Erythema multiforme as a consequence of COVID-19 infection

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Abstract

Cutaneous manifestations of the 2019 coronavirus disease (COVID-19) are diverse and may be the only clinical evidence of infection, particularly in children [1]. The authors report a 10-year-old girl with erythematous vesicular papules and targetoid lesions of the extremities two weeks after polymerase chain reaction confirmed severe acute respiratory syndrome coronavirus two (SARS-COV-2) infection. Biopsy depicted classic erythema multiforme and serology confirmed positive COVID-19 antibodies. This report demonstrates one of the first reported pediatric cases of typical clinical and histopathologic erythema multiforme in relation to confirmed COVID-19.

Keywords: COVID-19, erythema multiforme, interface dermatitis, necrotic keratinocytes

Introduction

The 2019 coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus two (SARS-CoV-2) is known to present with a variety of clinical manifestations [1]. Presentations range from asymptomatic to multisystemic and vary widely in severity. Cutaneous findings associated with COVID-19 in the pediatric population most commonly include purpuric, morbilliform/maculopapular, erythema multiforme-like, urticarial, vesicular, and Kawasaki-like eruptions [1]. Mechanisms may be secondary to direct virus-induced endothelial damage, vasculitis-like reactions, or consequences of systemic inflammation [1]. The majority of non-COVID erythema multiforme (EM) cases are associated with herpes simplex virus (HSV), mycoplasma pneumonia, and other viruses [2]. Erythema multiforme in young adults classically presents abruptly with erythematous to violaceous macules, papules, and vesicles with a characteristic targetoid appearance. Histopathology characteristically shows a vacuolar interface dermatitis with individual suprabasalar necrotic keratinocytes. Recent literature discusses the temporal relationship, histopathology, and possible mechanisms related to cutaneous manifestations associated with COVID-19. Herein, we present a patient with classic clinical and histologic EM related to COVID-19.

Case Synopsis

A 10-year-old healthy girl presented for evaluation of skin lesions on the hands, elbows, and feet present for one week. She reported no history of herpetic or similar lesions, recent medications, or known drug allergies. Two weeks prior to development of the eruption, the patient had a positive COVID-19 PCR after experiencing symptoms of a sore throat and nasal congestion. Physical examination revealed erythematous targetoid macules and crusted vesicular papules distributed symmetrically over the palms, ventral wrists, extensor elbows, feet, and ankles (**Figure 1**); there were no mucosal abnormalities. SARS-COV-2 RNA panel and

