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All human and animal studies are approved by an Institutional Review Board.

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The broad spectrum of dermatological manifestations in COVID-19: clinical and histopathological features learned from a series of 34 cases

Dear Editor,

Since the outbreak of coronavirus disease (COVID-19) pandemic began in Europe, a plethora of cutaneous manifestations have been related to this infection.^{1,2} However, their underlying

Table 1 Demographic and clinical characteristics of most frequently observed dermatological manifestations

	Maculopapular exanthem	Pseudo-chilblains/ Livedo	Targetoid lesions	Palpable purpura (2 with vesicles)	Acute urticaria/ Urticarial exanthem	Total of patients
N	10	10	5	4	4	34
Female, n (%)	6 (60)	5 (50)	2 (40)	3 (75)	3 (75)	20 (59)
Age (median and IR)	53 (31–61)	39 (17–62)	60 (40–78)	62 (57–69)	54.5 (37–65)	54.5 (31–66)
New drugs interference, n (%)	7 (70)	3 (30)	5 (100)	3 (75)	3 (75)	22 (65)
Biopsy, n	2	8	2	4	1	17
Diagnosis of COVID-19, n (%)						
Positive RT-PCR	6 (60)	2 (20)	4 (80)	2 (50)	2 (50)	17 (50)
Radiological diagnosis	3 (30)	2 (20)	1 (20)	1 (25)	1 (25)	8 (24)
Suspected (Negative RT-PCR)	1 (10)	6 (60)	0 (0)	1 (25)	1 (25)	9 (27)
Severity of COVID-19, n (%)						
Asymptomatic	0 (0)	3 (30)	0 (0)	0 (0)	0 (0)	3 (9)
Mild	2 (20)	3 (30)	0 (0)	1 (25)	2 (50)	8 (24)
Pneumonia (inpatient)	8 (80)	4 (40)	5 (100)	3 (75)	2 (50)	23 (68)
ICU	1 (10)	1 (10)	1 (20)	0 (0)	0 (0)	3 (9)
Coexisting conditions, n (%)						
Congestive heart failure	1 (10)	1 (10)	0 (0)	0 (0)	0 (0)	2 (6)
Hypertension	2 (20)	3 (30)	1 (20)	2 (50)	0 (0)	8 (24)
Diabetes	1 (10)	0 (0)	1 (20)	0 (0)	0 (0)	2 (6)
Chronic obstructive pulmonary disease	1 (10)	0(0)	2 (40)	0 (0)	0 (0)	3 (9)
Asthma	1 (10)	1 (10)	2 (40)	1 (25)	0 (0)	5 (15)
Time correlation between the appearance of cutaneous manifestations and COVID-19 onset, n (%)						
Before	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	1 (3)
≤10 days	3 (30)	3 (30)	0 (0)	1 (25)	2 (50)	10 (29)
>10 days	7 (70)	3 (30)	5 (100)	3 (75)	2 (50)	20 (59)

Percentages are for each column.



Figure 1 (a) Pseudo-chilblains lesions on toes of a 17-year-old patient. (b) Erythematopurpuric macules with undefined limits on the heel of a COVID-19 suspected patient. (c) Palpable purpura lesions on the lower extremities of a patient with COVID-19 pneumonia. (d) Polymorphic papulovesicular eruption on a patient presenting simultaneously with palpable purpura on the lower extremities. (e). Targetoid lesions at a delayed phase of COVID-19 pneumonia. (f) Maculopapular exanthem on a patient recovered from pneumonia; RT-PCR test persisted positive.

mechanism and prognostic relevance remain unclear. Thus, we collected data from all COVID-19 cases presenting with skin manifestations in our hospital in Madrid during one month. We registered 34 COVID-19 patients (Table 1), including confirmed cases by RT-PCR test (17/34) or radiological findings (8/34, 4 with negative RT-PCR assay), and patients with suspected infection and negative RT-PCR test (9/34) based on respiratory symptoms, fever and close contact with COVID-19 cases.

