COVID-19 SPECIAL FORUM

Clinical and histological characterization of late appearance maculopapular eruptions in association with the coronavirus disease 2019. A case series of seven patients

To the editor

Since the first report of cutaneous manifestations of the coronavirus disease 2019 (COVID-19) by Recalcati et al,[1] there has been described five clinical patterns including pseudo-chilblain lesions, vesicular eruptions, urticarial lesions, livedo and necrosis and maculopapular eruptions.[2] Several clinical reports have been published recently describing these clinical patterns although there is still a lack of information regarding histopathology of maculopapular eruptions.

We designed a retrospective study of patients attended in our department over the course of three weeks. We collected clinical data and pictures, and performed a biopsy when possible. Inclusion criteria were the presence of maculopapular eruptions as the reason for consultation in patients with previously confirmed infection for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by nasopharyngeal protein chain reaction (PCR). Exclusion criteria included patients that had taken any new medication in the previous two weeks as well as those who presented other type of lesions.

From a total of 18 initial patients, seven were included in the study. Patients´ information has been summarized in Table 1. Mean age was 66, 57 years (range 57–82 years). All the patients have had pneumonia before the onset of the cutaneous symptoms and consulted after they had been discharged from the hospital. The lesions appeared after a mean time of latency of 27,85 days (range 20–36 days). The clinical presentation and distribution of the lesions were similar in all the cases, being the trunk the most affected area Fig. 1a,b. Mean duration time of the aforementioned lesions after treatment commenced was 10,42 days (range 7–18 days) A second PCR was not performed at the time of the onset cutaneous manifestations and neither serological assays.

Biopsy was performed in four of the cases (57.14%). In all of them a mild superficial perivascular lymphocytic infiltrate was observed Fig. 1c,d.

Jimenez-Cauhe[3] et al. present a case of maculopapular eruption in a patient infected by SARS-CoV-2 and affirms the difficulty of assessing the origin of these reactions and subsequently unable to conclude if they are drug related or induced by the virus itself. Our findings suggest the latter since none of our patients had taken any new medication in the previous fifteen days and all of them showed similar findings in the biopsy.

Another interesting fact is the late time of onset in our patients. In a Spanish study, out of 375 patients with suspected or confirmed COVID19, 176 patients presented maculopapular eruptions. 108 of them appeared at the same time as the respiratory symptoms while only 60 appeared afterwards like in our

Table 1 Clinical and histological characteristics of patients with maculopapular eruptions

Case number	Sex	Age (years)	Location	Number of days since onset of		Duration of skin symptoms (days)	Treatment	Histology
				Symptoms	PCR			
1	M	67	Trunk, proximal upper limbs	20	12	18	None	Mild Superficial perivascular lymphocytic infiltrate
2	F	57	Trunk	28	26	9	Systemic CE	Mild Superficial perivascular lymphocytic infiltrate
3	F	82	Trunk, proximal upper limbs	32	32	7	Systemic CE	–
4	M	71	Trunk, proximal upper limbs	38	31	9	Systemic CE	–
5	F	64	Trunk, proximal upper limbs	21	24	9	Systemic CE	–
6	F	62	Trunk, proximal upper and lower limbs	20	27	14	Systemic CE	Mild superficial perivascular lymphocytic infiltrate, spongiosis
7	F	63	Trunk, proximal upper limbs	36	36	7	Systemic CE	Mild superficial perivascular lymphocytic infiltrate and spongiosis

CE, Corticoesteroids; F, Female; M, Male.

