Recurrent erythema multiforme in the setting of COVID-19 infection and oral candidiasis: A case for dysregulation of the T helper 17/interleukin 17 axis

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INTRODUCTION

Acute cases of erythema multiforme (EM) are frequently self-limited with rare evolution into recurrent or persistent EM. Pathogenesis is not fully understood; however, the interleukin (IL)-17 cytokine family has recently been implicated.[1] IL-17 is known to provide protective immunity against both viral and fungal infections.[2] For example, inhibition of the T helper (Th) 17/IL-17 axis with biologic therapies increases risk of candidal infections.[2] Here, we present a case of recurrent EM following COVID-19 infection in a patient with history of recurrent oral candidiasis. We postulate that shared IL-17 dysregulation could explain both his recurrent EM and candidal infections.

Abbreviations used:

EM: erythema multiforme
HSV: herpes simplex virus
IL: interleukin
Th: T helper

CASE REPORT

A 27-year-old male with history of recurrent oral candidiasis developed fever, chills, and headaches. He and numerous family members subsequently tested positive for COVID-19 with a home antigen test. Four days later, he developed a widespread, mildly pruritic rash. He presented to the emergency department, and upon examination, he was noted to have numerous red macules and papules on his face, trunk, and all extremities; mucosal and palmoplantar surfaces were spared. A viral exanthem in the setting of COVID-19 was suspected, and he was discharged with topical steroids. Six days later, he presented again with worsening, now painful rash, and new mucosal erosions. Notably, the patient had previously suffered from an episode of EM major in the setting of COVID-19 infection (positive polymerase chain reaction test) 1 year prior. Herpes simplex virus (HSV) positive polymerase chain reaction was negative at that time.

Physical examination revealed erythematous targetoid papules and plaques with dusky centers symmetrically distributed on the face, trunk, extremities, palms, soles, and genitals. He had mucosal erosions with yellow crusting (Figs 1 to 3), and significant conjunctival injection with ocular discharge. Leukoplakia on the hard palate, consistent with his previous episodes of oral candidiasis, was also noted. Abnormal laboratory results included a mild leukocytosis (12.1 thousand/μL) and thrombocytosis (428 thousand/μL). Workup for HSV, cytomegalovirus, human immunodeficiency, syphilis, and COVID-19 (positive 7 days prior by

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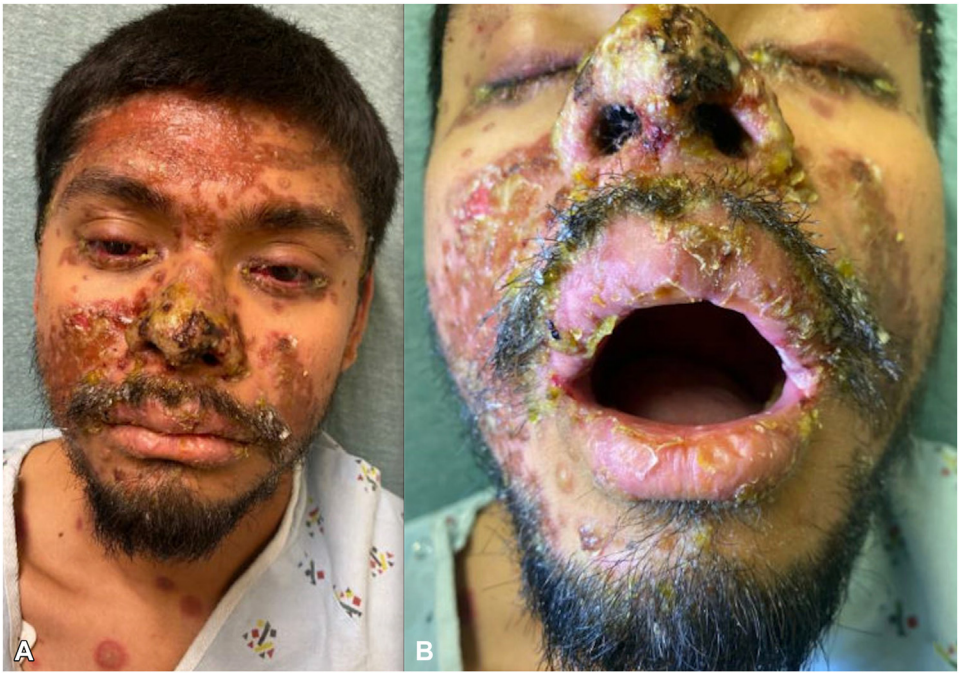

Fig 1. Erythema multiforme major presenting as erythematous, dusky, targetoid papules and plaques on the face, neck, and upper chest (**A**) with golden crust overlying the oral and nasal mucosa (**B**).

