

Clinical and histological characterization of vesicular COVID-19 rashes: a prospective study in a tertiary care hospital

D. Fernandez-Nieto,¹  D. Ortega-Quijano,¹  J. Jimenez-Cauhe,¹  P. Burgos-Blasco,¹
D. de Perosanz-Lobo,¹ A. Suarez-Valle,¹ J. L. Cortes-Cuevas,² I. Carretero,³ C. Garcia-Del Real³ and
M. Fernandez-Guarino¹

Departments of, Department of, ¹Dermatology; ²Microbiology; and ³Pathology, Ramón y Cajal University Hospital, Universidad de Alcalá de Henares, Instituto de investigación Sanitaria del Hospital, Ramón y Cajal (Irycis), Madrid, Spain

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Summary

COVID-19 is an infectious disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2). Vesicular skin rashes have been reported as associated with COVID-19, but there is little information about this cutaneous manifestation. We designed a prospective observational study of patients diagnosed with COVID-19 who had vesicular lesions. Clinical characterization of skin findings was conducted by dermatologists. When possible, histological analysis and detection of SARS-CoV-2 in the content of the vesicles was performed. In total, 24 patients were included. A disseminated pattern was found in 18 patients (75%), and a localized pattern was found in 6 (25%). Median duration of the skin rash was 10 days. Of the 24 patients, 19 (79.2%) developed the skin rash after the onset of COVID-19 symptoms. Histological examination in two patients was consistent with viral infection, SARS-CoV-2 was not detected in four patients. This single-centre study shows the clinical characteristics of vesicular skin rashes in patients with COVID-19.

COVID-19 is an infectious disease caused by SARS-CoV-2. COVID-19 may present with influenza-like symptoms such as dry cough, fatigue, shortness of breath and anosmia; however, it may also be asymptomatic.¹

In the first report of cutaneous manifestations in patients with COVID-19, a chickenpox-like exanthem was described.² A similar report was subsequently described in a multicentre case series of 22 patients in Italy.³ Vesicular eruptions were classified as one of the five main categories of COVID-19 skin lesions in the nationwide Spanish consensus study, which reported 34 of 375 cases (9%) having these.⁴ Compared with

other clinical patterns, which are less specific, vesicular lesions may be useful as indicators of disease.^{3,4}

Unfortunately, there is no complete characterization of these skin manifestations. There is also increasing concern whether skin rashes could be a part of a potential transmission route for SARS-CoV-2, as little is known about its aetiopathology.⁵

Report

The study was approved by an institutional review board and written informed consent was obtained from all participants.

We included all patients from Ramón y Cajal University Hospital who reported vesicular skin rashes between 1 March and 20 April 2020, and who had a positive nasopharyngeal swab for SARS-CoV-2. Demographics and clinical characteristics were collected using a standardized data collection instrument.

All patients with a skin rash and COVID-19 diagnosis were examined by a trained dermatologist, who

Correspondence: Dr Diego Fernandez-Nieto, Department of Dermatology, Ramón y Cajal University Hospital, Carretera Colmenar Viejo km 9.100, 28034, Madrid, Spain
E-mail: fnietodiego@gmail.com

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Table 1 Clinical characteristics of patients with COVID-19 vesicular rash.

Characteristic	Clinical pattern in COVID-19 vesicular rash			<i>P</i> ^a
	Diffuse <i>n</i> = 18	Localized <i>n</i> = 6	Total <i>n</i> = 24	
Age, years; median (range)	40.5 (19–62)	47.5 (43–65)	45 (19–65)	0.18
Sex, M/F	3/15 (16.7/83.3)	3/3 (50/50)	6/18 (25/75)	0.14
COVID-19 pneumonia, <i>n</i> (%)	5 (27.8)	5 (83.3)	10 (41.7)	0.05
Distribution of lesions, <i>n</i> (%)				
Head	4 (22.2)	0 (0)	4 (16.7)	0.54
Anterior trunk	17 (94.4)	4 (66.7)	21 (87.5)	0.14
Posterior trunk	12 (66.7)	2 (33.3)	14 (58.3)	0.19
Arms	8 (44.4)	0 (0)	8 (33.3)	0.07
Legs	10 (55.6)	0 (0)	10 (41.7)	0.02
Palms/soles	2 (11.1)	0 (0)	2 (8.3)	1.00
Duration of skin rash; median days(range)	10 (4–20)	8.5 (7–22)	10 (4–22)	0.82
Patients with skin rash before COVID-19 symptoms, <i>n</i> (%)	2 (11.1)	0	2 (8.3)	1.00
Interval before COVID-19 symptoms, days; median (range)	15 (10–20)	0	15 (10–20)	
Patients with skin rash coincident with COVID-19 symptoms	3 (16.6)	–	3 (12.5)	0.55
Patients with skin rash after COVID-19 symptoms, median time onset (range), days	13 (72.2)	6 (100)	19 (79.2)	0.28
Interval before skin rash, days; median (range)	14 (4–30)	10 (8–15)	14 (4–30)	

