



Report

Skin manifestations in patients hospitalized with confirmed COVID-19 disease: a cross-sectional study in a tertiary hospital

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Introduction

On January 7, 2020, a novel coronavirus, SARS-CoV-2, was isolated in patients with pneumonia in Wuhan, China.¹ This virus spreads rapidly, and in March 2020, a pandemic was declared. The first clinical findings associated with this virus were respiratory symptoms and fever. Later, diarrhea, anosmia, and ageusia were included.^{2,3} It was not until March 26 that Recalcati's article⁴ analyzed skin manifestations in COVID-19 patients for the first time. Since this date, a series of cases began to emerge in Spanish hospitals, and similar case series were reported.⁴⁻¹⁶ For this reason, a nationwide study was conducted in Spain to describe the cutaneous manifestation patterns of COVID-19 disease.¹⁷ Most of

Abstract

Background COVID-19 cutaneous manifestations have been recently described and classified in five different clinical patterns, including acral erythema-edema (pseudo-chilblain), maculopapular exanthemas, vesicular eruptions, urticarial lesions, and livedo or necrosis.

Objectives The objective of this study was to examine the skin of hospitalized patients with a confirmed diagnosis of COVID-19 disease and describe the real prevalence of skin manifestations.

Methods A cross-sectional study, which included hospitalized patients in Cruces University Hospital from April 14–30, 2020, with a laboratory-confirmed diagnosis of COVID-19 (with polymerase chain reaction and/or serology tests), was conducted. Entire body surface examination was performed by experienced dermatologists to search for cutaneous manifestations related to COVID-19 disease.

Results From a sample of 75 patients, 14 (18.7%) developed cutaneous manifestations possibly related to COVID-19. We found six patients with acral erythema-edema (pseudo-chilblain) (42.8%), four patients with maculopapular exanthemas (28.6%), two patients with urticarial lesions (14.3%), one patient with livedo reticularis-like lesions (7.15%), and one patient with vesicular eruption (7.15%).

Conclusions Our study provides a more plausible relationship between the main cutaneous patterns and COVID-19 in hospitalized patients as all of them had a confirmatory laboratory test. Skin manifestations are frequent but mild with spontaneous resolution. These findings are nonspecific and can be similar to other viral infections and adverse drug reactions in hospitalized patients.

these articles include confirmed and suspected COVID-19 patients seen in an outpatient clinic and are restricted to patients with cutaneous manifestations.

We decided to perform this study to describe the real prevalence and directly examine the skin findings in hospitalized patients in our institution with a confirmed diagnosis of COVID-19 disease.

Materials and methods

We performed a cross-sectional study, which included COVID-19 patients in Cruces University Hospital, Bizkaia, Spain, from April 14–30, 2020.

Inclusion criteria were patients admitted to the hospital with a laboratory-confirmed diagnosis of COVID-19 (with polymerase chain reaction and/or serology tests). All the patients gave their oral informed consent to participate in the study. Patients admitted to the Intensive Care Units were excluded due to the difficulties to obtain their informed consent. The final size of the sample was 75 patients.

Examination of the entire body surface was performed by experienced dermatologists to search for cutaneous manifestations possibly related to COVID-19 disease. We recorded age, gender, treatment during admission, the presence of cutaneous manifestations and whether they appeared during prodromal (one week prior to the first clinical symptoms), illness or decline periods, their type and location, and the occurrence of familial cases.

Based on recent reports^{4–16} and on the Spanish group classification in clinical patterns,¹⁷ we included acral erythema-edema (pseudo-chilblain), maculopapular exanthemas, vesicular eruptions, urticarial lesions, and livedo or necrosis areas.

To examine the patients, we entered their rooms using personal protective equipment (PPE) and transparent ziplock

bags to protect photographic devices along with dispensable biopsy instruments, as performed in other hospitals.⁹

Results

We recruited a total of 75 patients admitted to the hospital because of clinical manifestations of COVID-19 disease. The mean age of the sample was 67.5 years old (CI 95 64.5–70.5), and 64% (CI 95 53.1–74.9%) were men (Table 1).

We collected data of prescribed treatments during their hospital stay. The most frequently used therapy was a combination of hydroxychloroquine, lopinavir/ritonavir, and methylprednisolone pulses (42.7%) followed by double therapy of hydroxychloroquine and lopinavir/ritonavir (25.3%).