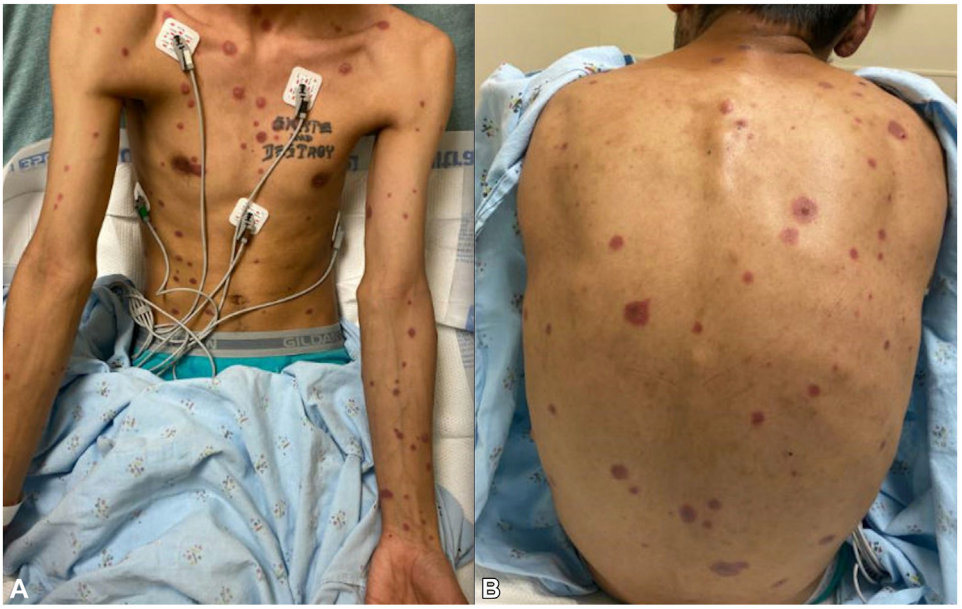

Fig 2. Erythema multiforme major presenting with erythematous, dusky, targetoid papules and plaques on the chest, upper extremities, palms (**A**), and back (**B**).

antigen test) were negative. Further workup for underlying immunosuppression and/or autoimmunity, including but not limited to full immunoglobulin panel, human leukocyte antigen 51/27, antinuclear antibody, and antineutrophilic cytoplasmic antibody, returned negative.

Skin biopsies revealed a subtle interface dermatitis with aggregates of necrotic keratinocytes giving rise to areas of extensive epidermal necrosis with blister formation, consistent with EM (Fig 4). Upon improvement with oral prednisone, the patient was discharged and started on continuous suppressive

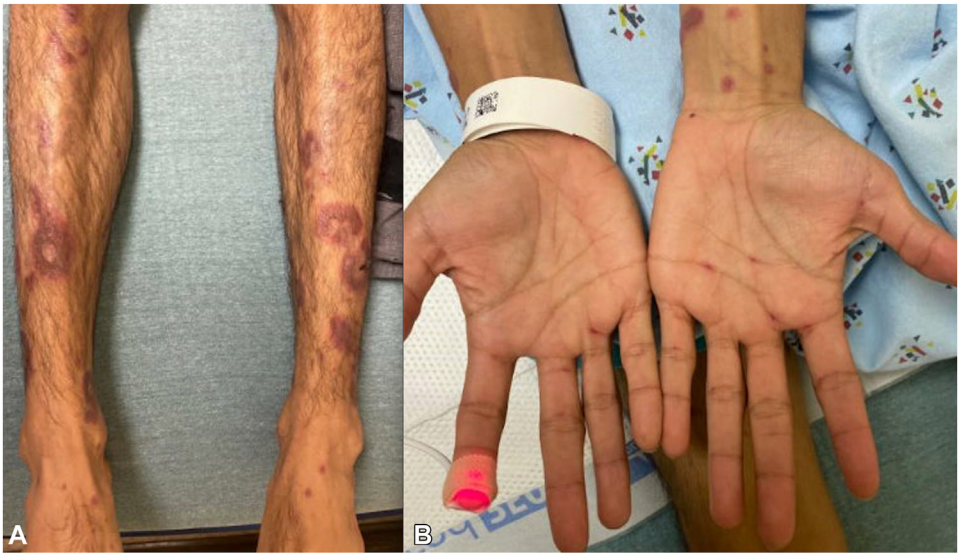

Fig 3. Erythema multiforme major presenting with erythematous, dusky, targetoid papules and plaques on the anterior shins (**A**), palms, and volar wrists (**B**).