^aMann–Whitney nonparametric *U*-test was used for comparison between qualitative variables, and Fisher exact test was used for comparison of qualitative variable with a quantitative one.

took clinical photographs. Lesion appearance, patient's medical history and clinical course were all reviewed by three independent dermatologists, who made the diagnosis of COVID-19 vesicular rash when other conditions were reasonably discarded. A biopsy was taken from two patients for histological analysis. For four of the patients, RNA was extracted from the fluid content of the vesicles, using an automated platform for nucleic acid extraction (NucliSens EasyMAG[®]; bioMerieux[®], France) in accordance with the manufacturer's instructions. Real-time reverse transcription (RT)-PCR for SARS-CoV-2 was performed using a commercial kit [TaqMan[™] 2019 nCoV Assay Kit v1 (cat. no. A47532); Applied Biosystems, Foster City, CA, USA].

Mann–Whitney nonparametric *U*-test was used for comparison between qualitative variables, and Fisher exact test for used for comparison of qualitative variable with a quantitative one. All statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA) and *P* < 0.05 was considered statistically significant.

In total, 53 patients fulfilled the inclusion criteria; of these, 29 patients were excluded because of other clinical diagnoses: herpes simplex/zoster (*n* = 15), miliaria (*n* = 7), impetigo/ecthyma (*n* = 5) and coma blisters (*n* = 2). Finally, 24 patients were diagnosed with COVID-19 vesicular rashes.

The clinical characteristics of the patients are summarized in Table 1. Median age was 40.5 years (range 19–62 years). Previous dermatological conditions were

found in seven patients (29.2%): atopic dermatitis (*n* = 5) and chronic urticaria (*n* = 2). Regarding COVID-19 severity, 14 patients (58.3%) presented mild COVID-19 symptoms and did not require hospitalization, while 10 patients (41.7%) developed pneumonia. Among these, only one patient (4.2%) required intensive care unit support. All patients survived.

Vesicular rash appeared after the COVID-19 diagnosis in 19 patients (79.2%), with a median latency time of 14 days (range 4–30 days). Seven patients (29.2%) had received treatments for COVID-19 before the appearance of the skin rash: lopinavir/ritonavir (*n* = 5), hydroxychloroquine (*n* = 6) and azithromycin (*n* = 2). The rash was pruritic in 20 patients (83.3%), while the other 4 (16.7%) did not report any associated symptoms.

Regarding clinical presentation, two different morphological patterns were described. A diffuse pattern was found in 18 patients (75%), which consisted of small papules, vesicles and pustules of varying sizes, of up to 7–8 mm in diameter. Different stages of the lesions appeared simultaneously. Although the lesions were clustered at some points, a tendency to widespread distribution from the trunk was seen, affecting > 1 corporal area, including the palms and soles in two cases (11.1%). Figure 1a–d shows the typical clinical findings in patients with a diffuse vesicular pattern due to COVID-19. Histological examination was performed in two patients, showing intraepidermal vesicles with mild acantholysis and ballooned keratinocytes (Fig. 1e,f).

A second localized pattern was found in 6/24 patients (25%). This pattern consisted of monomorphic lesions, of up to 3–4 mm in diameter, which were all at the same stage of evolution. No more than one central area was affected per patient, usually involving the mid chest/upper abdominal region or the back. Typical clinical findings are shown in Fig. 1g,h.

Multiplex PCR for herpesvirus and real-time RT-PCR for SARS-CoV-2 from vesicle content was performed in four cases (three diffuse and one localized) but gave negative results.

When we compared both disseminated and localized patterns, there were no statistically significant differences in age, sex, rash duration, concurrent COVID-19 pneumonia or latency period between typical COVID-19 symptoms and skin rash onset (Table 1).

Skin rashes associated with viral infections may be a manifestation of viraemia.⁵ Most viruses that produce skin manifestations act as inert foreign particles in the

skin, initiating an inflammatory process as a result of a reaction with circulating antibodies and sensitized lymphocytes.⁶ Vesicular exanthems are caused by viruses that can replicate in epidermal cells, including DNA viruses such as poxviruses, herpes simplex and varicella zoster.⁷ However, some RNA viruses, such as certain coxsackieviruses, also possess this ability.⁸

The histological findings described in the two patients who underwent a biopsy are similar to those encountered in hand, foot and mouth disease. The real-time RT-PCR for SARS-CoV-2 from the vesicles was negative in all four patients; however, a small viral load can result in false-negative results, and PCR assays in skin samples are not standardized. In a previous study, immunohistochemical analysis demonstrated the presence of SARS-CoV-2 in the endothelial cells of damaged skin.⁹ Based on our results, even if SARS-CoV-2 is present, the infective ability through vesicles would be low.

