Acute genital vulvar ulcerations are non-sexually acquired lesions characterized by sudden onset of a few genital ulcers, presented typically in girls and young women. The terms AGU or Lipschütz ulceration are used to describe ulcers associated with an immunologic reaction to a distant source of infection or inflammation.[6] The most common triggering factors are infectious diseases, specially flu-like and mononucleosis syndrome infections.[5,7] In many cases, the patients present also other symptoms, mainly oral aphthae, malaise, lymphadenopathy or fever,[8] and concomitant cutaneous manifestations such as erythema nodosum can also be observed.[6] Therapies for AGU include anti-inflammatory drugs, topical anaesthetics and corticosteroids. When a triggering infection is documented, antimicrobial agents are also useful for the management of the ulcerations. The lesions commonly resolve within 3 weeks.

Some virus species have been well defined as triggering agents of Lipschütz ulcers, specially Epstein–Barr virus. Although SARS Coronavirus 2 has been associated with oral ulcers,[9] we did not find previous reports of coronavirus-related AGU in the English literature. We report this case in order to describe a potential reactive dermatologic manifestation of the COVID-19. Moreover, we propose that Lipschütz ulcers could be triggered by SARS Coronavirus 2, comparably to other respiratory virus infections.

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Cutaneous manifestations of hospitalized coronavirus disease 2019 patients: a report of six cases with clinicopathologic features and viral RNA *in situ* hybridization

Dear Editor,

Novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global pandemic on March 2020.[1] Recalcati *et al*.[2] reported cutaneous manifestations in 20.4% of COVID-19 patients. We identified six patients (five female and one male) with COVID-19-associated cutaneous manifestations in April 2020 on the inpatient dermatology consultation service. The mean age was 51 years (range, 28–71 years). All patients presented with fever and upper respiratory symptoms. The median latency before onset of the rash was 9 days (range, 2–21 days). RNAscope ISH assay targeting the SARS-CoV-2 mRNA transcript for the spike protein (V-nCoV2019-S, ACD catalog #848569), validated on positive controls from COVID-19 autopsy lung tissue, was negative in all skin biopsy specimens. Three novel cutaneous patterns were identified: (i) COVID-19-associated exfoliative shock syndrome in two patients presenting with fever, hypotension and a diffuse exfoliative rash that spared mucous membranes (Fig. 1a,b). Skin biopsies demonstrated a subcorneal split with intracorneal neutrophils, parakeratosis and scant dermal inflammation (Fig. 1c,d). Pancultures were negative for staphylococcal infection. Given the overlapping features

of toxic shock syndrome (TSS) and staphylococcal scalded skin syndrome (SSSS), the patients were diagnosed with COVID-19-associated exfoliative shock syndrome. One patient expired, and the second patient improved with linezolid. (ii) COVID-19-induced rash and mucositis (CIRM) was diagnosed in one patient who developed a Stevens–Johnson syndrome (SJS)-like eruption in the absence of prior drug exposure. The SARS-CoV-2-positive patient presented with fever and oral erosions. She then developed widespread dusky targetoid papules and bullae with extensive denudation (Fig. 2a) and worsening mucous membranes involvement. Skin biopsy demonstrated full-thickness epidermal necrosis (Fig. 2b). (iii) COVID-19-associated calciphylaxis with thrombotic vasculopathy was identified in a patient presenting with painful retiform purpura consisting of angulated violaceous plaques with necrotic centres on the bilateral legs (Fig. 2c). Skin biopsy showed epidermal necrosis with vascular thrombi and calcification of small- to medium-sized vessels (Fig. 2d). Laboratory workup was remarkable for elevated D-dimer and fibrinogen. Creatinine, calcium and phosphorus levels were normal.

We present three novel COVID-19-associated cutaneous manifestations in hospitalized patients. Two patients presented with a COVID19-associated exfoliative shock syndrome. Recent reports describe a similar hyperinflammatory shock syndrome in children with overlapping features of Kawasaki disease and TSS.[3] Our patients also presented with fever, hypotension and an exfoliative skin eruption with overlapping features of TSS and SSSS. No gastrointestinal symptoms were observed. Staphylococcus aureus superinfection is a well-recognized event in the setting of viral diseases due to upregulation of IFN-α.[4] COVID-19 induces a cytokine storm, raising the levels of proinflammatory cytokines such as IFN-α,[5] thus potentially increasing host susceptibility for bacterial superinfection. It is unclear whether this presentation is a direct consequence of COVID-19-induced multisystem inflammatory syndrome in predisposed patients or an undetected staphylococcal superinfection. The second pattern identified was CIRM, an eruption that mimics SJS. Exfoliative mucocutaneous eruptions associated with infection are a well-recognized phenomenon.[6] CD8 cytotoxic T cells, together with the cytokine storm occurring in the setting of COVID-19, may contribute to this severe cutaneous reaction leading to necrosis of keratinocytes. The histopathologic findings of CIRM are indistinguishable from SJS; however, the time course of events, careful drug history and identification of concurrent infection can allow for distinction. COVID-19-associated calciphylaxis with thrombotic vasculopathy is the third pattern observed. The pathogenesis of nonuremic calciphylaxis is primarily related to a

