appear in late phases and not only as early manifestations of COVID. Thus, this type of skin lesions should be further studied to clarify its relation with COVID-19 and whether it may be useful to identify earlier COVID-19 patients.

But we must remember that even today, when it seems that all of our patients are affected of COVID-19 and all the skin diseases may be related to it, we have to ground on clinicopathological correlation and to maintain the same quality standards that we used to have before SARS-CoV-2 appeared. This will be the key to unravel our enemy in this battle.

Acknowledgement
The patients in this manuscript have given written informed consent to publication of their case details.

Funding sources
none to be declared.

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DOI: 10.1111/jdv.16618

A clinicopathological study of eight patients with COVID-19 pneumonia and a late-onset exanthema

Editor
Our hospital diagnosed the two first non-imported COVID-19 cases in Spain on 26 February. Up to date, a total of 1177 COVID-19-infected patients have been hospitalized. Eight of them were referred for dermatological examination. Due to the overwhelming situation, the incidence of cutaneous manifestations in our hospitalized COVID-19-infected patients is probably greater than this 0.7%.1,2

We studied four males and four females with a mean age of 72.2 years (Table 1). The mean hospital stay was 23.2 days. Two patients required intensive care. No patient has died so far.

Analytically, all the patients presented lymphopenia and elevated D-dimer and C-reactive protein. Patient 1 presented also neutrophilia, eosinophilia and elevated liver enzymes.

Most frequent drugs during hospitalization were hydroxychloroquine (HCQ), lopinavir/ritonavir and ceftriaxone. These treatments had finished at least 1 week before the onset of the cutaneous rash in all cases, except patient 2. Three patients had no new medications in the previous 15 days. Only two patients received new drugs in the previous 48 h.

Mean latency time from systemic symptoms to exanthema was 27.6 days. Exanthema varied from ill-defined erythematous...
| Patients | Gender/age (years) | Nasopharyngeal swab | Rash distribution | Lesions type | Duration (days) | New drugs in the previous 2 weeks | Days of evolution | when biopsied | Cutaneous latency time (days) | Histopathological findings |
|----------|------------------|---------------------|------------------|--------------|----------------|-------------------------------|------------------|--------------|----------------|-------------------------------|
| Case 1   | M/58             | Positive            | Generalized      | Coalescent erythematous maculopapules | 12 | None | Focal spongiosis, exocytosis of neutrophils, discrete perivascular and interstitial neutrophilic infiltrate with scarce presence of eosinophils | 4 | Subcutaneous pustules, spongiosis, papillary oedema, dense perivascular infiltrate with fibrin thrombi, melanophages |
| Case 2   | F/84             | Negative            | Trunk, flexures  | Coalescent erythematous maculopapules | 11 | Hydroxychloroquine, lopinavir/ritonavir, ceftriaxone | 2 | Subcutaneous pustules, spongiosis, papillary oedema, moderate perivascular infiltrate with discrete presence of eosinophils, focal thrombi, focal basal layer vacuolar degeneration |
| Case 3   | F/82             | Positive            | Coalescent       | Ill-defined erythematous patches     | 29 | Fosfomycin | Intraepidermal pustules, spongiosis, discrete perivascular and interstitial neutrophilic infiltrate with scarce presence of eosinophils | 1 | Subcutaneous pustules, spongiosis, papillary oedema, moderate perivascular infiltrate with dense perivascular and interstitial neutrophilic infiltrate, fibrin thrombi, focal thrombi, focal basal layer vacuolar degeneration |
| Case 4   | F/68             | Positive            | Proximal         | Ill-defined erythematous macules     | 28 | Metamizole, linezolid, piperacillin-tazobactam, amiodarone | 9 | Focal spongiosis, exocytosis of neutrophils, discrete perivascular and interstitial neutrophilic infiltrate with scarce presence of eosinophils | 10 | Subcutaneous pustules, spongiosis, papillary oedema, dense perivascular infiltrate with fibrin thrombi, focal thrombi, focal basal layer vacuolar degeneration |
| Case 5   | M/51             | Positive            | Proximal proximal | Coalescent erythematous maculopapules | 29 | None | Spongiosis, dense perivascular and interstitial neutrophilic infiltrate with discrete presence of eosinophils | 6 | Focal spongiosis, exocytosis of neutrophils, discrete perivascular and interstitial neutrophilic infiltrate with scarce presence of eosinophils |
| Case 6   | M/88             | Positive            | Face             | Coalescent erythematous maculopapules | 31 | Furosemide | Pustules, spongiosis, papillary oedema, dense perivascular infiltrate with fibrin thrombi, focal thrombi, focal basal layer vacuolar degeneration | 12 | Subcutaneous pustules, spongiosis, papillary oedema, moderate perivascular infiltrate with dense perivascular and interstitial neutrophilic infiltrate, fibrin thrombi, focal thrombi, focal basal layer vacuolar degeneration |
| Case 7   | F/69             | Positive            | Trunk, flexures  | Coalescent erythematous maculopapules, pustules, desquamation | 33 | None | Spongiosis, discrete perivascular and interstitial neutrophilic infiltrate with scarce presence of eosinophils | 15 | Subcutaneous pustules, spongiosis, papillary oedema, moderate perivascular infiltrate with dense perivascular and interstitial neutrophilic infiltrate, fibrin thrombi, focal thrombi, focal basal layer vacuolar degeneration |
| Case 8   | M/78             | Positive            | Trunk, face      | Ill-defined erythematous patches     | 30 | Piperacillin-tazobactam, linezolid | 8 and ongoing | Subcutaneous pustules, spongiosis, papillary oedema, dense perivascular infiltrate with fibrin thrombi, focal thrombi, focal basal layer vacuolar degeneration | 4 | Subcutaneous pustules, spongiosis, papillary oedema, dense perivascular infiltrate with fibrin thrombi, focal thrombi, focal basal layer vacuolar degeneration |

