson S, Katriyar N, Fetterman A. A 47-year-old Hispanic man who developed cutaneous vasculitic lesions and gangrene of the toes following admission to hospital with COVID-19 pneumonia. Am J Case Rep 2020;21:e926886.

Malone RW, Tisdall P, Fremont-Smith P, Liu Y, Huang XP, White KM, et al. COVID-19: famotidine, histamine, mast cells, and mechanisms. Front Pharmacol 2021;12:216.

Morán Blanco JI, Alvarenga Bonilla JA, Homma S, Suzuki K, Fremont-Smith P, Villar Gómez de Las Heras K. Antihistamines and azithromycin as a treatment for COVID-19 on primary health care - a retrospective observational study in elderly patients. Pulm Pharmacol Ther 2021;67:101989.

Brambilla L, Maronese CA, Tourlaki A, Veraldi S. Herpes zoster following COVID-19: a report of three cases. Eur J Dermatol 2020;30:754–6.

Chow JH, Khanna AK, Kethireddy S, Yamane D, Levine A, Jackson AM, et al. Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. Anesth Analg 2021;132:930–41.

Colmenero I, Santonja C, Alonso-Riaño M, Noguera-Morel L, Hernández-Martín A, Andina D, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol 2020;183:729–37.

Elsaie ML, Nada HA. Herpes zoster (shingles) complicating the course of COVID19 infection. J Dermatol Treat 2020:1–3.

Elsaie ML, Youssef EA, Nada HA. Herpes zoster might be an indicator for latent COVID 19 infection. Dermatol Ther 2020;33:e13666.

Ferreira ACAF, Romão TT, Macedo YS, Pupe C, Nascimento OJM. Fellow of the American Academy of Neurology (FAAN). COVID-19 and herpes zoster co-infection presenting with trigeminal neuropathy. Eur J Neurol 2020;27:1748–50.

Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Desai SR, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. J Am Acad Dermatol 2020a;83:1118–29.

Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Takeshita J, et al. Pernio-like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries. J Am Acad Dermatol 2020b;83:486–92.

Haga S, Yamamoto N, Nakai-Murakami C, Osawa Y, Tokunaga K, Sata T, et al. Modulation of TNF-alpha-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-alpha production and facilitates viral entry. Proc Natl Acad Sci USA 2008;105:7809–14.

Hong W, Chen Y, You K, Tan S, Wu F, Tao J, et al. Celebrex adjuvant therapy on COVID-19: an experimental study. Front Pharmacol 2020;11:1795.

Khan AR, Misdary C, Yegya-Raman N, Kim S, Narayanan N, Siddiqui S, et al. Montelukast in hospitalized patients diagnosed with COVID-19. J Asthma 2021:1–7.

Kim J, Lee S, Jeoung D, Kim YM, Choe J. Activated human B cells stimulate COX-2 expression in follicular dendritic cell-like cells via TNF-α. Mol Immunol 2018;94:1–6.

Le Balc'h P, Pinceaux K, Pronier C, Seguin P, Tadié JM, Reizine F. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. Crit Care 2020;24:530.

Morimoto K, Shirata N, Taketomi Y, Tsuchiya S, Segi-Nishida E, Inazumi T, et al. Prostaglandin E2–EP3 signaling induces inflammatory swelling by mast cell activation. J Immunol 2014;192:1130–7.

Novara E, Molinaro E, Benedetti I, Bonometti R, Lauritano EC, Boverio R. Severe acute dried gangrene in COVID-19 infection: a case report. Eur Rev Med Pharmacol Sci 2020;24:5769–71.

Osborne TF, Veigulis ZP, Arreola DM, Mahajan SM, Röösli E, Curtin CM. Association of mortality and aspirin prescription for COVID-19 patients at the Veterans Health Administration. PLoS One 2021;16:e0246825.

Ricke DO, Gherlone N, Fremont-Smith P, Tisdall P, Fremont-Smith M. Kawasaki disease, multisystem inflammatory syndrome in children: antibody-induced mast cell activation hypothesis. Journal of Pediatrics and Pediatric Medicine 2020;4:1–7.

Seirafianpour F, Sodagar S, Pour Mohammad A, Panahi P, Mozafarpoor S, Almasi S, et al. Cutaneous manifestations and considerations in COVID-19 pandemic: a systematic review. Dermatol Ther 2020;33:e13986.

Shim WS, Oh U. Histamine-induced itch and its relationship with pain. Mol Pain 2008;4:29.

Tartari F, Spadotto A, Zengarini C, Zanoni R, Guglielmo A, Adorno A, et al. Herpes zoster in COVID-19-positive patients. Int J Dermatol 2020;59:1028–9.

Tomera K, Malone R, Kittah J. Hospitalized COVID-19 patients treated with celecoxib and high dose famotidine adjuvant therapy show significant clinical responses. SSRN 2020a.

Tomera KM, Malone RW, Kittah J. Brief report: rapid clinical recovery from severe COVID-19 with high dose famotidine and high dose celecoxib adjuvant therapy. Enliven: Pharmacovigilance and Drug Safety 2020b.

Wang W, Ye L, Ye L, Li B, Gao B, Zeng Y, et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. Virus Res 2007;128:1–8.

Xu R, Zhou Y, Cai L, Wang L, Han J, Yang X, et al. Co-reactivation of the human herpesvirus alpha subfamily (herpes simplex virus-1 and varicella zoster virus) in a critically ill patient with COVID-19. Br J Dermatol 2020;183:1145–7.

Yan X, Hao Q, Mu Y, Timani KA, Ye L, Zhu Y, et al. Nucleocapsid protein of SARS-CoV activates the expression of cyclooxygenase-2 by binding directly to regulatory elements for nuclear factor-kappa B and CCAAT/enhancer binding protein. Int J Biochem Cell Biol 2006;38:1417–28.