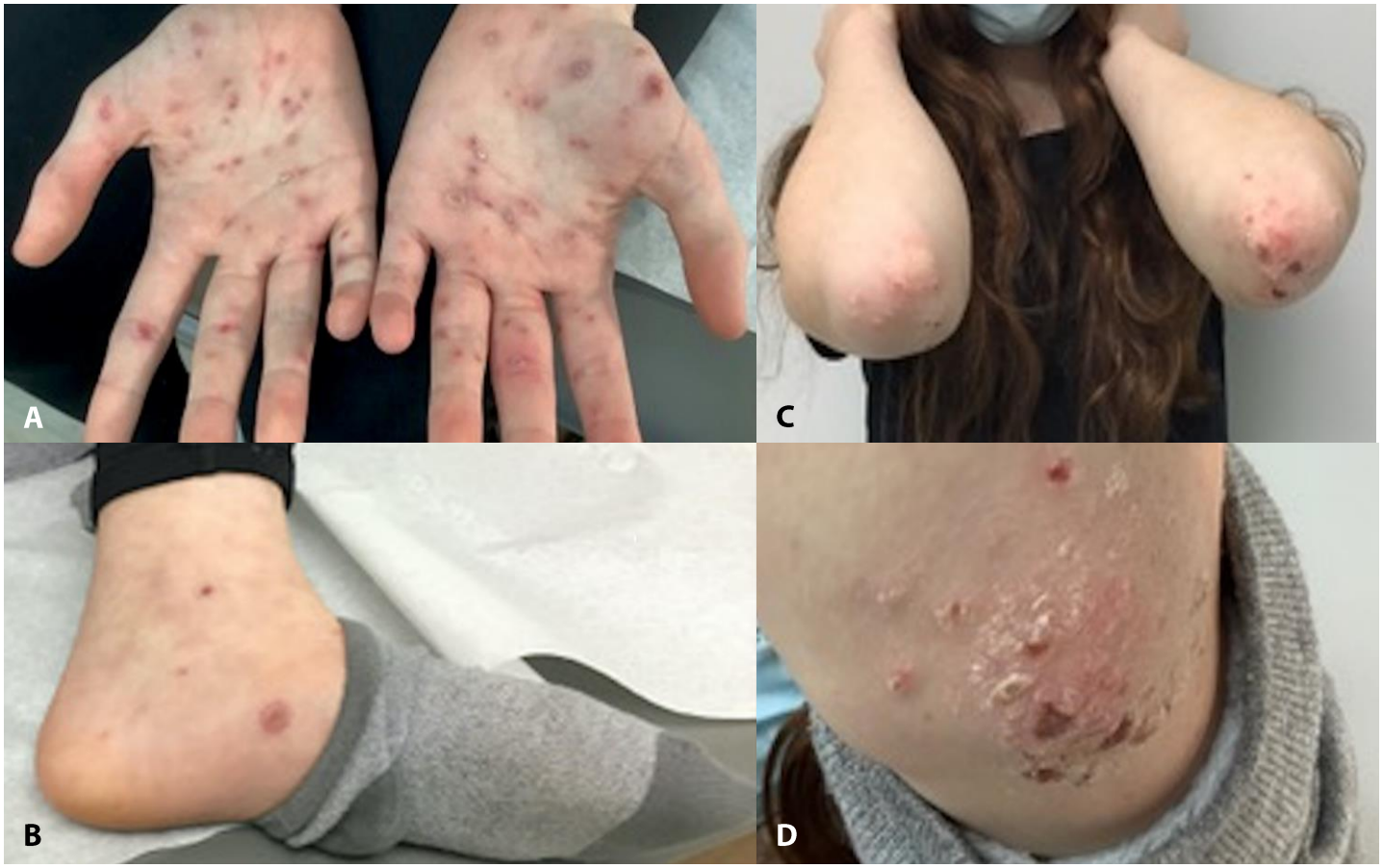

Figure 1. *Erythematous targetoid macules and crusted vesicular papules distributed symmetrically over the **A)**. palms, ventral wrists **B)**. feet, ankles and **C,D).** extensor elbows.*

antibodies were positive whereas Coxsackievirus A antibody titers were negative.

A shave biopsy revealed superficial crust over a vacuolar interface dermatitis with scattered necrotic keratinocytes and a superficial perivascular infiltrate, depicting classic erythema multiforme (**Figures 2, 3**). A diagnosis of EM secondary to COVID-19 was made. Treatment was initiated with topical betamethasone dipropionate 0.05% ointment twice daily and at follow-up two weeks later, the patient exhibited near complete clearing of the eruption.

Case Discussion

COVID-19 associated EM-like eruption has been reported in various age groups, most commonly children without or with inconclusive corresponding COVID-19 testing. Larenas-Linnemann first used the term "EM-like" in reference to COVID-19 eruptions presenting in an acral distribution in young persons and children who tend to be more pernio-like on histopathology and in appearance, with lesions being smaller, <1cm, and only rarely targetoid. In the largest case series to date, 37 of 122 COVID-19 related cutaneous eruptions were described as EM-like lesions with an average patient age of 12 years [3]. No confirmative histology or temporal relationship to suspected COVID-19 accompanied this series.

When histology has been reported, most suspected COVID-19-associated EM have not revealed characteristic EM findings leading to these eruptions being described as "EM-like"; the authors believe this case to be one of the first reported COVID-19 positive pediatric cases depicting classic clinicopathologic correlation. Late EM-like lesions in four of 22 patients were described in one study of patients presenting with COVID-19 associated pernio [4]. Unlike our patient, biopsies obtained from these four patients showed findings consistent with pernio as opposed

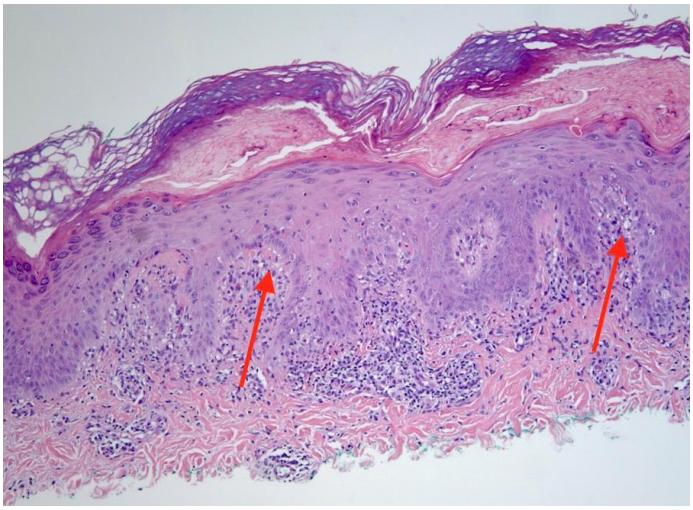

Figure 2. *Low magnification view of the right ventral wrist shave biopsy reveals a crusted vacuolar interface dermatitis with a superficial perivascular infiltrate and vacuolar changes (red arrows). H&E, 10×.*