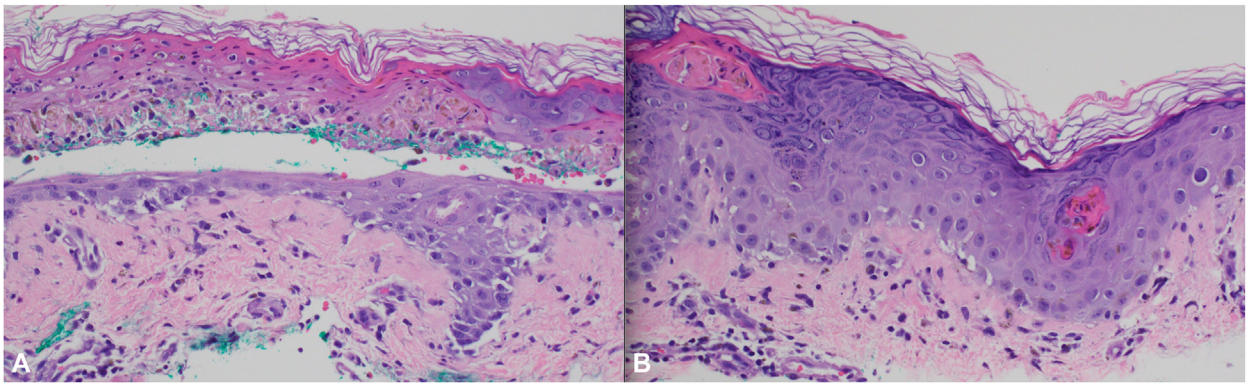

Fig 4. A, Shave biopsy findings reveal a subtle interface dermatitis with confluent epidermal necrosis and blister formation. **B,** An interface dermatitis with aggregates of necrotic keratinocytes is redemonstrated (hematoxylin and eosin, 20×).

therapy (valacyclovir 500 mg once daily) without further episodes for over 10 months.

DISCUSSION

EM is an uncommon immune-mediated reaction of the skin. Recurrent EM, like acute EM, is largely precipitated by infectious etiologies, most commonly HSV, along with autoimmune diseases and medications.[3] Overall, the pathogenesis of EM remains unclear, but several studies have highlighted several key immunologic pathways. HSV-associated EM was initially considered a $CD4^+$ Th 1 cellular response. EM lesions have shown strong expression of interferon-γ and chemokines that bind CXC chemokine receptor 3, which is highly expressed on Th1 $CD4^+$ T cells.[4,5] However, a later study showed CXC chemokine receptor 3-dependent recruitment of Th17 cells.[6] In addition, IL-17 has been demonstrated to be overexpressed in EM lesions, suggesting Th17/IL-17 axis dysregulation.[1] Interestingly, CXC chemokine receptor 3 and chemokine receptor 6 identify T helper cells that secrete both interferon-γ and IL-17, potentially explaining why cytokine production characteristic of both Th17 and Th1 cells is observed in EM lesions.[7] Clinically, IL-2, IL-6, IL-8, and IL-17 have particularly been demonstrated to be increased in the sera of patients with EM, whereas interferon-γ has not.[1]

Overall, both Th1 and Th17 pathways are also known to play critical roles in fighting viral and fungal infections. These infections include COVID-19 and candidiasis, which concurrently affected our patient.

With COVID-19, impaired production of type 1 interferons contributes to the severity of infection

and potently suppresses IL-17 expression and Th17 differentiation.[8] Unsurprisingly, SARS-CoV-2 has been shown to elevate Th17 cells and IL-17, the degree of which correlates with disease severity and progression. A dysregulation of the Th17/IL-17 axis, potentially initiated by type 1 interferon deficiency, may play a role in cases of EM following COVID-19 infection or vaccination.[9]

Perhaps, the infection most linked to Th17 dysregulation is candidiasis.[2] Downregulation of IL-17 from a genetic mutation in Dectin-1 results in recurrent mucocutaneous candidal infections, and inhibition of IL-17 with biologic therapies increases risk of candidal infections.[2]

Our patient suffered from both recurrent EM in the setting of COVID-19 and recurrent oral candidiasis. Given what we understand, we suspect an impairment in his Th17/IL-17 immune pathway to explain the shared susceptibilities. This is supported by another case report that describes recurrent EM major in the setting of concomitant COVID-19 infection and oral candidiasis.[10]

As for treatment of recurrent EM, antiviral therapy is first-line, even in cases not clearly associated with HSV.[3] If ineffective, immunomodulation/immunosuppression is considered. Apremilast, an oral phosphodiesterase-4 inhibitor that downregulates IL-17, has been shown to suppress recurrent EM.[11] Similarly, normalization of the Th17 axis by Janus kinase and signal transducer and activator of transcription inhibition treats EM.[12] Ultimately, further research into the pathogenesis of EM, including in the setting of COVID-19, may help identify additional therapies for patients with persistent or recurrent EM.

In summary, our case highlights a rare, important clinical phenomenon of recurrent EM major due to COVID-19. Given this is the second reported case of recurrent EM in the setting of concomitant COVID-19 infection and oral candidiasis, but likely not the last, we highlight a possible link between dysregulated IL-17 and recurrent EM due to COVID-19.[10] Clinicians should be aware of this potential phenomenon and possible increased susceptibility in the setting of oral candidiasis.

Conflicts of interest

Dr Min is on the advisory boards of BMS and Horizon. She is an investigator for Priovant, Amgen, and BI. Author Leigh, Drs Horton, and Lee have no conflicts of interest to declare.

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