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Erythema multiforme-like eruption in patients with COVID-19 infection: clinical and histological findings
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Cutaneous manifestations in patients with COVID-19 infection are increasingly being reported. Several patterns have been described since the initial report by Recalcati,1 including erythematous maculopapular,2 urticarial,1,2 chickenpox-like,1,3 purpuric periflexural,4 transient livedo reticularis,5 and acroischaemic or chilblain-like lesions.6,7
We report the observation a new pattern with erythema multiforme (EM)-like lesions in four hospitalized patients with COVID-19 infection.

All four patients were women, with a mean age of 66.75 years (range 58–77 years). Mean interval between the onset of COVID-19 symptoms to the appearance of cutaneous lesions was 19.5 days (range 16–24 days). One patient developed the skin rash during hospitalization, while the remaining three patients had been previously discharged after clinical, analytical and radiological improvement, and a negative COVID-19 PCR test.

These three patients returned to the emergency department because of the skin rashes at 6, 7 and 4 days after discharge, respectively. Laboratory tests at the time of presentation showed worsening of one or more parameters (C-reactive protein, D-dimer or lymphocyte count), compared with those at the time of discharge. However, none of the patients presented recurrence of clinical symptoms of COVID-19. Microbiological studies were performed in two patients, which excluded other infectious diseases (Table 1). In all patients, the skin lesions had begun as erythematous papules on the upper trunk, which progressively turned to erythematoviolaceous patches with a dusky centre, and a pseudovesicle in the middle. Typical EM targetoid lesions were observed in two patients. Lesions coalesced markedly on the back, and then spread to the face and limbs within 1 week, without involvement of the palms or soles (Fig. 1). These patients underwent oral cavity examination, which revealed palatal macules and petechiae.

Histological examination was similar in all patients, revealing a normal basket-weave stratum corneum, and mild to moderate spongiosis in epidermis. The dermis showed dilated vessels filled with neutrophils, extravasation of red blood cells, and lymphocytic perivascular and interstitial infiltrate. Basal vacuolar changes with interface dermatitis were observed in one patient, and lymphocytic exocytosis in another (Fig. 2). All patients were treated with systemic corticosteroids with progressive improvement, and a negative COVID-19 PCR test.

We are facing challenging times in dermatology. New information and details of cutaneous manifestations possibly related to COVID-19 are emerging every day. Further studies are needed to evaluate whether these lesions are associated with the virus, the drugs used or any other conditions. EM is linked to infectious agents in 90% of cases, while drug-associated EM is reported in <10%. Herpes simplex virus and Mycoplasma pneumoniae are the main agents, but other viruses have been reported, such as adenovirus, coxsackievirus and parvovirus B19. We suggest that this EM-like or target-like exanthem might be another pattern of exanthem associated with COVID-19 infection. Recent articles have also reported targetoid lesions in exanthems of patients with COVID-19 infection. In addition, the presence of pseudovesicles and enanthem are two clues that suggest an infectious cause rather than a drug reaction. However, we cannot positively exclude the involvement of the various drugs administered to the patients. To our knowledge, this is a first observation that will require further investigation.

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**Table 1 Clinical and laboratory findings of the four patients with erythema multiforme-like eruption.**

| Patient | Sex | Age, years | Days after symptoms | Days after treatment | Drugs                                                                 | Microbiological tests                                                                 | Worsening of laboratory parameters |
|---------|-----|------------|---------------------|---------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 1       | F   | 63         | 19                  | 16                  | L/R, H, A, Cs, Ce                                                     | Not performed                                                                         | Elevation of CRP and D-dimer       |
| 2       | F   | 77         | 16                  | 11                  | L/R, H, A, Cs                                                       | Negative for HIV, EBV, CMV, VZV, HSV, M. pneumoniae, syphilis                           | Not performed                     |
| 3       | F   | 58         | 24                  | 15                  | L/R, H, A, Cs, Ce                                                   | Not performed                                                                         | Elevation of D-dimer; decrease in lymphocyte count                                   |
| 4       | F   | 69         | 19                  | 10                  | L/R, H, A                                                          | Negative EVB for HIV, EBV, CMV, VZV, HSV, M. pneumoniae, syphilis, HSV PCR found in vesicle swab | Elevation of CRP and D-dimer; decrease in lymphocyte count |

A, azithromycin; Ce, ceftriaxone; Cs, corticosteroids; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein–Barr virus; H, hydroxychloroquine; HIV, human immunodeficiency virus; HSV, herpes simplex virus (PCR multiplex); LR, lopinavir/ritonavir; M, Mycoplasma; VZV, varicella zoster virus. *Days from the onset of COVID-19 symptoms and from the start of treatment to the appearance of cutaneous lesions, respectively; †worsening of laboratory parameters at the time of skin lesions, compared with those at the time of discharge.
Figure 1 Clinical presentation of erythema multiforme (EM)-like exanthem in (a) Patient 1; (b) Patient 2; (d) Patient 3; and (e) Patient 4 showing coalescing erythematous violaceous patches with a dusky centre, some of them with pseudovesicles in the middle, located on the back. Typical EM targetoid lesions were observed on (c) the buttocks of Patient 2 and (f) the thigh of Patient 4.

Figure 2 (a) Histological examination of Patient 1 showed normal basketweave stratum corneum, mild to moderate spongiosis and lymphocytic exocytosis in the epidermis, while the dermis showed dilated vessels filled with neutrophils, extravasation of red blood cells, and lymphocytic perivascular and interstitial infiltrate. (b) Patient 3 had basal vacuolar changes with interface dermatitis.
Cutaneous manifestations in COVID-19: familial cluster of urticarial rash

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Coronavirus disease (COVID-19) is a new infectious disease that is rapidly spreading across the world. Many clinical manifestations of the virus have been described, and new symptoms are emerging, but only a few cases of skin manifestations have been described since the pandemic was announced by the World Health Organization in March.\(^1^2\) Common clinical features of COVID-19 reported include fever, cough, myalgia, fatigue, headache, shortness of breath and diarrhea.\(^1\)

Some reports have suggested that skin manifestations are present in up to 20.4% of patients with COVID-19, and reports suggest a wide range of skin conditions being related to the virus, including widespread urticaria, morbilliform rash, erythematous rash, chickenpox-like vesicles, purpuric rash, dusky acrocyanosis, dry gangrene, petechiae rash coexisting with thrombocytopenia, transient livedo reticularis and red papules on fingers resembling chilblains.\(^2^\)\(^3^\) Unfortunately, some of these reports do not have clinical pictures to show the relation between COVID-19 and the skin manifestations.

We report a family of five members living in the city of Monterrey, Mexico who tested positive for COVID-19, as a result of one of the members becoming infected during a trip to New York in February 2020. All five patients had anosmia, ageusia, chills and dizziness, and two of them had skin manifestations associated with COVID-19.

Patient 1 was a 50-year-old woman, and Patient 2 was a 20-year-old woman, who was the daughter of Patient 1. Both patients had a bilateral disseminated rash on the shoulders, elbows, knees and buttocks, characterized by erythematous annular and irregular weals on the skin that appeared suddenly and disappeared within < 24 h (Fig. 1). The rash appeared after the cough and fever appeared. Neither patient had any history of similar lesions, and no trigger factors other than the viral context were identified. No other clinical or laboratory examinations were positive.

A diagnosis of urticaria associated with COVID-19 was made. Both patients were treated with antihistamines and moisturizers, and 48 h after treatment was started the urticaria resolved.

Although urticarial rash is the most common skin manifestation described in COVID-19 infection, cases can be classified into two groups: those related to the virus and those associated with complications and management.\(^5\)