to EM. Another report described two out of eleven patients who developed targetoid lesions on the hands and elbows and were suspected of having COVID-19 infection despite negative PCR testing. Histology of these lesions was suggestive of urticaria, revealing mild superficial perivascular dermatitis and no other findings characteristic of EM [5].

Timing of COVID-19 EM in adolescents and children has been limited and inconsistent with onset being described before or after a confirmed COVID diagnosis [6,7]. In adults, however, multiple studies have reported the temporal relationship between cutaneous findings and onset of symptoms or suspected contraction of SARS-CoV-2. Timelines ranged from 12 to upward of 24 days with most reports describing an average interval of approximately two weeks [8-10]. These findings are consistent with the timing of our patient's lesions which developed two weeks after positive PCR.

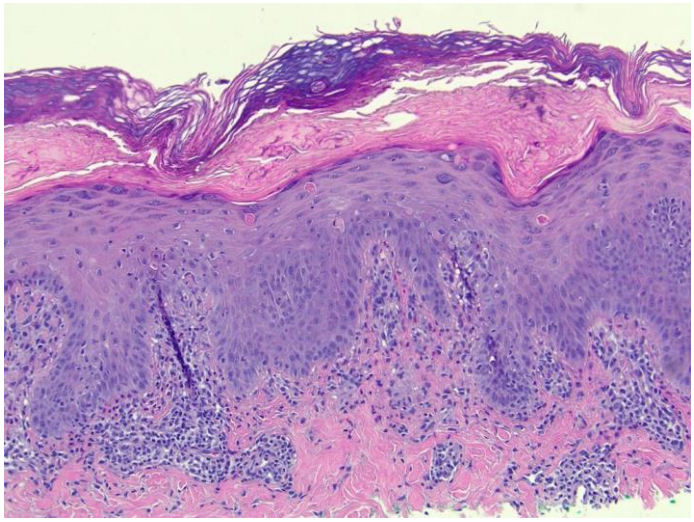

Figure 3. *High magnification view of the right ventral wrist shave biopsy demonstrates vacuolar interface dermatitis with individual suprabasalar necrotic keratinocytes. H&E, 20×.*

Historically, EM is thought to be a cell mediated immune response that occurs in predisposed individuals in the setting of bacterial or viral infection, with HSV being the most common [4]. The pathophysiology of COVID-19-associated EM is yet unknown but is suspected to be consistent with other virally-induced EM. A potential pathway for SARS-CoV-2 penetration into cells involves spike protein S binding angiotensin-converting enzyme two (ACE2), a membrane-bound receptor [1]. *ACE2* expression in basal keratinocytes and eccrine sweat glands prominent in the palms, could explain the distribution seen in EM [1]. Immune system activation after entry could account for cutaneous COVID-19 manifestations along with autoimmune-like endothelial type III hypersensitivity reactions, cytokine production in dermal dendritic cells, lymphocytes, and mast cells, and or dermal capillary complement deposition [1]. Considering that relatively few HSV or COVID-19 infections manifest in EM, this suggests many factors potentially contribute including differences in cell subsets, genetic material processing, viral protein expression, and genetic susceptibility [4].

Conclusion

Our patient's presentation, chronology, and evolution of her cutaneous eruption in conjunction with positive serology is highly suggestive of SARS-CoV-2-related EM. The clinicopathologic correlation in this case is thought to be one of the first reported pediatric COVID-19 positive patients to exhibit both cutaneous findings consistent with EM in conjunction with classic histology. Positive COVID-19 serology and consistent timeline further support this diagnosis. More research is necessary to reveal underlying pathophysiologic mechanisms and potential patient susceptibilities. However, given both the novelty and persistence of the SARS-CoV-2

virus it is important to have awareness of the diverse cutaneous manifestations, particularly this relationship between EM and COVID-19.

Potential conflicts of interest

The authors declare no conflicts of interest.

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