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DOI: 10.1111/jdv.16732

Histological findings in chilblain lupus-like COVID lesions: in search of an answer to understand their aetiology

To the Editor,

We read with great interest the article by Piccolo *et al.*¹ describing chilblain-like lesions (CLL) on feet and hands during the COVID-19 pandemic. They mention the rate of association to autoimmune conditions was very low, which led to exclude a note autoimmune disorder as main cause of CLL. Here, we hypothesize the possible relationship between the development of these lesions and immune-chained phenomena following viral infection in a certain group of patients.

Although perniosis is a frequent phenomenon, it seems reasonable to establish a causal relationship between these lesions and the coronavirus given the significant increase in these lesions in the epidemiological context that we are living in.^{1,2}

Kolivras *et al.*³ have recently described the histological manifestations in a 23-year-old caucasian male with pernicious lesions and a confirmed rt-PCR positive for COVID-19 without other analytical alterations.

We reaffirm the similarity between these lesions and those found in lupus chilblain. We present another case of an 17-year-old male, caregiver of a patient convalescing from COVID pneumonia, who presented acral lesions of 2 days' evolution compatible with the acromanifestations described (Fig. 1). Blood analysis revealed an elevation of IgA. Antinuclear antibodies were negative, and cryoglobulins were not detected. Rt-PCR for COVID resulted negative and serologies showed positive IgG with negative IgM. CBC showed no cytopenias and haemostasis, including D-dimer, was normal. A 4 mm punch biopsy was performed on one of the lesions (Fig. 2a–d), where marked

hydropic degeneration of the basal layer was observed with isolates necrotic keratinocyte. In the papillary and reticular dermis, a moderate lymphocyte infiltration was observed around the vessels as sleeves. The endothelium was conspicuously prominent, without visualizing fibrinoid necrosis. A dense perieccrine infiltration was also evident. Immunohistochemistry with CD 123 resulted positive, notably around vessels and sweat glands. No direct immunofluorescence was performed.

The similarity of these acral lesions with chilblain lupus lesions in this population group, mostly young patients, may be due to the type of immune response triggered by the interaction of COVID-19 with the immune system of these individuals. IFN type I levels are known to correlate with age.⁴ Infection of COVID-19 (as well as other viruses such as respiratory syncytial virus) would produce, in paediatric patients, an IFN-mediated response that, when induced prematurely, would control the viral infection. However, in adults, SARS-Cov-2 infection would produce a mute of interferon pathway regulatory genes (ISG) which prevents successful inhibition of viral spread.⁴

The understanding of the molecular basis of innate immunity has led to identification of IFNs as a central mediator in the pathogenesis of systemic lupus erythematosus (SLE).⁵ Type I



Figure 1 Periungueal erythema in second and third finger toe.