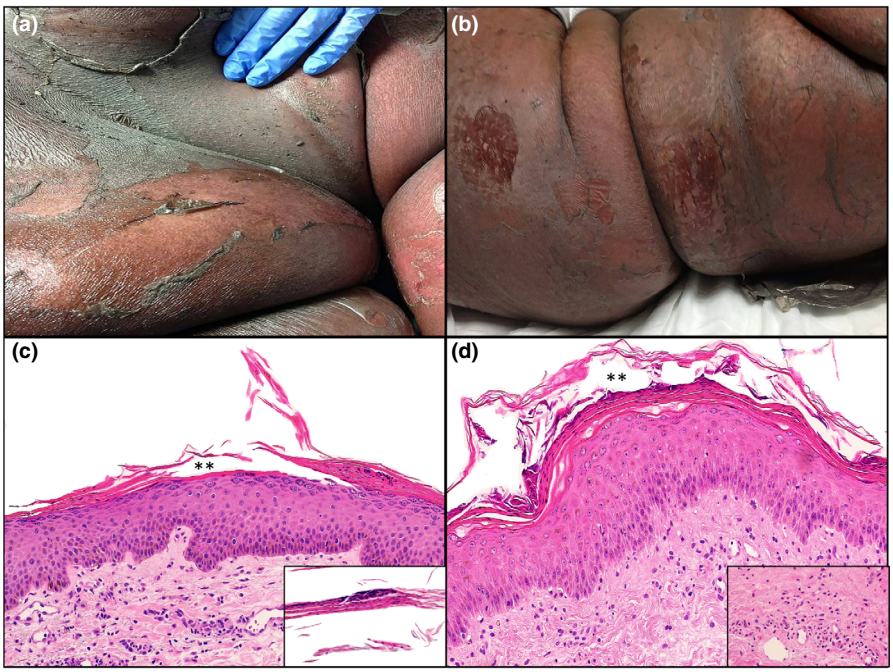

Figure 1 Clinical and histopathologic features of patients with COVID-19-associated exfoliative shock syndrome. Patient 1: (a) Erythematous plaques with superficial exfoliation on the abdomen. (b) Patient 2: Erythematous to dusky plaques with superficial exfoliation on the trunk. Patient 1: (c) Haematoxylin and eosin stain of punch biopsy showing subcorneal split (**) with parakeratosis and intracorneal neutrophils (original magnification ×100). Inset showing parakeratotic scale with neutrophilic fragments (original magnification ×200). (d) Patient 2: Haematoxylin and eosin stain of punch biopsy showing subcorneal split (**) with parakeratosis and intracorneal neutrophils (original magnification ×100). Inset showing scant superficial dermal neutrophilic infiltrate (original magnification ×200).