From the 75 patients, 14 (18.7%) developed cutaneous manifestations that could be attributed to COVID-19. Twelve of the lesions were directly observed by the dermatologist, and two patients referred past lesions, not present during clinical evaluation. Pictures of all the cutaneous lesions were taken.

According to the recent classification in clinical patterns of cutaneous manifestations of COVID-19 disease,¹⁷ we found six

Table 1 Demographic characteristics and skin manifestations of patients with confirmed COVID-19 disease in hospital setting

Patient demographics			
Age	Mean (CI 95%)		
Years	67.5 (64.5–70.5)		
Sex	% (CI 95%)		
Male	64 (53.1–74.9)		
Treatment	No (%)	Plus antibiotherapy	Without antibiotherapy
Hydroxychloroquine	7 (9.3)	6	1
Hydroxychloroquine + lopinavir/ritonavir	19 (25.3)	10	9
Hydroxychloroquine + lopinavir/ritonavir + methylprednisolone	32 (42.7)	23	9
Hydroxychloroquine + methylprednisolone	4 (5.3)	3	1
Methylprednisolone	3 (4.0)	0	3
Antibiotherapy	5 (6.7)		
Supportive treatment	5 (6.7)		
Previous ICU stay, no (%)	15 (20)		
Results			
Skin lesions	No (%)		
No	61 (81.3)		
Yes	14 (18.7)		
Confirmed	12 (16)		
Self-reported	2 (2.7)		
Lesion type	No	% Total lesions (n = 14)	% Total patients (n = 75)
Acral erythema-edema	6	42.9	8
Rash	4	28.6	5.3
Urticarial	2	14.3	2.7
Vesicular	1	7.1	1.3
Livedoid	1	7.1	1.3
Median time from onset after COVID-19 symptoms	Days		
Any lesion	6		
Acral erythema-edema	-		
Rash	20		
Urticarial	1.5		
Vesicular	4		
Livedoid	2		



Figure 1 Clinical features of COVID-19 positive patient with skin vascular symptoms. An 82-year-old male with pseudo-chilblain pattern on distal fingers of the hand beginning 9 days before respiratory symptoms and lasting a duration of 2 weeks

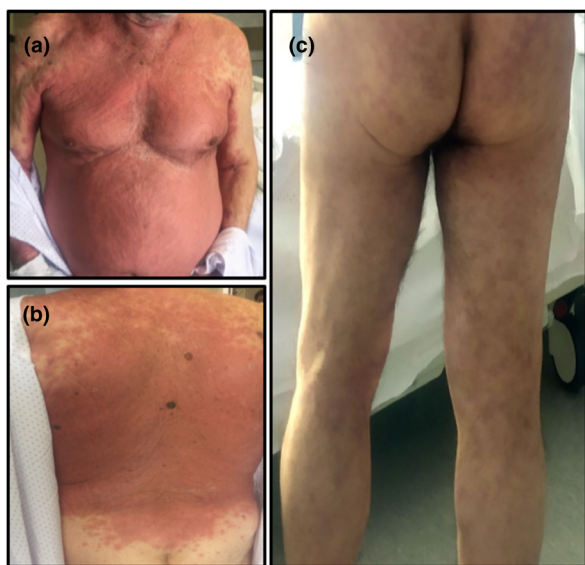


Figure 2 Clinical images (a) and (b) of widespread erythematous exanthema with predilection for the trunk in an 84-year-old man. The exanthema began 2 weeks after the onset of respiratory symptoms with spontaneous resolution after 15 days. (c) A 71-year-old man with livedo reticularis-like lesions on both legs and buttocks

patients with areas of acral erythema-edema (pseudo-chilblain), which represents 42.8% of the cases (Fig. 1); four patients with maculopapular exanthemas (28.6% of the cases) (Fig. 2a,b);



Figure 3 Vesicular pattern on the trunk of an 86-year-old male. The vesicles appeared 4 days after the onset of respiratory disease. A sample of one of the vesicle's fluid was taken for PCR of COVID-19, herpes simplex, and varicella zoster virus with a negative result

two patients with urticarial lesions; one patient with livedo reticularis-like lesions; and one patient with vesicular eruption.