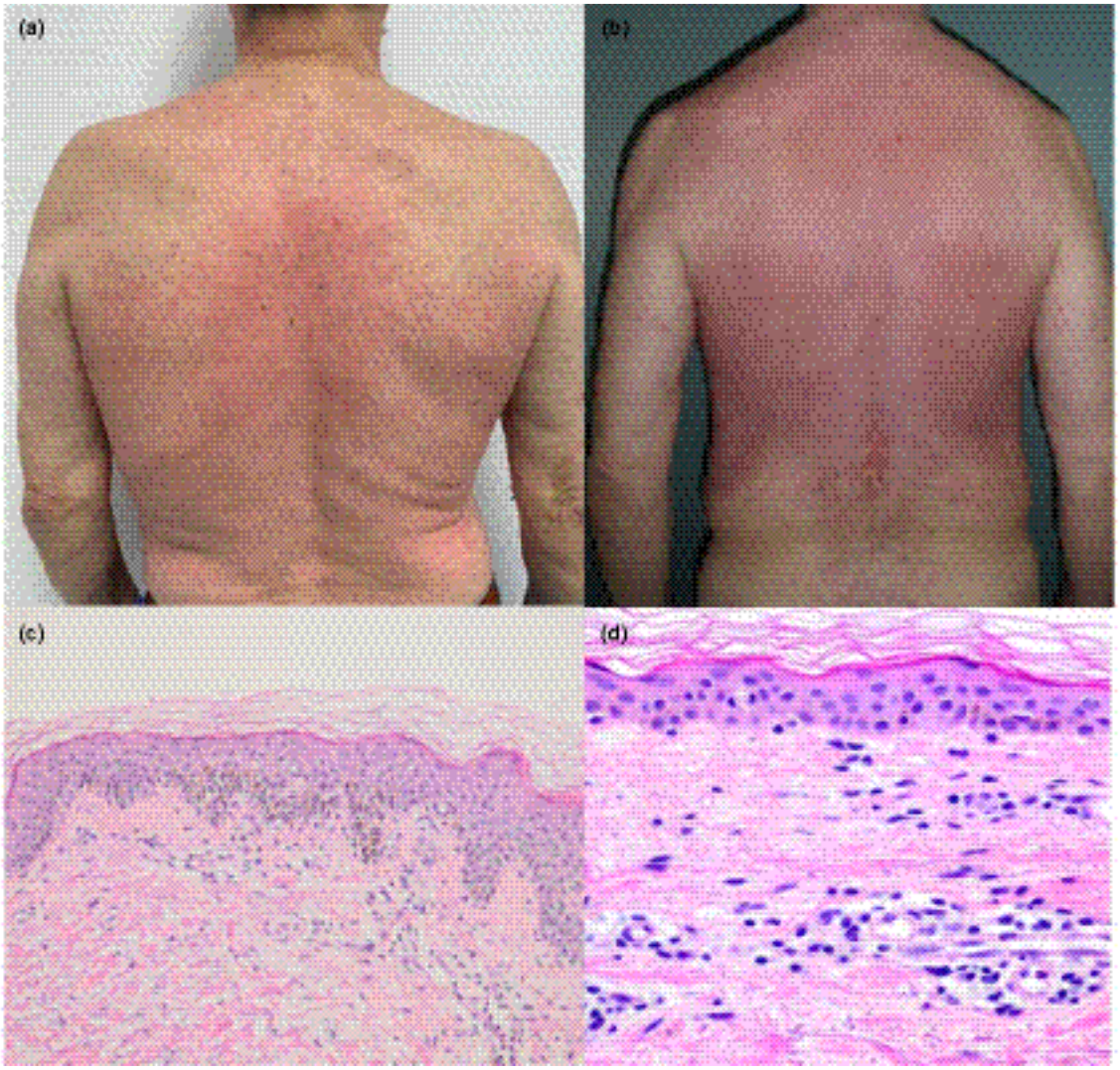

Figure 1 a) Patient 4. Confluent maculopapular exanthem affecting predominantly the trunk and proximal extremities. b) Patient 1. More extensive involvement of the trunk, with areas of unaffected skin. c) HE stain ×20. Mild superficial perivascular lympohcytic infiltrate, spongiosis and interface dermatitis. d) HE ×40. Mild superficial perivascular lymphocytic infiltrate.

series.[2] Due to the fast onset of some of the cutaneous manifestations and considering several patients were taking different medications at the time, we suspect some of them to be drug induced reactions. Another possibility is a different response to the viral infection in the cases where the lesions appear with the other symptoms or as a late-onset cutaneous involvement.

Regarding histopathology, Herrero-Moyano et al. observed dense neutrophilic infiltrates in 8 patients with late maculopapular eruptions.[4] Seven of them had taken new drugs the previous week, as had 5 of our cases with similar findings, which were excluded from the study. We thought that this might condition a different immune response to viral infection that would justify the heterogeneity of the histological findings.

We conclude these reactions to be late manifestations of COVID19. Furthermore, it would be interesting to perform a SARS-CoV-2 PCR and serological test during the onset of these lesions to conclude if these are directly induced by the virus or are a late immune response manifestation.

