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Urticarial vasculitis in COVID-19 infection: a vasculopathy-related symptom?

Editor,

The novel coronavirus disease (COVID-19) outbreak has been recently declared a pandemic by the World Health Organization (WHO), being Italy and Spain the worst-hit European countries. Although the main clinical picture consists of fever and respiratory symptoms, an increasing number of studies have reported associated skin manifestations. Herein, we present two patients with urticarial vasculitis arising in the context of COVID-19 infection.

The first case is an elderly woman who was admitted to the hospital with bilateral pneumonia testing positive for COVID-19. She had been receiving treatment with hydroxychloroquine, lopinavir/ritonavir and azithromycin for 5 days. The Dermatology Department was consulted for the appearance of painful erythematous patches on her trunk and hips, which left residual purpura when fading (Fig. 1a). A cutaneous biopsy was performed, revealing histologic changes characteristic of small-vessel vasculitis (Fig. 1b). A sudden worsening of her respiratory condition led to the patient's death, and therefore, no treatment could be prescribed.

Our second case is a middle-aged man who presented to the Emergency Department with a 2-week history of fever, cough and

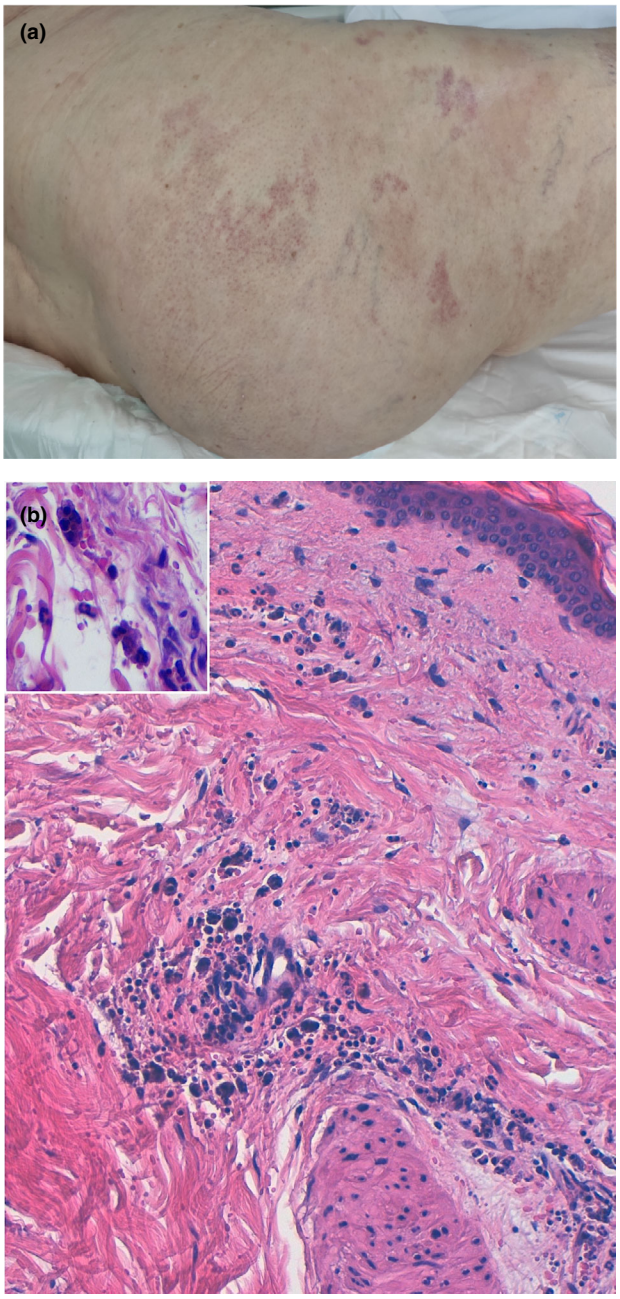

Figure 1 First patient. (a) Clinical lesions on the buttocks and hips. Some erythematous patches are observed, along with other purpuric ones. (b) Histopathological images (H/E × 20) revealing blood extravasation and neutrophilic perivascular inflammation with prominent karyorrhexis. There are some macrophages with a cytoplasm full of nuclear debris (inset: H/E × 40).

