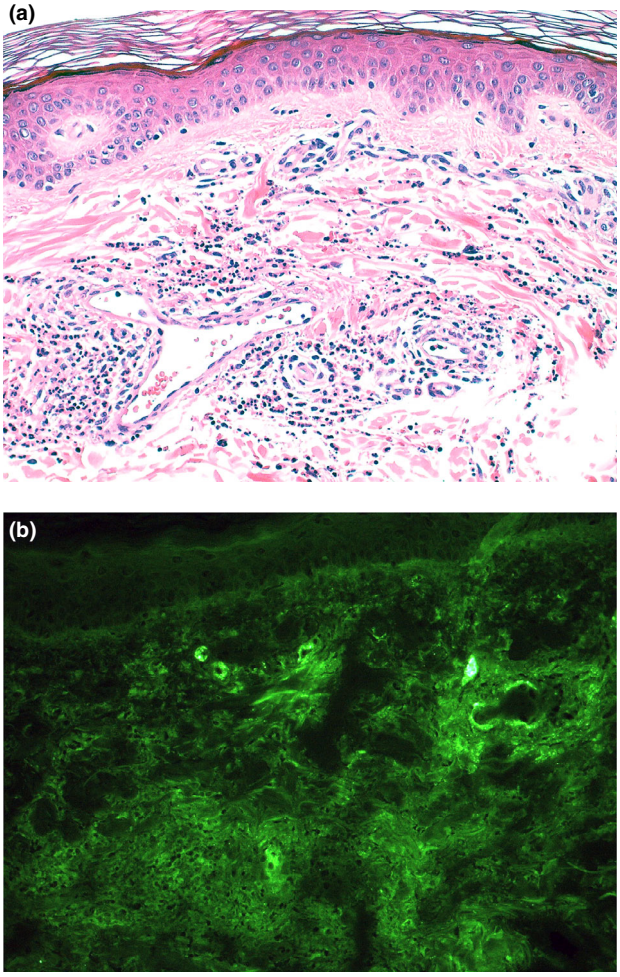

Figure 2 (a) High magnification (H&E stain; ×20) showing perivascular inflammatory infiltrate, composed of small and mature lymphocytes, neutrophils, nuclear dust and red blood cell extravasation. (b) (C3 direct immunofluorescence, ×10) DIF shows positive immunofluorescence for C3 in a granular pattern within vessel walls.

carry viable viruses, and the second being a lack of sensitivity of the test.

By sharing this case we hope to improve the scarce knowledge we have on this disease. Doctors dealing with CSVV in undiagnosed patients during this pandemic may take into consideration testing for SARS-CoV-2.

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Conflict of interest

The authors have no conflict of interest to declare.

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A case of cefditoren-induced acute generalized exanthematous pustulosis during COVID-19 pandemics. Severe cutaneous adverse reactions are an issue

Dear editor

We read with interest the article by Recalcati *et al*. about the report of cutaneous manifestations in Coronavirus disease 2019 (COVID-19) patients. We would like to highlight that some potentially severe manifestations in these patients are not directly related to the coronavirus but to the medications administered.[1]

A 49-year-old woman with morbid obesity, and no other relevant antecedents, was admitted in the Intensive Care Unit, due to severe respiratory failure. Chest X-ray showed bilateral lung diffuse opacities predominantly involving the upper and middle

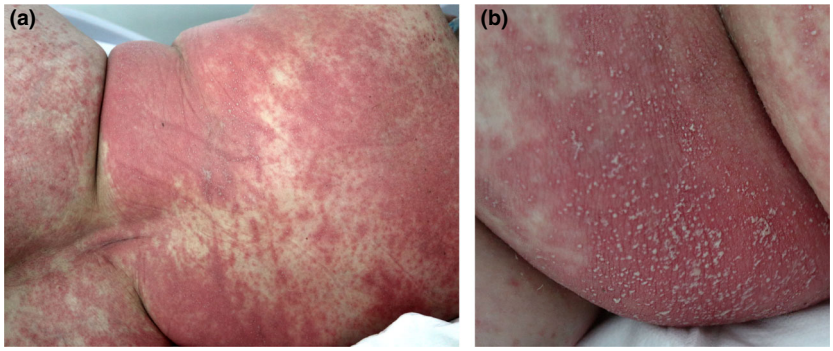

Figure 1 Clinical features. (a) Diffuse erythema with multiple small pustules. (b) Small grouped pustules on the abdomen.

fields. Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) reverse transcription-polymerase chain reaction (RT-PCR); rendered a positive result. The patient required invasive ventilatory support in the intensive care unit for 24 days. Throughout this period, treatment with interferon beta (250 mg/24 h), hydroxychloroquine (200 mg/12 h); azithromycin (500 mg/24 h), ceftriaxone (2 g/12 h), lopinavir-ritonavir (800–200/24 h); methylprednisolone (40 mg/12 h) and tocilizumab (600 mg single dose) was administered. After successful extubation, the patient was transferred to the pneumology ward remaining asymptomatic. All the drugs were interrupted except for methylprednisolone (tapered to 16 mg daily). Seven days later, respiratory worsening was observed with cough and crackles on pulmonary auscultation. Empiric treatment with cefditoren (400 mg/12 h) was started. The following day, the patient suffered an episode of fever (38.4°C). Blood tests revealed neutrophilia [7.75 × 10^3/μL; Normal Range (NR), 1.9–7.3 × 10^3/μL; last measurement, 3.11 × 10^3/μL] and C-reactive protein level of 59 mg/L (NR, 0–5 mg/L). At that time, a skin rash was noticed.

