

## CASE REPORT

# A pediatric case of exudative erythema multiforme probably associated with asymptomatic COVID-19

Yoshihiro Wada<sup>1</sup>, Kayoko Minami<sup>2</sup>, Masaru Natsuaki<sup>1</sup>, Nobuo Kanazawa<sup>1,\*</sup>

<sup>1</sup> Department of Dermatology, Hyogo Medical University, Nishinomiya 663-8501, Japan

<sup>2</sup> Department of Dermatology, Uegahara Hospital, Nishinomiya 662-0884, Japan

\* Corresponding author: Nobuo Kanazawa, nkanazaw@hyo-med.ac.jp

---

## ABSTRACT

COVID-19 is a pandemic involving severe acute respiratory syndrome-coronavirus SARS-CoV-2, which started in China at the end of 2019 and has spread globally. Among COVID-19 patients, 17.8% are under 20 years of age. Most children infected with SARS-CoV-2 are asymptomatic or only oligosymptomatic and can easily be overlooked. We followed an 11-year-old boy showing exudative erythema multiforme, which appeared during isolation at home following a positive polymerase chain reaction (PCR) test for COVID-19. Our case, although otherwise asymptomatic, showed typical clinical and histological manifestations of the erythema multiforme-like lesions associated with COVID-19. The presence of such an asymptomatic SARS-CoV-2 carrier who developed erythema multiforme-like skin lesions provides the possibility that some undefined infectious organisms, such as SARS-CoV-2, could be the origin of exudative erythema multiforme cases without any apparent cause.

**Keywords:** COVID-19; severe acute respiratory syndrome-coronavirus-2; polymerase chain reaction; asymptomatic; exudative erythema multiforme

---

## ARTICLE INFO

Received: 13 July 2023  
Accepted: 17 August 2023  
Available online: 31 August 2023

## COPYRIGHT

Copyright © 2023 by author(s).  
*Trends in Immunotherapy* is published by  
EnPress Publisher, LLC. This work is licensed  
under the Creative Commons  
Attribution-NonCommercial 4.0 International  
License (CC BY-NC 4.0).  
<https://creativecommons.org/licenses/by-nc/4.0/>

## 1. Introduction

Exudative erythema multiforme (EEM), also called erythema multiforme (EM) major, is a mucocutaneous reaction to various environmental antigens, such as infectious agents, foods and drugs, characterized by atypical target lesions with exudative inflammation. Although infection with *Streptococcus* species, *Mycoplasma* and herpes viruses are known to be associated, no apparent antigens have been revealed in some cases.

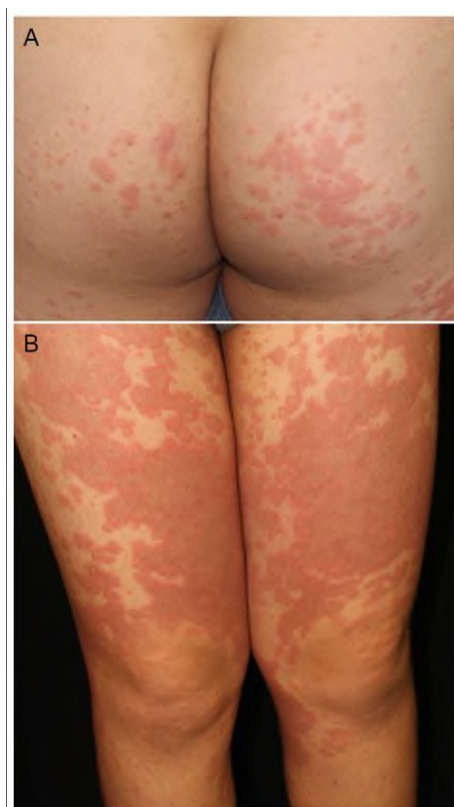
COVID-19 is a pandemic involving severe acute respiratory syndrome-coronavirus SARS-CoV-2, which started from China at the end of 2019, and has spread globally. Coronavirus is one of the main origins of the common cold and is known to easily generate mutated strains. The early detection and appropriate isolation of infected persons is considered critical to avoid spreading the infection. The amplification of virus RNA from the nasopharyngeal swab with real-time quantitative polymerase chain reaction (PCR) has been established and widely applied for the early detection of infected individuals, not only among symptomatic (fever, sore throat, malaise, abdominal pain, etc.) persons, but also among asymptomatic persons who had close contact with infected patients.

