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Lack of skin manifestations in COVID-19 hospitalized patients during the second epidemic wave in Spain: a possible association with a novel SARS-CoV-2 variant – a cross-sectional study

Editor

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Skin lesions have been described in confirmed COVID-19 patients as potential manifestations of the disease.[1] Different prevalence rates have been reported in hospitalized patients from January to May 2020, ranging from 0.2% to 20.5%.[2–5] Prevalence rates in studies where dermatologists did not perform the initial physical examination may be underestimated.[2,5,6] A second wave of the COVID-19 epidemic has emerged in European countries starting in late August. Spain has been one of the most affected regions. However, cutaneous findings have been scarcely reported during this time period.

We designed a cross-sectional study. COVID-19 hospitalized patients, confirmed by rt-PCR, were evaluated by three independent dermatologists on 16 October 2020 at Ramon y Cajal University Hospital. Dermatological conditions not associated to COVID-19 were excluded. The required sample size to estimate de population proportion was 139 for a level of confidence of 95% and a margin of error of 5% (expected prevalence 10%). We tabulated baseline patient characteristics and used descriptive analyses on them. All analyses were done with R software (version 3.6.2).

A total of 144 patients fulfilled inclusion criteria. Mean age was 71.5 years (range, 27–99 years), and 63.9% were male. CURB-65 score for pneumonia severity had a mean value of 1.4. Thirteen patients (9.0%) received COVID-19 treatments (excluding dexamethasone). Skin manifestations associated to COVID-19 were present in five patients (3.5%), including one patient (0.7%) with maculopapular rash and four patients (2.8%) with livedoid lesions. Vesicular, urticarial and chilblain-like lesions were absent. Clinical characteristics compared with other prevalence studies are available in Table 1.

Most previous studies are based in consecutive case series or retrospective registries, with intrinsic difficulties to estimate either prevalence or incidence values. The present cross-sectional study estimates the prevalence with an adequate methodology, only including confirmed cases. We failed to detect any of the previously suggested specific COVID-19 manifestations. Mainly livedoid lesions were present, which are supposed to be related

Table 1 Demographic characteristics and skin manifestations of COVID-19 hospitalized patients

Characteristic	Study					
	Present study (*n* = 144)	**Guan *et al.* (*n* = 1099)**	**Recalcati S. (*n* = 88)**	**Hedou *et al.* (*n* = 103)**	**Giavedoni *et al.* (*n* = 2771)**	**Mendez-Maestro et al. (n = 75)**
Country	Spain	China	Italy	France	Spain	
Time frame	16 October 2020	11 December 2019–29 January 2020	March 2020	15 March–2 April 2020	01 April–01 May 2020	April 14–30 2020
Type of patient	Hospitalized patients	Hospitalized patients	Hospitalized patients	Hospitalized patients: 27 (36.2%)	Hospitalized and non-hospitalized patients	Hospitalized patients
Positive rate of rt-PCR SARS-CoV-2, *n* (%)	144/144 (100%)	1099/1099 (100%)	100% COVID-19 positive patients (unspecified)	103/103 (100%)	29/58 (50%)	75/75 (100%) (rt-PCR or serologies)
Estimated prevalence	3.8%	0.2%	20.5%	4.9%	2.1%	18.7%
Assessment method	All patients directly evaluated by dermatologists	All patients evaluated by non-dermatologists	All patients evaluated by dermatologists (directly or indirectly)	Prospective registry (not specified)	First evaluation performed by an emergency physician, then dermatologists were directly consulted	All patients directly evaluated by dermatologists
Age	Mean 71.5 Range (27–99)	Median 47 IQR (25.0–58.0)	Not specified	Mean 47 (20–88)	Median 72 IQR (38.7–69.3)	Mean 67.5 CI 95 (64.5–70.5)
Sex, *n* (%)	Males: 92 (63.9%) Females: 52 (36.1%)	Males: 639 (58.1%) Females: 460 (41.9%)	Not specified	Males: 32 (31.1%) Females: 71 (68.9%)	Males: 31 (53.4%) Females: 27 (47.6%)	Males: 48 (64%) Females: 27 (36%)
Previous treatments, *n* (%)	Specific COVID-19 treatments: 13 (9.0%) Remdesivir: 11 (7.6%) Tocilizumab: 2 (1.4%) Other treatments: Glucocorticoids (dexamethasone): 96 (66.7%) Antibiotics (beta-lactam): 32 (22.2%) Antibiotics (non-beta-lactam): 8 (5.6%)	Oseltamivir: 393 (35.8%) Immunoglobulins: 144 (13.1%) Antibiotics: 637 (58.0%) Antifungals: 31 (2.8%) Glucocorticoids: 204 (18.6%)	Not specified Patients with a history of new medicines 15 days before were excluded	Not specified	Specific COVID-19 treatments: 36 (62.1%) Hydroxychloroquine: 36 (62.1%) Azithromycin: 34 (58.6%) Lopinavir/ritonavir: 30 (51.7%) Tocilizumab: 15 (25.9%) Remdesivir: 5 (8.6%) Anakinra: 5 (8.6%) Siltuximab: 2 (3.4%) Glucocorticoids: 25 (43.1%)	Hydroxychloroquine: 7 (12.1%) Hydroxychloroquine + lopinavir/ritonavir: 19 (32.8%) Hydroxychloroquine + lopinavir/ritonavir + methylprednisolone: 32 (42.7%) Hydroxychloroquine + methylprednisolone: 4 (5.3%) Methylprednisolone: 3 (4.0%) Antibiotherapy: 5 (6.7%)
ICU stay, *n* (%)	19 (13.2%)	55 (5%)	Not specified	4 (3.9%)	19 (32.8%)	15 (20%)
Skin lesions, *n* (%)	Maculopapular: 1 (0.7%) Urticarial: 0 (0%) Vesicular: 0 (0%) Chilblain-like: 0 (0%) Livedoid: 4 (2.8%) Total: 5 (3.5%)	Rash (unspecified): 2 (0.2%) Total: 2 (0.2%)	Maculopapular: 14 (15.9%) Urticarial: 3 (3.4%) Vesicular: 1 (1.1%) Total 18 (20.5%)	Maculopapular: 2 (1.9%) Urticarial: 2 (1.9%) Other (herpes reactivation): 1 (1.0%)	Maculopapular: 12 (20.7%) Urticarial: 4 (6.9%) Papulo-vesicular: 8 (13.8%) Chilblain-like: 17 (29.3%) Livedo reticularis: 4 (6.9%) Other: 13 (22.4%)	Maculopapular: 4 (5.3%) Urticarial: 2 (2.7%) Vesicular: 1 (1.3%) Livedoid: 1 (1.3%) Chilblain-like: 6 (8%) Total: 14 (18.7%)