Upon physical examination, a confluent reddish macular rash was observed, mainly on the trunk, but also involving the neck, face, arms, and axillary and neck folds. Small widespread pustules developed over the macules (Fig. 1). No mucosal involvement was seen. Clinical diagnosis of Acute Generalized Exanthematous Pustulosis (AGEP) was issued. Therefore, cefditoren was interrupted and methylprednisolone was raised (0.3 mg/kg/day of prednisone). Skin lesions improved along with the general condition of the patient.

Histological analysis showed subcorneal pustules with abundant inflammatory infiltrate, papillary oedema, and few eosinophils within superficial dermis (Fig. 2). Subsequent cultures of pustular content were negative. Thus, the diagnosis of AGEP was confirmed. The Euro- Severe cutaneous adverse reaction (SCAR) score was 11 points. Cefditoren, a cephalosporin-derived beta-lactam, was the probable culprit drug (Naranjo score of 7).[2]

Severe cutaneous adverse reactions (SCARs) constitute a group of high morbidity dermatosis. Among them, AGEP consist of the acute onset of fever and a maculopapular rash – started on the trunk or flexural areas – usually within 48 h of taking the drug responsible. Antibiotics are the main cause of AEGP. It is characterized by the development of dozens to thousands of small sterile pustules on an erythema background. Withdrawal of the suspected drug is followed by the rapid resolution of symptoms.[2] Additionally, R1 side chains of cephalosporins are highly conserved and have been demonstrated to promote cross-reactions with penicillins containing similar structures. Indeed, ceftriaxone and cefditoren share similar R1 side-chains.[3] As a matter of debate, our patient was previously treated with ceftriaxone with no adverse effects. However, it could be easily argued that she was receiving a high dose of corticosteroids at the same time as ceftriaxone, whereas the corticosteroid had been tapered when cefditoren was established.

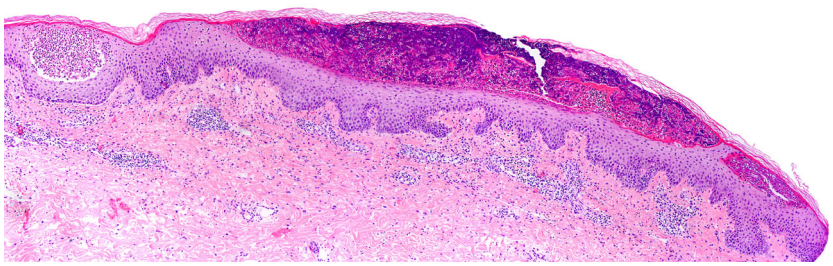

Figure 2 Histological findings. Epidermis with three subcorneal pustules and perivascular infiltrate composed of neutrophils and scattered eosinophils (H & E stain, ×200 original magnification).

Hence, corticosteroids could have prevented the initial development of AEGP.

Lastly, to date SCARs have been reported with the use of ceftriaxone, but there is only one reported case of DRESS related to cefditoren, among other causes.[4,5]

Surrounding the COVID-19 pandemic, many dermatoses are being reported as possibly SARS-CoC-2 induced. Here, we highlight the importance of considering other etiologies as causes of skin lesions arising on the background of SARS-CoV-2 infection. Special effort has to be made to identify drugs as the source of these events, as they may lead to SCARs.

Finally, further studies should investigate cross-reactions between cephalosporins, and the role of cefditoren as causative agent of SCARs.

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Erythema multiforme and Kawasaki disease associated with COVID-19 infection in children

Dear Editor

We read with interest the publications in the JEADV which reported dermatological manifestations associated with COVID-19, such as pityriasis rosea, urticaria, rash, vascular signs or chilblain-like lesions.[1–6] Herein, we report two life-threatening cases of children presenting with fever and eruptions with mucous membrane involvement – erythema multiforme and Kawasaki disease – associated with COVID-19.

Case 1: A 6-year-old male was hospitalized for painful cheilitis that develops during the week before admission and rapidly became associated with a rash of the extremities, and conjunctivitis. The patient was reported to have had a loss of appetite, without any other symptoms. The father reported having transient anosmia 2 weeks before. There was no history of recent medication. At admission, clinical examination revealed severe erosive cheilitis (Fig. 1a) with diffuse gingival erosions and thick haemorrhagic crusts, bilateral conjunctivitis, associated with multiple target lesions (Fig. 1b,c). Respiratory function was normal. The clinical picture led to a diagnosis of erythema multiforme. *Mycoplasma pneumoniae* serology was negative. The herpes simplex virus (HSV) polymerase chain reaction (PCR) test, on buccal erosions, was also negative. A first COVID-19 test, carried out by PCR, was negative; however, a second test was positive. The child's condition improved, and he was discharged 2 weeks after.

Case 2: A 3-year-old male was hospitalized for fever >39.0°C for 8 days. The fever was associated with asthenia, generalized exanthema, cheilitis, stomatitis and bilateral conjunctivitis. His mother had been diagnosed with COVID-19, 3 weeks earlier. Clinical examination revealed generalized exanthema (Fig. 2a), bilateral palmar oedema, glossitis and cervical lymphadenopathy. Desquamation of the extremities was noted during a subsequent examination (Fig. 2b). Laboratory tests showed an increase in inflammatory biomarkers: CRP = 195 mg/L and hyperleukocytosis (leucocytes = 17 400/mm^3). A COVID-19 PCR test performed at admission was negative. The CT scan revealed ground-glass opacities and consolidation in the right posterobasal area (<10% of the lung parenchyma), suggestive of COVID-19 pneumonia (Fig. 2c). We concluded a final diagnosis of COVID-19-associated Kawasaki disease. The child was treated with an initial dose of intravenous gamma globulin (2 g/kg).

This case report provides a detailed description of severe cutaneous manifestations occurring in two children with COVID-19. The manifestations reported in our first case are typical of erythema multiforme, with particularly severe mucosal lesions being noted in this child. The main causes of erythema