

Letter to the
Editor

Do Pruritus and Urticaria Predict For Response to Antihistamine Therapy in COVID-19 Patients with Pulmonary Symptoms?

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Author's Contribution

^{1,3} Conception of study

^{1,2} Analysis/Interpretation/Discussion

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³ Critical Review

^{1,2} Facilitation and Material analysis

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Dear Editor,

Skin manifestations and respiratory symptoms are commonly seen in patients with COVID-19. While infection by SARS-CoV-2 and an accompanying cytokine storm are proposed to account for respiratory symptoms, additional inflammatory mediators including histamine may also contribute. In this regard, we report the resolution of dyspnea associated with urticaria in a 61-year-old female patient acutely infected with SARS-CoV-2. The patient's medical history is significant for idiopathic thrombocytopenic purpura, hypertension, and gastroesophageal reflux disease, and her long-standing medications consisted of eltrombopag, hydrochlorothiazide, lisinopril, and pantoprazole. The patient had no prior history of urticaria, angioedema, or respiratory illness. Due to the severity of her symptoms which developed over the course of a few days, the patient was referred to an urgent care clinic where intravenous methylprednisolone was administered, and tapering doses of prednisone were prescribed starting at 50mg. Nevertheless, all of her symptoms, particularly the urticaria (Figure 1 a,b), continued to worsen, prompting her to visit our dermatology clinic where

she was started on hydroxyzine 25mg q.d. and topical triamcinolone acetonide 0.1%. A first-generation antihistamine was selected to address both pruritus and associated insomnia. Additionally, prednisone was discontinued as there was no response to the medication. The patient experienced relief of urticaria within 4 hours after starting hydroxyzine and reported improvement of her dyspnea by the following morning. A SARS-CoV-2 test performed at the urgent care clinic was positive for the detection of viral antigen. The patient's symptoms completely resolved within 5 days after initiating hydroxyzine. The signs and symptoms of mast cell activation including urticaria and pruritus and response to antihistamines suggest that mast cells and their chemical mediators play a significant role in the pathophysiology of some COVID-19 patients. While case reports have described improvement of urticaria and other mast cell-mediated symptoms in COVID-19 patients following the administration of antihistamines, these cases were co-founded by the concomitant addition of new medications; this issue is less relevant in our report.¹



Figure 1: Wide-spread urticarial rash involving the chest (a) and arms (b)

Urticaria is a common dermatologic manifestation of COVID-19 patients, with an incidence of 19% in a prospective study of 375 patients.² No correlation between urticaria and disease severity, or timing of onset has been described.³ Possible etiologies of urticaria in COVID-19 patients include a reaction to viral infection, medications, and stress. The SARS-CoV-2 virus itself may directly activate mast cells via toll-like receptors or signaling molecules such as interferon type 1, TNF- α , and/or chemokines.⁴ It is thought that mast cell degranulation may either be caused directly by the virus or indirectly through viral stimulation of complement fragments C3a and C5a activating G-protein-coupled receptors.⁴

While cytokine storms, and more recently, bradykinin storms, are proposed as mediators in the pathophysiology of COVID-19, mast cells and histamine may also contribute to the development of pulmonary manifestations of COVID-19 patients.⁵ The clinical course of our patient indicates her respiratory symptoms appeared solely related to SARS-CoV-2 induced urticaria. Release of histamine, prostaglandin-D₂, and leukotriene-C₄ by mast cells cause bronchoconstriction.⁶ Further, the release of mast cell cytokines such as IL-1 and IL-6 contribute to the development of pulmonary and systemic inflammation, as well as urticaria in COVID-19 patients.^{3,4,6,7} Preliminary clinical trial reports suggest antihistamine treatment mitigates pulmonary symptoms in COVID-19 patients. Trials of dual-histamine receptor blockade with cetirizine-famotidine in hospitalized COVID-19 patients with severe pulmonary symptoms resulted in marked reductions

in rates of intubation, mortality, and length of hospital stay.⁸ Additionally, a retrospective study of 1,620 COVID-19 patients who received the H₂ receptor antagonist famotidine, showed a statistically significant reduction in the rates of intubation and death.⁹

Based on the observations that urticaria and pruritus may accompany pulmonary symptoms, we postulate these patients may better respond to antihistamine therapy. Therefore, we suggest these dermatologic findings are incorporated into the analysis plans of clinical studies assessing antihistamines in COVID-19 patients with pulmonary symptoms. Further, we suggest considering antihistamines as a component of the first-line treatment for COVID-19 patients with urticaria.

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