Among the COVID-19 patients, 17.8% are under 20 years of

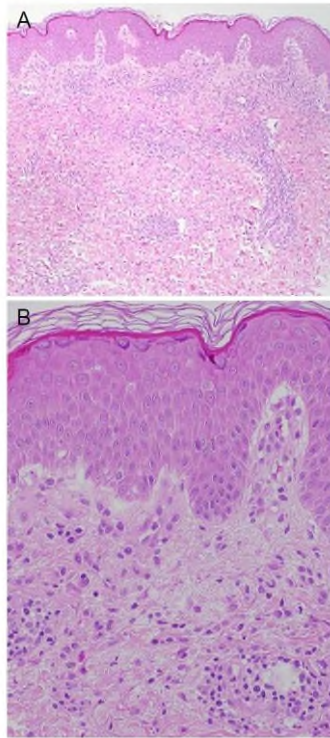
age<sup>[1]</sup>. Most pediatric SARS-CoV-2 cases are asymptomatic or only oligosymptomatic and can easily be overlooked not only by the patients, but also by doctors, because of the lower sensitivity of PCR in cases with milder symptoms or lower viral loads<sup>[2]</sup>.

## 2. Case report

An 11-year-old boy was presented to the Dermatological Department of Hyogo Medical University Hospital with multiple well-demarcated exudative erythemas on the trunk and extremities. They appeared as small erythematous macules (**Figure 1A**) and fused to form large erythematous plaques (**Figure 1B**). He had no special issues in his medical history or family history. Notably, he had been at home during the two-week isolation period after a positive COVID-19 PCR test. Due to a clustered infection of COVID-19 which occurred in his class of the elementary school, although asymptomatic, he tested positive in the SARS-CoV-2 PCR test. After 12 days, itchy erythemas appeared on the right side of the abdomen. Although a topical steroid was applied, they spread to the trunk and extremities. Histological analysis showed marked vacuolar changes with lymphocytic infiltration along the basement membrane and mild spongiosis, but apparent epidermal necrosis did not accompany this (**Figure 2**). Perivascular lymphocytic infiltration with occasional eosinophils and the degeneration of collagen bundles were observed in the edematous upper and middle dermis. A blood test was not performed to clarify the involvement of other infectious agents. No drugs or supplements were applied before the appearance of the skin rash. Based on these findings, he was diagnosed with EEM probably associated with asymptomatic COVID-19. Topical diflorasone diacetate and oral olopatadine hydrochloride improved the eruptions and they mostly disappeared, with pigmentation, in a month.



**Figure 1.** Clinical pictures of the skin lesions. (A) various-sized, small erythematous macules in the buttock; (B) irregularly shaped, well-demarcated, large erythematous plaques in the thighs.



**Figure 2.** Histological pictures of the skin lesion (hematoxylin and eosin stain). **(A)** original magnification is  $\times 40$ ; **(B)** original magnification is  $\times 200$ .

### 3. Discussion

In systematic reviews, the prevalence of skin manifestations of COVID-19 was reported to range from 0.25% to 3% in pediatric cases<sup>[3,4]</sup>. In a review of the English and Chinese literature from December 2019 until October 2020, 90 pediatric COVID-19 cases with skin manifestations from 13 countries and regions were analyzed to show that the median age was 9.01 years (ranged from 0.17 to 19 in 84 cases with known onset age), 59% were male (in 78 cases with known gender), and the period from the appearance of systemic symptoms to that of skin manifestations ranged from 17 to 28 days<sup>[5]</sup>. Notably, otherwise asymptomatic cases were estimated as 4.7%, while fever (81.4%), multisystem inflammatory syndrome (73.3%), gastrointestinal involvement (68.6%), cardiac involvement (65.1%) and lung involvement (39.5%) were observed in 86 cases with systemic symptoms. Erythematous papules, plaques, macules and maculopapules were the most common skin manifestation (62.1%), followed by conjunctivitis (59.8%) in 87 cases with cutaneous symptoms. The face was the most commonly affected location (72.1%), including lips, eyes, eyelids, conjunctiva and tongue, followed by toes, soles, feet and heels (38.4%) and palms, fingers and hands (32.6%) in 86 cases with known location of lesions. Itching and pain were reported in 72.7% and 45.5% patients, respectively, in 11 cases with lesional skin sensations. Most (72%) of the skin lesions improved or disappeared and their median duration was 8.93 days (from 2 to 16 days), while 1.3% and 4% recurred and died, respectively, in 75 cases with known outcomes. In another review, skin manifestations in child COVID-19 cases were classified as chilblain-like (COVID toe), Kawasaki disease-like (Kawa-COVID-19), EM-like, acute urticaria, acro-ischemic, chickenpox-like (varicelliform), mottling, eyelid dermatitis, livedo-like, acral erythema and dactylitis, generalized maculopapular rash, rash with petechiae and purpura, and miliaria-like lesions<sup>[2]</sup>. In the case of EM-like lesions, other possible origins, such as other viral and bacterial infections, should be excluded. Wollina et al.<sup>[6]</sup> described, in a review of COVID-19-associated cutaneous lesions in patients of all ages, that chilblain-like, purpuric, and EM-like lesions are reportedly associated with children and young adult patients who are asymptomatic or show milder symptoms<sup>[6,7]</sup>. In contrast, acro-ischemic lesion and maculopapular rash are often observed in adult patients with a more