Maculopapular exanthems were the most frequent manifestation observed (10), followed by pseudo-chilblain (9), targetoid lesions (5), palpable purpura (4), acute urticaria (3) and vesicular lesions (2). The remaining three cases showed livedo reticularis, urticarial exanthem and prurigo lesions.

Maculopapular exanthems (Fig. 1f) were unspecific and mostly appeared at a late stage of COVID-19. The morphology observed in early exanthems, prior pharmacological interference,

was indistinguishable from those in the delayed presentations. In early-onset cases, histopathology showed moderate epidermal spongiosis and perivascular lymphocytic infiltrate with eosinophils in the dermis, whereas the analysis of the delayed lesions showed perivascular lymphocytic infiltrate and histiocytes amongst collagen fibres without mucin deposits.

Numerous patients with COVID-19 pneumonia displayed atypical targetoid lesions (Fig. 1e), with histopathological features of erythema multiforme, around 20 days after respiratory symptoms onset. Although the lesions appeared when COVID-19 treatment had commenced in all cases, given the dramatic increase of frequency, we believe that the underlying mechanism is a delayed immune response to the virus.

Palpable purpura lesions (Fig. 1c) were more frequent in middle-aged patients during recovery from severe COVID-19. We noticed a surprising increase in atypical clinical presentations of small vessel leukocytoclastic vasculitis: two patients displayed palpable purpura lesions along with an atypical polymorphic papulovesicular eruption (Fig. 1d), and one patient showed an urticarial exanthem.

In patients who had initiated pharmacological treatment, we cannot reliably link the dermatological symptoms to a single causative mechanism. Histopathology is not conclusive for either causes, and skin lesions like the aforementioned have been reported as side effects in most frequent COVID-19 treatments.

Pseudo-chilblain (Fig. 1a,b) were more commonly found in young patients with mild respiratory symptoms, and the timing of the onset was highly variable. Although RT-PCR test was negative in most cases, pseudo-chilblain have been related to COVID-19 due to the unusual increase in incidence during warm spring-time coinciding with the pandemic.^{1,3} The histopathological examination revealed different patterns. Most of them showed focal vacuolar degeneration of the basal layer and regenerative changes in the epidermis, with perivascular lymphocytic cuffs in the dermis, involving sweat glands, along with thrombi in some of them. One sample revealed perivascular neutrophilic cuffs with noticeable swollen endothelium and epidermal necrosis. As pointed out before,⁴ clinical and histopathological features are similar to chilblain lupus erythematosus, with additional evidence of intense platelets aggregation. Therefore, these lesions might be caused by a mixed mechanism including cellular immune response and prothrombotic state triggered by the virus.

Although the age distribution in our sample is similar to those reported in overall COVID-19 patients,⁵ the mortality rate (0%) is far lower and the proportion of affected females is higher in our cohort. Such trend amongst the study population is mirrored in previous COVID-19 skin manifestations series.¹ Thus, we think that cutaneous signs of the infection are more frequent in women and appear to be associated with a better prognosis. Therefore, the dermatological indicators in COVID-19 may act as prognostic factors and heralding signs and henceforth guide diagnostic and isolation protocols for affected patients.

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

Conflicts of interest

Dr. Rubio-Muniz, Dr. Puerta-Peña, Dr. Falkenhain-López, Dr. Arroyo-Andrés, Dr. Agud-Dios, Dr. Rodríguez-Peralto, Dr. Ortiz-Romero and Dr. Rivera-Díaz have nothing to disclose.

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Two cases of cutaneous eruptions due to CoVID-19 infection in Singapore: new insights into the spectrum of clinical presentation and histopathology

Dear Editor,

The dermatological manifestations of CoVID-19 infection (CI) are variable, including livedo/necrosis, pseudochilblains, vesicular (monomorphic vesicles unlike varicella), urticarial and