Acral erythema-edema lesions were mainly observed in feet. These lesions were very subtle and asymptomatic, so they were unnoticed by patients. For this reason, the median time of onset since the beginning of respiratory symptoms is unknown. The maculopapular exanthemas showed predilection for trunk and proximal extremities (80%), and there was also one case of flexural involvement (20%). Some patients referred mild pruritus. The median time of onset of the rash was 17 days (range 15–28 days) from the first symptoms of COVID-19. The patient with the vesicular pattern had lesions over the trunk (Fig. 3). A sample from one vesicle liquid was taken for PCR of COVID-19, herpes simplex, and varicella zoster, which were all negative. The vesicles appeared 4 days after the onset of respiratory symptoms. One of the patients with urticarial pattern had a lumbar raised rash one week prior to COVID-19 clinical findings, and the other had urticarial lesions on the arms, legs, and face 10 days after the symptoms. Finally, there was one patient with livedoid pattern on the trunk and extremities (Fig. 2c). Additionally, we asked all patients about the existence of family members with cutaneous lesions with the above-mentioned patterns, and this was negative for all of them.

Discussion

Analyzing the collected demographic data, the mean age in our sample is 67.5 years old, and 64% are men. Compared with previous studies,^{9,17} our study includes older patients and a higher proportion of males. This can be explained because only hospitalized patients with laboratory confirmed SARS-CoV-2

were considered. As described in the existing literature,^{18,19} elderly men suffering from COVID-19 are more frequently hospitalized compared to women and young people. In this way, we aimed to achieve a representative sample of the profile of COVID-19 hospitalized patients.

To our knowledge, this is the first series in which data collection has been directly performed by experienced dermatologists and with a systematic cutaneous exploration of all patients. All skin findings can be included in the recently described clinical patterns of cutaneous manifestations of COVID-19 disease.¹⁷ Results show a similar percentage of skin manifestations to other case series.⁴ In our sample, the most frequently observed cutaneous pattern was acral erythema-edema (pseudo-chilblain), and the second in frequency was the maculopapular exanthema.

One of the latest studies¹⁷ reported the pseudo-chilblain pattern appeared in young patients, later in the course of the disease, was associated with less severe infection, and included patients who did not require hospitalization. As mentioned above, we carried out an exhaustive dermatological exploration on all admitted patients. For this reason, we may have included some lesions as pseudo-chilblain patterns that could be explained by other causes or which were not exactly manifestations but rather a variety of normal skin conditions. Therefore, we may have overestimated the number of patients with acral erythema-edema.

We would like to highlight that all the skin manifestations observed, regardless of the clinical pattern, were mild, did not affect mucous membranes, and did not cause epidermal detachment. In addition, these lesions did not require any specific treatment nor did they change the course, management, prognosis, or hospitalization days of the patients as they resolved spontaneously.

As described in other studies,¹⁷ it would appear that each clinical dermatological pattern has a time of onset in the disease: vesicular lesions precede other symptoms, urticarial and maculopapular lesions concur with respiratory symptoms, and pseudo-chilblain pattern appears later in the course of the disease. Given our low number of patients with skin findings, we are not able to make any conclusion on this area.

Galván *et al.*¹⁷ referred there might be a correlation between the clinical patterns and the severity of the disease. In our study, we did not correlate the severity of the COVID-19 disease with the different skin patterns because all of the patients we included had very similar clinical characteristics of COVID-19 (moderate–severe infection that required hospitalization).

We are aware that our study has its limitations. Firstly, the limitations are inherent to a cross-sectional study; it does not allow a monitoring over time; and it cannot determine cause and effect relationship. Secondly, we could not analyze other possible or alternative causes of skin manifestations such as medications. Finally, we are not able to correlate skin patterns with the time of onset of the disease and severity of the infection. Well-designed

prospective studies are needed to explore the cause–effect relationship of these skin manifestations.

Conclusions

This study provides a more plausible relationship between COVID-19 disease and its main cutaneous patterns in hospitalized patients, since all of them had a confirmatory laboratory test. It seems important to emphasize that skin manifestations in this subgroup of patients are frequent but mild in nature and in all cases with spontaneous resolution. Furthermore, they are non-specific because they are similar to other viral infections and drug reactions observed in patients admitted to the hospital.

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