severe disease course<sup>[6]</sup>. Thus, it is expected that the exhibition of an EM-like rash predicts a milder course of COVID-19 in pediatric patients.

In addition to the lung, the liver, gastrointestinal and urinary system, blood vessel endothelial cells, conjunctiva epithelial cells, cornea cells, sweat gland epithelial cells, and basal layer keratinocytes express angiotensin-converting enzyme (ACE)-2 receptors, which were used for the entry of SARS-CoV-2<sup>[2]</sup>. Therefore, skin manifestations with vacuolar changes in the basement membrane, cutaneous vessel vasculitis, and conjunctivitis can be expected in COVID-19 cases. Indeed, cytoplasmic granular-pattern staining of the SARS-CoV/SARS-CoV-2 spike protein was revealed in dermal endothelial cells and the acrosyringia epithelial cells of the EM-like lesion in a pediatric COVID-19 case<sup>[7]</sup>. However, SARS-CoV-2 RNA has never been detected by PCR from these skin lesions<sup>[2]</sup>. These results suggest that EM-like lesions represent a temporal allergic reaction to the remaining viral proteins, without or after the proliferation of SARS-CoV-2. Importantly, it has been suggested that COVID-19-associated EM-like lesions can be histologically differentiated from other EM lesions by the absence of necrotic keratinocytes and the presence of lymphocytic inflammation in the deep dermis with vascular involvement<sup>[7]</sup>. Although the involvement of other infectious agents has never completely been excluded, the histological manifestation of our case, showing an absence of necrotic keratinocytes, is compatible with the COVID-19-associated EM-like lesions. More studies should be conducted to clarify the clinical and histological variations and the mechanisms underlying the development of these COVID-19-associated skin manifestations.

Collectively, our case, although otherwise asymptomatic, showed mostly typical clinical and histological manifestations of the EM-like lesions probably associated with COVID-19. The presence of such an asymptomatic SARS-CoV-2 carrier who developed EM-like skin lesions provides the possibility that some undefined infectious organisms, such as SARS-CoV-2, could be the origin of EEM cases without any apparent cause.

## Funding

This research was funded in part by a grant from the Japan Society for Promotion of Science 19K08798 (N.K.).

## Conflict of interest

The authors declare no conflict of interest.

## References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *Journal of the American Medical Association* 2020; 323(13): 1239–1242. doi: 10.1001/jama.2020.2648
2. Khalili M, Iranmanesh B, Mohammadi S, Aflatoonian M. Cutaneous and histopathological features of coronavirus disease 2019 in pediatrics: A review article. *Dermatologic Therapy* 2021; 34: e14554. doi: 10.1111/dth.14554
3. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: A systematic review. *eClinicalMedicine* 2020; 24: 100433. doi: 10.1016/j.eclinm.2020.100433
4. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in pediatric emergency departments in Italy. *The New England Journal of Medicine* 2020; 383(2): 187–190. doi: 10.1056/NEJMc2007617
5. Li H, Zhao Y, Zhou L. Cutaneous manifestations in children with SARS-CoV-2 infection and/or COVID-19: What do we know after 10 months under this pandemic? *International Journal of Dermatology* 2022; 61: 39–45. doi: 10.1111/ijd.15882
6. Wollina U, Karadağ AS, Rowland-Payne C, et al. Cutaneous signs in COVID-19 patients: A review. *Dermatologic Therapy* 2020; 33(5): e13549. doi: 10.1111/dth.13549
7. Torrelo A, Andina D, Santonja C, et al. Erythema multiforme-like lesions in children and COVID-19. *Pediatric Dermatology* 2020; 37(3): 442–446. doi: 10.1111/pde.14246