

LETTER

Cutaneous manifestations of COVID-19: An unusual presentation with edematous plaques and pruritic, erythematous papules, and comment on the role of bradykinin storm and its therapeutic implications

Dear Editor

A plethora of cutaneous manifestations have been reported in association with COVID-19, including among others acral lesions resembling pseudo-chilblains (40.4%), and maculopapular (21.3%), vesicular (13.0%), urticarial (10.9%), and vascular (4%) eruptions.¹ Suggested pathogenetic mechanisms of such eruptions include an immune response against severe respiratory syndrome coronavirus 2 (SARS-CoV-2) and thrombotic vasculopathy.² However, the latter has not been identified in most erythematous lesions,² and the pathogenesis of many other cutaneous findings such as urticarial eruptions remains unknown.

A 57-year-old Caucasian female with no medical history presented with low-grade fever, malaise, myalgias, dry cough, and nasal congestion. She was tested positive for coronavirus (PCR testing on specimen taken with nasal swab). Her general condition was stable, and she remained at home quarantine. She was treated with acetaminophen and dextromethorphan. She had taken these medications before without problems and had no history of drug allergies. Four days later she developed ageusia and anosmia, and 3 days thereafter she noticed a pruritic eruption with areas of swelling on her extremities. A skin examination showed edematous plaques and itchy, erythematous papules on the extremities (Figure 1). Some of the papules looked petechial. There was no history of contact allergen or external insult such as arthropod bite. A biopsy from an edematous plaque showed dermal edema, and perivascular infiltrate with eosinophils. Oral antihistamines and triamcinolone 0.1% cream were added to her treatment. The eruption resolved over a period of 11 days.

This eruption is uncommon in that it combines edematous plaques and pruritic, erythematous papules. To our knowledge, such eruption has not been reported in association with COVID-19. This case shares some similarities with the case described by Estébanez et al.³ However, the case by Estébanez showed hardened, bright erythematous plaques and confluence of lesions that affected only the heels. The areas of swelling in our patient indicate vasodilation and increased vascular permeability, as evidenced by the histopathologic finding of dermal edema. Bradykinin is a very potent vasodilator, and bradykinin storm is one of the most recent theories about how SARS-CoV-2 can cause lung injury and cardiovascular complications.⁴ The kallikrein-kinin system (KKS) results in bradykinin

production and is linked with the contact system (CS). It has been suggested that the CS plays a pivotal role in the innate immune response against SARS-CoV-2, and that a kinin-dependent local lung angioedema via bradykinin B1 and eventually B2 receptor occurs.⁵ The bradykinin theory fits with a surprising number of COVID-19's unique manifestations.⁴

Bradykinin-induced vasodilation and enhanced vascular permeability-edema can translate in edematous, urticarial-looking lesions and erythematous eruptions. Increased vascular permeability could also explain "Covid toes".⁶ Also, bradykinin causes pain

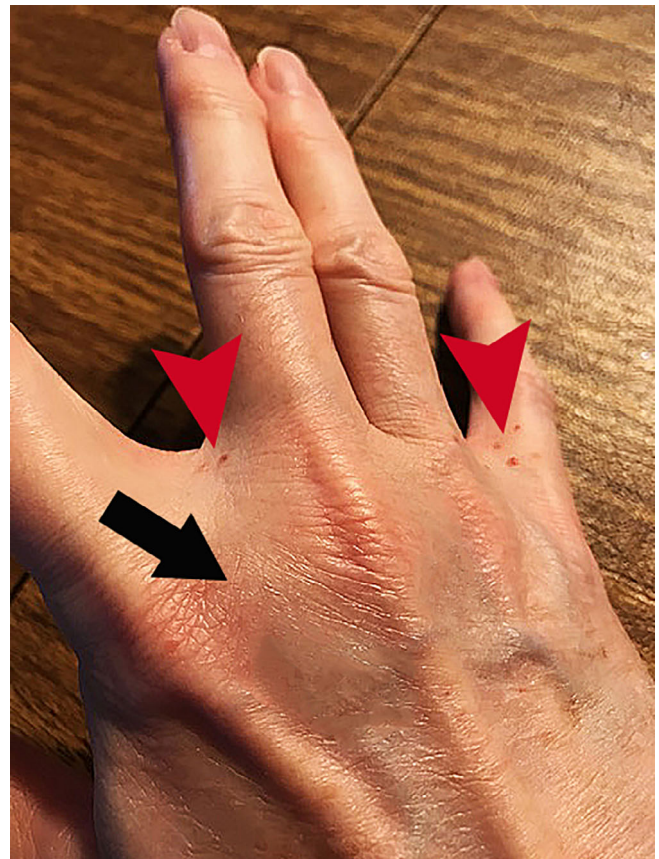


FIGURE 1 Edematous plaques (black arrow) and pruritic papules (red arrows) are shown on the dorsum of right hand

and itching and has an overall pro-inflammatory effect.⁷ Bradykinin receptors increase chemotaxis of neutrophils, and neutrophils engage KKS to open up the endothelial barrier in acute inflammation.^{8,9} Furthermore, activation of bradykinin receptors increases the levels of interleukin 6, an inflammatory cytokine that appears to correlate with disease severity.⁵ These effects increase the trend towards inflammation that already exists secondary to increased cytokine production in COVID-19. There is possibly interplay between bradykinin-related mechanisms and immune response (cytokine) effects when it comes to tissue inflammation in COVID-19. Activation of coagulation/fibrinolysis system, which is part of CS, can result in pathologic thrombus formation and often occurs simultaneously with activation of KKS (bradykinin production).⁵

The above mechanisms could underlie most cutaneous manifestations of COVID-19, especially those involving edema and inflammation. Bradykinin receptor antagonists may have beneficial effects on skin manifestations related to COVID-19, and it would be worth trying them in large-scale studies.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the author upon reasonable request.

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[Correction added on 29 January after first online publication: COVID was changed to COVID-19 in the title.]

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