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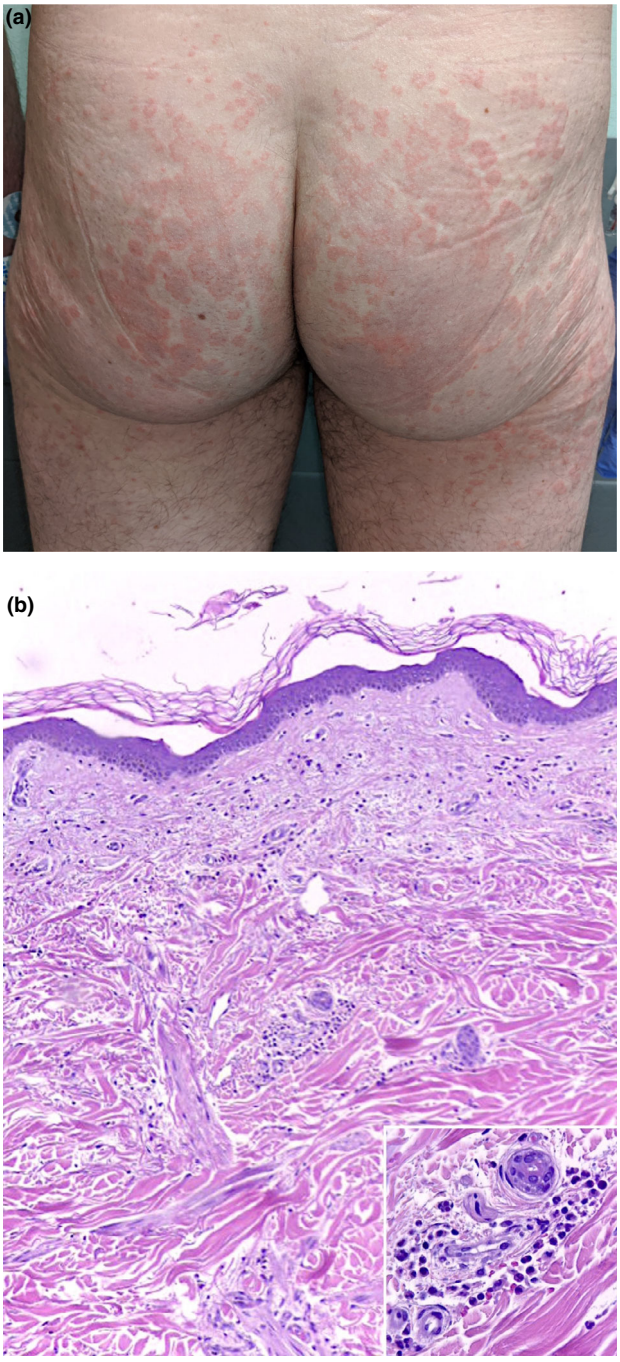

Figure 2 Second patient. (a) Clinical lesions on the buttocks, consisting of erythematous plaques with an active border and a purpuric centre. (b) Histopathological images (H/E × 10) showing preserved epidermis with moderate perivascular neutrophilic inflammation and blood extravasation in the dermis. There is endothelial swelling, necrosis and fibrin deposition (inset: H/E × 40).

anosmia. Two days before consulting, he had developed a pruritic rash on his buttocks. On examination, the patient had erythematous and oedematous plaques with a purpuric centre (Fig. 2a). A skin biopsy was performed, showing evidence of small-vessel damage (Fig. 2b). Therapy with hydroxychloroquine and azithromycin was started as treatment for COVID-19. Additionally, prednisone and antihistamines were administered for his skin condition. Two weeks later, the patient was asymptomatic.

Urticarial vasculitis is one of the multiple clinical expressions of leucocytoclastic vasculitis. Drugs, viruses and autoimmune diseases, such as systemic lupus erythematosus, can be found among its most frequent causes. A type III hypersensitivity mechanism with deposit of immunocomplexes is thought to be behind this condition. Clinically, it is characterized by the appearance of urticarial lesions similar to weals, but with individual lesions lasting more than 24 h. Although usually asymptomatic, the lesions can be accompanied by a burning sensation, pain or sometimes even by fever. Laboratory findings can include hypocomplementaemia, especially in cases linked to connective tissue diseases.