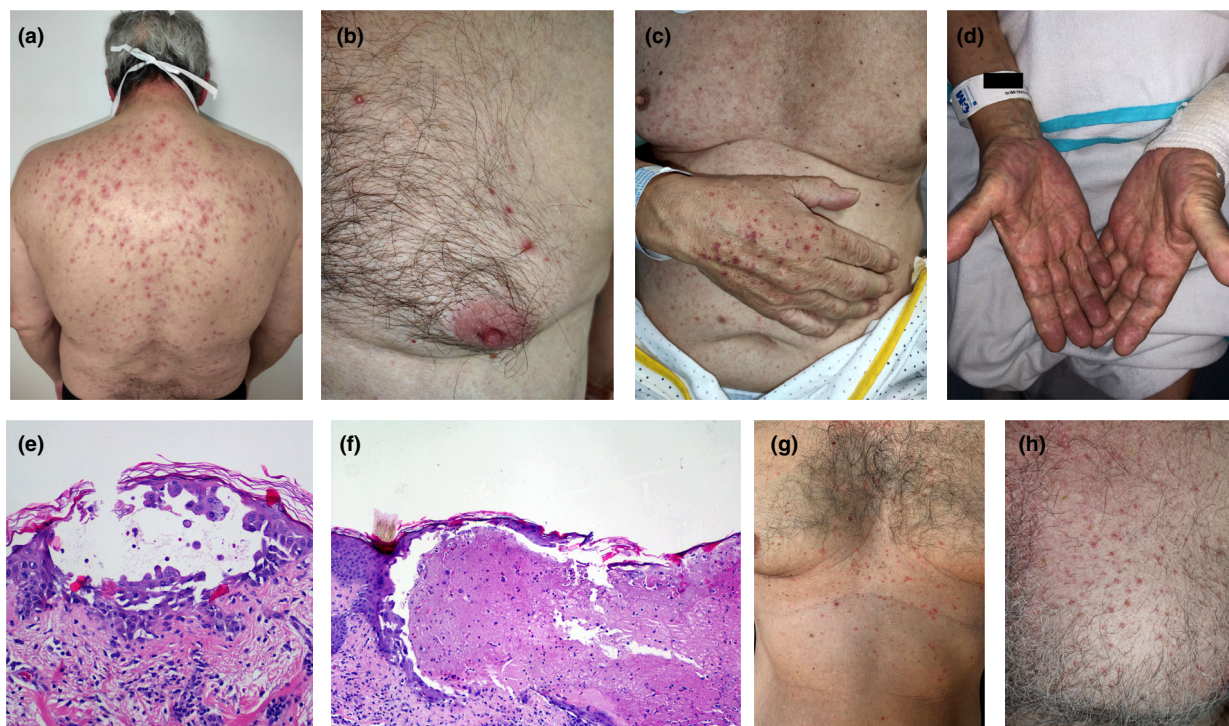


Figure 1 (a–h) Disseminated vesicular rash associated with COVID-19. (a) Patient 1: papules and vesicles of varying sizes affecting the whole trunk, proximal arms and legs. (b) Patient 2 had scattered vesicles and pustules on the trunk, with a slight tendency to cluster. (c, d) Patient 3 had (c) morbilliform rash involving the whole trunk, with disseminated vesicles predominantly affecting upper extremities and (d) the palms were also involved. (e, f) Histological examination showing (e) an intraepidermal vesicle containing scattered multinucleated and ballooned keratinocytes, with mild acantholysis, while (f) a deeper section of the vesicle reveals more extensive damage, with epidermal detachment and confluent keratinocytic necrosis, and the vesicle contains fibrinoid material with acute inflammation. Haematoxylin and eosin, original magnification (e) $\times 200$; (f) $\times 100$. (g, h) Localized COVID-19 vesicular rash: (g) monomorphic papules and vesicles exclusively located on the anterior trunk, at an early stage; (h) close-up view of the monomorphic vesicles and pustules on the chest.

Only seven patients (29.2%) were under systemic treatment for COVID-19 before the rash onset, and most patients without COVID-19 pneumonia were not taking any medication at all. Based on our results, it is highly unlikely that the current available treatments for COVID-19 are aetiologically related to vesicular COVID-19 rashes.

In this study, we could only evaluate patients who required medical attention. However, telemedicine consultations in Spain suggest that similar rashes can be present in asymptomatic or mildly symptomatic people. We identified two patterns: the first is the diffuse pattern (in the present study 18/24 patients; 75%) with similar characteristics to hand, foot and mouth disease,¹⁰ and the second is the localized pattern (6/24; 25%) resembling chickenpox but mostly with only trunk involvement. At this point, we cannot discern if each pattern has a different aetiological mechanism. Furthermore, we cannot categorically affirm that these lesions are directly or indirectly caused by the SARS-CoV-2 itself. More studies are needed to elucidate this point.

Learning points

- The vesicular rash associated with COVID-19 has two different presentation patterns: diffuse and localized.
- The diffuse pattern is polymorphic and has a tendency to a widespread distribution, while the localized pattern is monomorphic and involves only the trunk.
- The COVID-19 vesicular rash usually appears after the onset of typical COVID-19 symptoms, but it can also appear before them.
- The COVID-19 vesicular rash has no causal relation with antiviral drugs or other treatments.
- Histological findings are consistent with a viral infection.
- PCR assays failed to detect the presence of SARS-CoV-2 inside vesicles.

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