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References

1 Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol* 2020. [Epub ahead of print].
2 Galván-Casas C, Catalá A, Carretero-Hernández G *et al*. Classification of the cutaneous manifestations of COVID-19: A rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020. [Epub ahead of print].
3 Jiménez-Cauhe J, Ortega-Quijano D, Prieto-Barrios M, Moreno-Arrones OM, Fernandez-Nieto D. Reply to "COVID can present with rash and mistaken for dengue": Petechial rash in a patient with COVID-19 infection. *J Am Acad Dermatol* 2020. [Epub ahead of print].
4 Herrero-Moyano M, Capusan TM, Andreu-Barasoain M *et al*. A clinicopatological study of 8 patients with COVID-19 pneumonia and a late-onset exanthema. *J Eur Acad Dermatol Venereol* 2020. [Epub ahead of print].

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COVID-19 and outbreak of chilblains: are they related?

Editor

SARS-CoV-2 is a new coronavirus that causes COVID-19, a disease associated with severe pneumonia.[1] Many other clinical manifestations have been associated with the disease (diarrhoea, anosmia, dysgeusia, etc.) and patients can be healthy carriers of the virus.[2] Several dermatologic manifestations associated with COVID-19 have been reported.[3] Among them are numerous cases of chilblain-like lesions (CBLLs) in young patients in good general condition, often not tested, or tested negative, for the SARS-CoV-2.[4,5] In a recent study on 375 Spanish patients with suspected or confirmed COVID-19, these CBLL accounted for 19% of all cutaneous lesions;3 they were observed in young patients with mild systemic symptoms and seemed to appear late in the course of the disease. Of note, CBLL is rarely observed in hospitalized patients;[6] however, the causal association of these CBLL with SARS-CoV-2, although suspected, remains so far unproven.

We examined 45 outpatients referred to our department for CBLL, who were otherwise in good general condition. There were 26 men (58%) and 19 women (42%), of a mean age of 30.1 years. Twelve patients (27%) mentioned non-specific systemic symptoms preceding the onset of CBLL. Fifteen patients (33.3%) considered a possible contamination from a family member. All patients presented red-violaceous acral lesions (Fig. 1a) on the toes (82%), the fingers (4%) or on both sites (13%). Prior pruritus or pain was reported by 51% and 62% of patients, respectively.

Seventeen of these patients benefited from detailed explorations.

Nasopharyngeal PCR test for SARS-CoV-2 was negative in 17/17. Laboratory work-up showed no lymphopenia, inflammatory markers, D-dimers or autoimmunity markers. An increased interferon score was detected in 6/15 patients (40%). Microscopic examination of skin biopsy (n = 17) (Fig. 1b) showed a hyperplastic epidermis containing scattered or confluent necrotic keratinocytes. The dermis contained extravasated red blood cells and a heavy lymphocytic infiltrate, occasionally also extending to the upper part of the hypodermis. Direct immunofluorescence examination often showed IgM, C3 and sometimes IgA deposits on skin vessels. Search for SARS-Cov-2 was performed with PCR in skin biopsies from 11 patients and proved invariably negative. Serological tests for anti-SARS-CoV-2 antibodies performed after a median delay of 14 days (range 6–40) after the onset of symptoms were negative in all 17 patients.

Our virological (nasopharyngeal and *in situ* PCR) and serological findings do not allow to confirm a direct causal link between SARS-CoV-2 infection and the apparent epidemic of chilblains observed in the French population in the context of COVID-19. However, such a link cannot be formally excluded. A particularly effective immune response against the infection could lead to a clinical presentation with very few symptoms, early negativity of nasopharyngeal PCR and delayed appearance of specific antibodies. Some studies have shown an impaired IFN-type 1 activity associated with severe forms of COVID-19 and suggest that patients with type 1 IFN deficiency could be a high-risk population.[7,8] The increased interferon score found in 40% of our patients tested may reflect a specific type of immune response, as has been reported in chilblain lupus and chilblains associated with interferonopathies, such as the Aicardi-Gouttières and SAVI syndromes.[9,10] We speculate that this intense IFN response could help the patients to contain the replication of SARS-CoV-2 and would explain why they usually remain asymptomatic and merely develop CBLL. This hypothesis should be confirmed by later serologies of these patients, who could become seropositive long after the onset of symptoms.

In conclusion, our findings do not demonstrate a formal causal relationship between these CBLL and SARS-CoV-2; however,