COVID-19 has been associated with a variety of skin manifestations, including varicella-like exanthemas, dengue-like petechial rashes[1,2] or urticarial eruptions.[3] However, not only have viral rashes been related to COVID-19, but also other types of skin symptoms that are reminiscent of a vascular disease, such as acro-ischaemic lesions described by Zhang et al.[4] and chilblain-like lesions.[5,6]

Emerging theories claim that this novel coronavirus can produce endothelial activation and possibly microocclusive disease, which could be the cause of acute respiratory distress syndrome.[7,8] These aetiopathogenic theories may even explain the neurological manifestations that have been observed in patients with severe disease.[9] Although acro-ischaemic lesions have been initially attributed to a hypercoagulable state, endothelial activation could play a key role in their development. In both cases, a tendency towards small-vessel affection by COVID-19 cannot be denied. Postmortem examinations have not only revealed the presence of hyaline thrombi in small lung vessels, in the presence of virus detectable by PCR, but also in other organs without evidence of coronavirus infection.[10] This suggests the possibility of vascular involvement in remote tissues, producing diverse manifestations. For example, in immunologically predisposed individuals, urticarial vasculitis may appear, as seen in these two patients. Although urticaria-like rashes have been associated with COVID-19, urticarial vasculitis has not been described in this population to date. This could be due explained by the lack of skin biopsies performed in patients with COVID-19, either because lesions are usually mild or because of fear of contagion. We are certain more cases like these could be observed and therefore encourage dermatologists to remain alert to any possible new lesions in these patients. Much is still unknown about this new virus and its effects on the organism, and only

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our observation and research will allow us to increase this knowledge.

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Conflicts of interest

The authors declare that there are no conflicts of interest related to this article. Dr. de Perosanz-Lobo, Dr Fernandez-Nieto, Dr. Burgos-Blasco, Dr. Selda-Enriquez, Dr. Carretero, Dr. Moreno and Dr. Fernández-Guarino have nothing to disclose.

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Urticaria (angioedema) and COVID-19 infection

Editor,

The novel coronavirus, otherwise known as COVID-19, has fast become a major health concern.[1,2] It has been reported that in addition to the conventional respiratory symptoms, patients also display skin manifestations such as Urticaria and angioedema.[3] Here, we present a case study of an elderly man who first presented with generalized pruritic hives ranging from 1.5 to 8.0 cm in diameter on the 5th of March 2020 (Fig. 1). The patient was investigated for another differential diagnosis of Urticaria such as parasitic and bacterial infection, for which negative results were found. On the 5th of March 2020, the patient reported these symptoms plus general malaise, fatigue, 37.90°C temperature and sore throat. Initial biochemical tests showed that the patient presented with low numbers of white blood cells (WBC) (WBC = 2.75×10^3). The most hallmark issue, which is lymphopenia, was detected in this case (lymphocytes = 852).[4] The other blood tests results were found to be normal. Real-time polymerase chain reaction (RT-PCR) for COVID-19 was not performed due to the time lapse between starting the symptoms and hospital admission. Therefore, the CT chest was carried out, which showed pneumonia with bilateral and subpleural areas of ground-glass opacification, consolidation affecting the lower lobes and confirming the diagnosis of COVID-19 (Fig. 2).

The relationship between Urticaria and infection has rarely been reported; this is probably due to the difficulty in establishing a cause and effect relationship.[5] Literature suggests that Urticaria and angioedema can be induced by viral and bacterial infection.[6,7] Urticaria has previously been associated with Cytomegalovirus, Herpesvirus and Epstein–Barr virus. A systematic review undertaken in 2016 found that viral infections could also act as potential triggers and sometimes even as the main etiologic agent in causing both acute and chronic Urticaria. Additionally, they found that in adults, hepatitis viral infections appeared to be the most frequent cause of Urticaria, whereas, in children, herpesviral infections were more frequent. To further support these data, it was also found that urticarial manifestations cleared up after the viral infections were treated or controlled.[5] Another study found that acute Urticaria is a common manifestation of viral infections for both children and adults but more so for children. Infections were also identified as the primary cause of Urticaria in approximately 37% of cases.[8]

Currently, there are no significant data regarding the association between skin manifestations such as Urticaria and COVID-19.[9] One study, in which a group of dermatologists analysed the cutaneous involvement in COVID-19, found that from 88 patients, 20.4% portrayed cutaneous manifestation. Of these, 8 patients developed the manifestations at disease onset whereas 10 developed the manifestations after hospitalization. These cutaneous

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