F. female; M, male.
patches to coalescent maculopapules, some of them with violaceous centre (Fig. 1). The trunk was invariably involved with predilection for the back and folds. Patient 7 developed pustules and desquamation (Fig. 1f). Mean duration of the exanthema is 11.6 days so far.

Histologically, patients showed in a variable degree: spongiotic dermatitis, non-follicular subcorneal pustules, neutrophilic exocytosis, an interstitial neutrophilic infiltrate and scarce eosinophils (Table 1, Fig. 2). Three patients presented signs of vascular injury with microthrombi inside dermal capillaries and hematic extravasation (Fig. 2a,b). Fibrinoid necrosis of the vessel walls was not found. The presence of microorganisms was ruled out.

Cutaneous manifestations of COVID-19 have recently been classified in five different clinical patterns3.

Our patients presented maculopapular eruptions that shared a late onset. This fact leads us to hypothesize that the rash could be caused by the cytokine storm of the hyperinflammatory phase4 rather than by the virus itself.

A common histological pattern was found, and it was more striking in patients whose biopsies were performed later; therefore, it might be the same process in different stage of
evolution. Three patients showed microthrombi in dermal capillaries as the ones described by Gianotti et al.\(^5\) in two cases. Recent publications have found evidence of direct viral infection of the endothelial cell in different organs that could explain the impaired microcirculatory function of this disease\(^6\). In our cases, microthrombi could be a clue for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. They could also be an epiphenomenon of a possible acute generalized exanthematous pustulosis (AGEP), but this has not been described before.\(^7\) A further in situ hybridization or SARS-CoV-2 immunohistochemistry would help to clarify this question.

We found difficulty to distinguish the viral or drug origin of the rashes. However, only two patients started new medications during the few days before, as usually occurs in AGEP.\(^8\) Furthermore, clinically no patient except one resembled a classical AGEP. Patch tests need to be performed to determine a possible drug responsibility.

An atypical form of AGEP, generalized pustular figurate erythema, has been described as a delayed reaction to HCQ.\(^9\) Nevertheless, the incidence of this adverse effect to HCQ is infrequent.\(^10\) Thus, if the type of exanthema we are describing here is related to HCQ, there may be another factors (as SARS-CoV-2 virus itself) playing a role.

To conclude, we present a series of eight patients with COVID-19 pneumonia who developed a late-onset maculopapular exanthema with a distinct histological pattern. Microthrombi may be a clue for SARS-CoV-2 endothelial infection.

**Acknowledgements**

We thank all the health workers of Hospital Universitario de Torrejón for their extraordinary work during this pandemic. All patients in this manuscript have given written informed consent to the publication of their case details and pictures.

**Conflict of interest**

None.

**Funding sources**

None.

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**Figure 2** (a) Case1 (H&E, 10×). Subcorneal pustule, a dense perivascular and interstitial mixed neutrophilic and lymphocytic infiltrate with moderate presence of eosinophils and erythrocyte extravasation. (b) Case 1 (H&E, 40×). Fibrin thrombi in papillary dermis capillaries and erythrocyte extravasation. Fibrinoid necrosis of the vessel walls was not found. (c) Case 1 (H&E, 40×). More detailed view of the perivascular and interstitial neutrophilic infiltrate and spongiosis. (d) Case 2 (H&E, 40×). Subcorneal pustule and spongiosis.

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Fever with rash in COVID-19: viral exanthema or secondary lesions?

Dear Editor,

COVID-19 was originated in Wuhan, China, and has developed into a pandemic since late 2019. The virus possesses powerful pathogenicity and transmissibility. Many open questions remain, including the description of potential involvement of other organs than the respiratory tract. Most patients have mild influenza-like symptoms. A minority, especially patients with chronic lung disease, develops lethal disease including severe pneumonia, pulmonary oedema, rapidly developing acute respiratory distress syndrome (ARDS), multiple organ failure and septic shock. From a study conducted in Italy on 88 COVID-19-positive patients, 20.4% had skin involvement, which did not correspond to disease severity. Of these, 9% developed skin manifestations at symptom onset and 11.3% after hospitalization. Erythematous rash, widespread urticaria and vesicles were found mostly on the trunk, which resolved spontaneously. Itching was absent or insignificant. Other coronaviruses can cause skin symptoms, including acute haemorrhagic oedema of infancy associated with coronavirus-NL63 infection in an 8-month infant. Coronavirus OC43/HKU1 was associated with Kawasaki disease resulting in hyperaemia of the tongue and oral mucosa, bilateral bulbar conjunctival injection without exude, maculopapular rash on trunk and abdomen, oedema on medial region of feet and facial pallor.

We have seen two COVID-19 patients with skin symptoms. We observed skin manifestations in those patients, however...