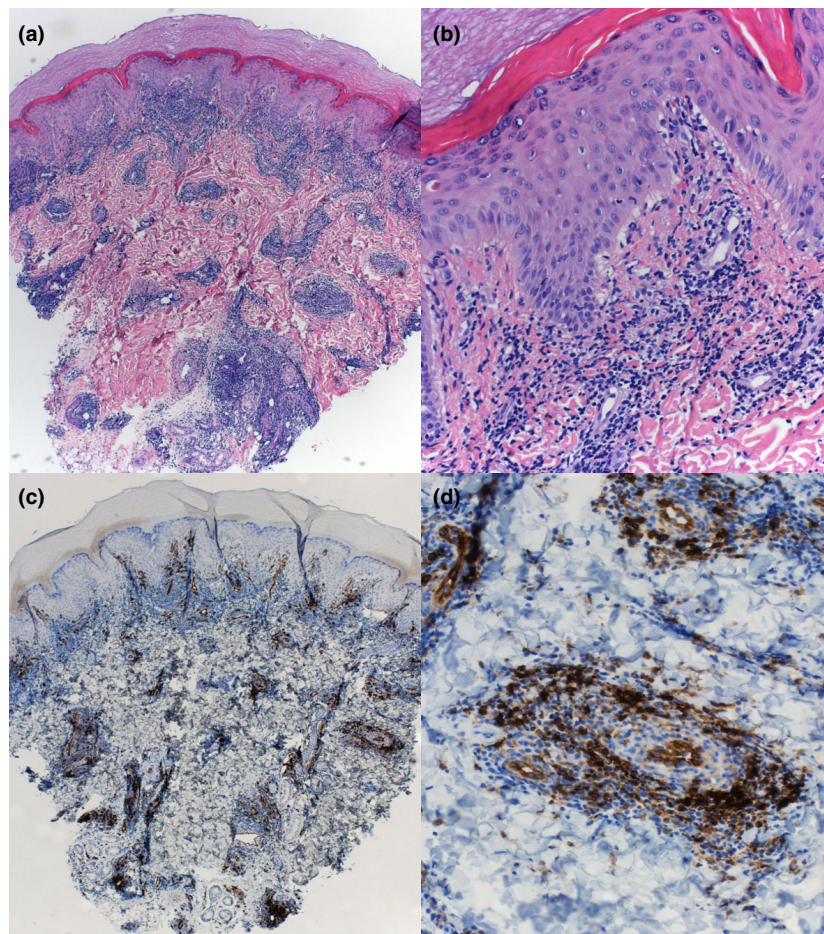


Figure 2 (a) Haematoxylin–eosin 4× stain: hydropic degeneration of the basal layer with isolates necrotic keratinocyte. In papillary and reticular dermis, moderate lymphocyte infiltrate around the vessels. Note the endothelium conspicuously prominent, without visualizing fibrinoid necrosis. A dense periecrine infiltration was also evident. (b) Closer look up, 20×. (c) Positive Immunohistochemistry CD123 4×, mostly around vessels and adnexal structures. (d) Closer look up 20×: positive CD 123 around vessels.

IFNs, produced mainly by plasmacytoid dendritic cells, have been claimed important in the pathogenesis of SLE skin lesions. We propose that the detection of these subspecialized cells by immunohistochemistry with the CD 123 marker, as producers of IFN in skin, may help to understand the underlying pathophysiology.

The combination of these two facts could be responsible for the appearance of lupus-like lesions preferably in young patients.

We describe as well a dense and striking inflammatory infiltration in the vascular wall with tumefaction of the endothelial cells, without finding any fibrinoid necrosis nor microthrombi as discussed by Landa *et al.*⁶ It has been already proven the existence of viral inclusion bodies and viral particles in endothelial cells and the detection of mononuclear cell infiltrates within the intima of vessels in different organs.⁷ We propose that similar changes are responsible for the endothelitis observed in our skin specimen.

However, there are still unanswered questions, such as the delay in the appearance or why other skin lesions resembling lupus have not been described to date. Further research is needed to answer these questions.

Acknowledgement



The patients in this manuscript have given written informed consent to the publication of their case details. The authors would like to thank all the hospital workers that have been battling in this pandemic, a special recognition of the Dermatology department of Hospital Principe de Asturias, fully involved in this fight.

Conflicts of interest

The authors have no conflict of interest to declare.

Funding sources

The article has no funding source.

A. Rodríguez-Villa Lario,^{1,*}  D. Vega-Díez,¹ 
 M. González-Cañete,¹ A. Gómez-Zubiaur,¹ 
 R. Pérez-Mesonero,¹  M. Bandini,¹ I. Polo-Rodríguez,¹
 D. Vélez-Velázquez,² L. Trasobares-Marugán¹

¹Dermatology Department, Hospital Universitario Príncipe de Asturias, Madrid, Spain, ²Pathology Department, Hospital Universitario Príncipe de Asturias, Madrid, Spain

*Correspondence: A. Rodríguez-Villa Lario. E-mail: anarvlario@gmail.com

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

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DOI: 10.1111/jdv.16733

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.