IQR, Interquartile range; CI 95, 95% Confidence Interval.

to coagulation anomalies rather than immunological responses.[1] We propose three different explanations for the lack of skin manifestations in COVID-19 patients during the second epidemic wave:

First, different baseline characteristics in COVID-19 hospitalized patients, including comorbidities, disease severity and received treatments. The second epidemic wave appears to be associated to a decreased case fatality rate, partially explained by the harvesting effect.[7] Mild and asymptomatic cases are treated earlier. Only remdesivir, tocilizumab and dexamethasone are being used in most European hospitals, compared to the previous combination of hydroxychloroquine, lopinavir/ritonavir and azithromycin, which may cause adverse cutaneous reactions.

Second, some COVID-19 skin manifestations could have been produced by different aetiological agents, including other viral infections. Preventive measures difficult the capability of directly examining the skin of the patients and their follow-up. Many studies included indirect reports of other healthcare professionals or patients, even via mobile messaging platforms like Whatsapp®.[8]

Finally, variations in SARS-CoV-2 antigenicity that would induce a different immunologic response. A multi-country genomic surveillance study has detected the 20A.EU1 variant of SARS-CoV-2, with mutation S:A222V in the spike protein. It emerged in early summer 2020, presumably in Spain, and afterwards spread to multiple European countries.[9] Genomic diversity of SARS-CoV-2 may affect its antigenicity, virulence and transmissibility.[10] Unfortunately, there are no studies correlating SARS-CoV-2 variants with skin manifestations.

In conclusion, skin manifestations in COVID-19 hospitalized patients appear to be less frequent during the second epidemic wave. As a cross-sectional study, subjects were not followed over a period of time, and short duration skin manifestations may be underestimated. More prevalence studies are needed including other regions to confirm this finding.

Conflicts of interest

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Wearing a mask and skin disease: patients with atopic dermatitis speak it out

Dear Editor,

In almost all countries worldwide, wearing a mask is mandatory in public places, public transportation services and in hospitals and is strongly recommended in other open or closed areas to avoid the transmission of coronavirus.

However, wearing a mask over a longer period may also cause, especially in sensitive and atopic skin, pruritus, erythema, and allergic contact dermatitis and potentially resulting in the worsening of existing skin diseases such as atopic dermatitis (AD).[1–6]

In June 2020, the French Eczema Association assessed the impact of wearing a mask on their daily life in AD patients. All participants were invited via e-mail or via social networks to complete an anonymous short questionnaire created by members of the association (Fig. 1). The questionnaire focused on the different perceptions and symptoms related to wearing a mask and their consequences.

Between 1 and 17 June 2020, 321 individuals replied. A total of 45% stated that they systematically wore a mask when going

