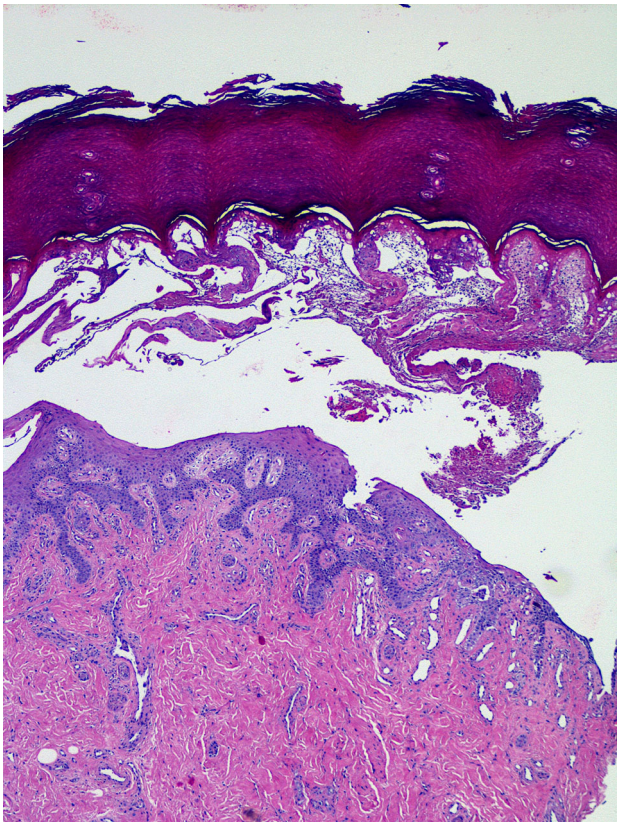

Figure 2 Acral skin that shows an intra-epidermal vesicle. It has ischaemic necrosis on its roof, containing preserved cell outlines without nuclei, and reticular changes. The vesicle is associated with an acute inflammatory infiltrate. The dermis shows dilated vessels (H&E stain; x4).

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Acute generalized exanthematous pustulosis with erythema multiforme-like lesions induced by Hydroxychloroquine in a woman with coronavirus disease 2019 (COVID-19)

Dear Editor,

The antimalarials, chloroquine and hydroxychloroquine (HCQ), and the antivirals lopinavir/ritonavir have been recently recorded as having anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) effects.[1] In particular, regarding Italy, one of the countries most affected by the pandemic, the Italian Society of Infectious and Tropical disease (Lombardy section) has recommended the use of HCQ for treatment of coronavirus disease 2019 (COVID-19).[2] HCQ is widely used to treat dermatologic and rheumatologic diseases, and it has been described as one of the main drugs triggering acute generalized exanthematous pustulosis (AGEP).[3,4] Only one single case of AGEP induced by HIV post-exposure prophylaxis with lopinavir/ritonavir has been reported.[5]

Figure 1 (a) Widespread acute rash on an erythematous–oedematous base, with scattered pinhead-sized pustules involving the face, trunk and upper limbs; the patient is wearing a surgical mask and gloves in accordance with the hospital's anti-coronavirus disease 2019 recommendations. (b) Extensive desquamation with scattered pustules on the abdomen and targetoid lesions on the thigh. (c) Erythematous–oedematous targetoid lesions covered by discrete small pustules and scales.

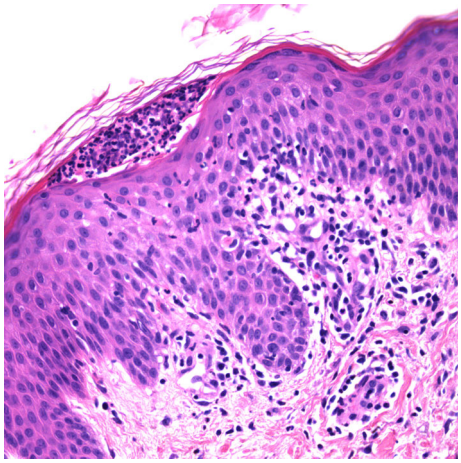

Figure 2 Subcorneal neutrophilic pustule, slight spongiosis with acanthosis, neutrophilic exocytosis, rare keratinocyte necrosis and a perivascular infiltrate consisting of lymphocytes with rare neutrophils and eosinophils (haematoxylin–eosin stain; original magnification: ×20).

A 70-year-old Italian woman with no personal/family history of psoriasis was admitted to our clinic for the rapid onset of a diffuse, pruritic pustular eruption. Three weeks before, she had been treated for SARS-CoV-2 pneumonia with lopinavir/ritonavir 200/50 mg two tablets and HCQ 200 mg bid for 10 days with a good response. Three days after the withdrawal of the treatment, she referred the onset of a skin eruption on the upper arms, rapidly spreading to the trunk. She consulted her primary care physician and began treatment with oral prednisone 0.3 mg/kg daily. Seven days later, due to the worsening of her skin eruption, the patient decided to consult the emergency department.