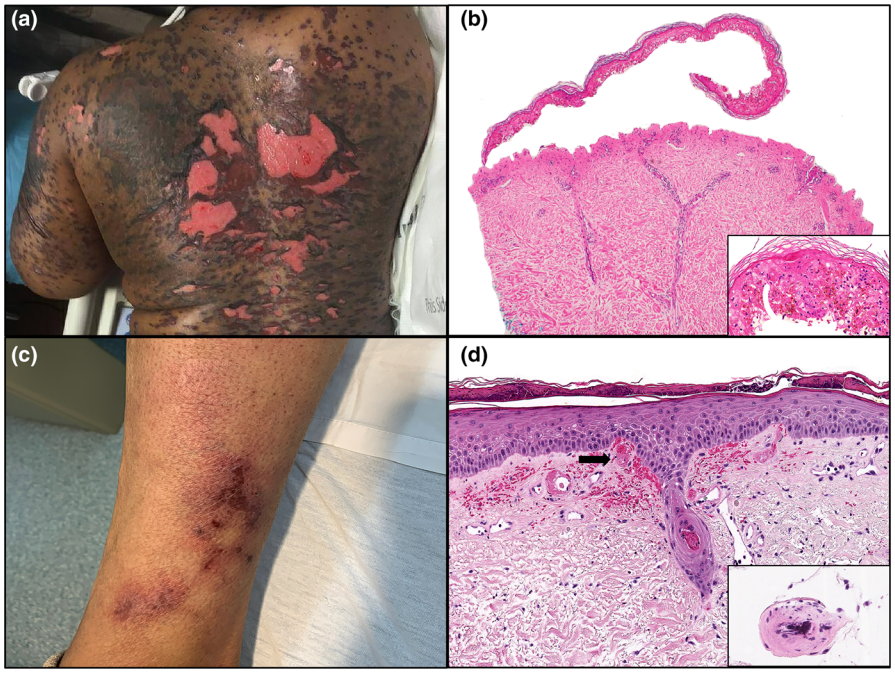

Figure 2 Clinical and histopathologic features of patients 3 and 4. Patient 3: (a) Dusky vesicles and bullae coalescing into plaques with denudation on the back. (b) Haematoxylin and eosin stain of punch biopsy showing full-thickness epidermal necrosis (original magnification ×100). Inset highlighting confluent epidermal apoptosis (original magnification ×200). Patient 4: (c) Retiform purpura consisting of violaceous angulated plaques with necrotic centres on the lower extremity. (d) Haematoxylin and eosin stain of punch biopsy showing vascular thrombi (arrow) (original magnification ×100). Inset highlighting vessel wall calcium deposition (original magnification ×200).

hypercoagulable state and thrombotic vasculopathy.[7] COVID-19-associated coagulopathy with initial signs of increased D-dimer and fibrinogen as seen in our patient is well-documented.[8] The abrupt onset of calciphylaxis with thrombotic vasculopathy and concomitant COVID-19 infection is suspect and suggests that COVID-19 infection may increase susceptibility for nonuremic calciphylaxis. Finally, in two patients we observed COVID-19-associated morbilliform exanthems that demonstrated a superficial perivascular dermatitis on histopathology.

Viral mRNA was not detected using RNA ISH for SARS-CoV-2, suggesting that cutaneous manifestations associated with COVID-19 are secondary to dysregulation of the immune and coagulation pathways rather than direct viral skin toxicity.

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Authors contributions

Drs. Bitar, Lowe and Andea had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SARS-CoV-2, skin lesions and the need of a multidisciplinary approach

Editor

COVID-19 is a disease caused by severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus (SARS-CoV-2). It was first described in Wuhan (China) on December 2019 and has spread to become a pandemic. Its clinical presentation is mainly characterized by cough, fever and dyspnoea, although many other symptoms have been described within its presentation pattern. In some cases, it causes an acute respiratory distress that has lead to the death of thousands of people around the world. Furthermore, different types of skin lesions have been described during the infection period of illness.[1] In this exceptional situation of global health emergency, physicians are undertaking research work in order to achieve notions on the aetiopathogenesis of these skin lesions. The first report of cutaneous manifestations described different forms of skin lesions such as erythematous rash, urticaria and chickenpox-like vesicles.[2] Further studies have classified 5 different type of skin lesions and associated them with patient demographics, timing in relation to symptoms of the disease, severity and prognosis.[1] Acro-ischaemic lesions have also been notified and attributed to disseminated intravascular coagulation and to the expression of secondary microthrombosis due to endothelial damage.[3-5] However, to date, there is no clear understanding on whether the skin lesions are secondary to the viral infection nor why there are different presentations of skin lesions for the same viral infection.

We present 4 patients with COVID-19, confirmed by positive polymerase chain reaction, who were referred to our service due to the appearance of skin lesions (Fig. 1). Two of them developed skin lesions during hospitalization whilst presenting respiratory symptoms, and the other two developed skin lesions many days after hospital discharge. Demographic data, description and histology of skin lesions, blood parameters, clinical symptoms and drugs administered are shown in Table 1. The algorithm of the spanish pharmacovigilance system (ASPS), which evaluates the possible implication of a drug reaction as a cause of the skin lesions,[6] was also applied. The ASPS analyzes i) the interval between drug administration and the apparition of skin lesions, ii) the degree of knowledge of the relationship between the drug and the effect described in literature, iii) the evaluation of drug withdrawal, iv) the rechallenge effect and v) alternative causes. Each item receives an individual subscore, and a total sum ≥6 indicates a probable causality.[6]

As mentioned above, skin lesions appear to be a sign within patients suffering from COVID-19. To date, no hypothesis has been proposed to explain if the lesions (including the different types) are attributable to the virus, to drug adverse reactions or to any other clinical condition. Histopathological study alone cannot conclude an aetiology, as it does not distinguish between a possible viral exanthema and a toxicoderma (Fig. 1). In our series, small enough to draw conclusions, we have found no differences between the multiple types of skin lesions and analytical or clinical features. Even in lesions with apparent vascular involvement, which have been associated with alterations in coagulation,[3-5] the analytical parameters did not differ from those with other types of skin lesions. Regarding drug involvement, since all the patients were exposed to multiple drugs at the same time, the ASPS was not able to differentiate the possibility of drug implication nor the immune mechanisms involved. Thus, further assays with selective (*in vitro* or *in vivo*) tests for each drug seem necessary in order to completely rule out drug involvement. In addition, since many patients worldwide are being infected with SARS-Cov-2, and many of them present similar medical history and receive the same treatments, it seems necessary to investigate the existence of an individual predisposition that facilitates the development of skin lesions. For all these reasons, in order to correctly study the aetiology of the skin lesions, a multidisciplinary approach should be carried out.

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Conflicts of interest

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