Physical examination revealed a widespread eruption on an erythematous–oedematous base, with scattered pinhead-sized pustules and scales, involving the face, trunk and upper limbs. Targetoid lesions studded with small pustules were present in a symmetric pattern over buttocks, thighs and legs (Fig. 1). Mucous membranes, palms and soles were spared. The patient denied any other recent drug intake. A skin biopsy taken from the thigh showed a subcorneal pustule with mild focal acanthosis and spongiosis, neutrophilic exocytosis, sparse keratinocyte necrosis, and a perivascular lymphocytic infiltrate with rare neutrophils and eosinophils (Fig. 2), consistent with AGEP. The patient was suggested to gradually taper prednisone within 30 days with a slow but progressive resolution.

Acute generalized exanthematous pustulosis is classically characterized by a sudden onset of widespread non-follicular sterile pustules arising within large areas of oedematous erythema; it has been attributed to drugs in 90% of cases.[6] Rarely, AGEP can manifest itself in an atypical fashion with the development of target-like lesions. This presentation, also reported as generalized pustular figurate erythema or AGEP with erythema multiforme-like lesions or atypical AGEP, has been described especially in patients taking HCQ.[7–9] Although we cannot rule out that lopinavir/ritonavir could be implicated into the rash,[5] we suggest that HCQ was the probable triggering drug in our COVID-19 patient because this antimalarial is considered one of the most frequently mentioned drugs causing AGEP both in its typical and atypical form.[3,6] Infectious viral agents such as parvovirus B19, cytomegalovirus and coxsackie B4 have also been reported as exceptionally AGEP related.[3,6] Although some skin eruptions have been recently associated with SARS-CoV-2 including varicella-like exanthems, erythematous or urticarial rashes, the development of pustular lesions has never been described in COVID-19.[10]

AGEP is considered a self-limiting disease with good prognosis that usually resolves in 15 days after the causative drug is withdrawn.[3,6] However, HCQ-induced AGEP accompanied by erythema multiforme-like lesions seems to follow a more recalcitrant course than usual, as it occurred in our patient. It predominantly involves women and is characterized by a longer latent period and a protracted course requiring systemic corticosteroid administration.[7]

Because of the actual spreading use of HCQ, not only for dermatological and rheumatological conditions but also for the treatment of COVID-19 patients, it is likely that clinicians could observe an increased number of cases of HCQ-induced AGEP in the near future.

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Urticaria-like lesions in COVID-19 patients are not really urticaria – a case with clinicopathological correlation

Dear Editor,

We have read with great attention the article by 1 considering urticarial lesions as a coronavirus disease 2019 (COVID-19)-associated skin manifestation. They observed two patients with erythemato-oedematous lesions surrounded by whitish halo, thus similar to hives but without additional data on their evolution.[2] A previous report of COVID19-related urticarial lesions had also been first published by Recalcati.[1] However, none of these two published articles detailed if the lesions were evanescent, as it is mandatory for urticaria, nor did a pathological study.

Madrid, Spain, has been considered by the World Health Organization as an area of SARS-CoV-2 of community transmission.[3] Since then, we began to observe different skin manifestations in patients with COVID-19 infection. We present the case of a patient with non-evanescent urticarial lesions and its clinicopathological correlation.

A 60-year-old woman was admitted to the hospital for dry cough and pyrexia in the previous 3 weeks. In the last 5 days, she developed an urticarial eruption (Fig. 1). The patient had no relevant past medical history and had only suffered one episode of pompholyx 3 years ago. When the cutaneous rash appeared, she was not under any medication. She presented a bilateral interstitial pneumonia on X-ray, and blood test revealed a mild lymphopenia (370/mm^3) and increased liver enzymes (GOT, GPT, LDH, GGT three times normal). A cutaneous punch biopsy was performed showing slight vacuolar-type interface dermatitis with occasional necrotic keratinocytes. No oeosinophils were encountered. These histological alterations were compatible with an erythema multiforme-like pattern (Fig. 2).

On follow-up, the lesions were persistent on the same locations without evolving to blistering. Surprisingly, in the work by Marzano *et al*.,[4] reporting varicella-like lesions on COVID-19 patients, the histological image included in their report resembles our case.

In conclusion, we want to highlight that histopathological studies are important to characterize COVID-19-related skin lesions. In our experience, these urticaria-like lesions may also

Figure 1 Confluent weals on anterior (a) and posterior (b) trunk.

