











Report

International registry of dermatological manifestations secondary to COVID-19 infection in 347 Hispanic patients from 25 countries

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Abstract

Background The infection by coronavirus disease 2019 (COVID-19) has been associated with multiple cutaneous manifestations, although characterization of them in Hispanic patients with darker skin phototypes is lacking. The objective of this study is to characterize the clinical dermatological manifestations associated with COVID-19 infection in cases with few or without general symptoms in patients from Latin America.

Methods Cross-sectional study using a questionnaire that was made for health professionals (physicians with a specialty in dermatology) to investigate dermatological lesions associated with COVID-19 infection in patients from 25 countries of Latin America. The survey was active from June 9 to July 30, 2020.

Results In this study, information was collected from a total of 347 patients. We found a female gender predominance: 179/347 (51.6%). The mean age at presentation was 40.87 years. The most frequent dermatological manifestations were maculopapular rash and urticarial lesions, followed by papulovesicular lesions, vesicular lesions, chilblain-like lesions, papular lesions, ecchymosis, petechial purpura, pityriasis rosea-like lesions, pruritus, palmoplantar dysesthesias, transient livedo, acral necrosis, palpable purpura, livedo racemosa, and retiform purpura. As far as we know, there are no previous reports of pruritus and palmoplantar dysesthesias.

Conclusions This registry emphasizes skin manifestations as an important criterion for establishing the diagnosis of COVID-19 infection in Latin American countries. This information will be useful for the early identification of suspected cases by health professionals (dermatologists and nondermatologists) and will allow contact tracing to mitigate the impact on health systems at different levels.

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Introduction

Pandemic coronavirus disease (Coronavirus disease 2019, [COVID-19]) is caused by a new pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), isolated for the first time in December 2019 in Wuhan, China.¹ The most common clinical presentation is respiratory, but other organs can also be affected, including the skin. It is estimated that approximately 20% of patients affected by COVID-19 have skin lesions, 45% at onset and 55% during hospitalization or over the course of the disease, and there is no evidence to date that skin lesions occur by viral replication in situ. The dermatological manifestations do not seem to be related to the viral load, although acro-ischemic lesions have been described more frequently in paucisymptomatic (oligosymptomatic) young patients.^{2,3} There is also a relationship between some cutaneous manifestations and the overall prognosis of the patient, such as necrotic and ecchymotic forms associated with more severe disease.⁴

As far as we know, there have been no descriptions of skin manifestations of COVID-19 infection in Latin American patients; thus, we are lacking information in patients of skin of color (Fitzpatrick phototypes III-V). The characterization of these patterns can help dermatologists and attending physicians in Latin American countries to identify paucisymptomatic patients.

To fill this gap, we performed a cross-sectional study using a questionnaire.

Materials and methods

The Ibero-Latin American School of Dermatology (Colegio Ibero-Latinoamericano de Dermatología—CILAD) and the Mexican Society of Dermatology (Sociedad Mexicana de Dermatología) developed a questionnaire (Adapted from: COVID-19 skin signs by Dr. Noufal Raboobe, available as supporting information in Spanish and Portuguese) to investigate dermatological lesions associated with COVID-19 infection in Latin America. With this instrument, information on the dermatological phototype and preexisting dermatological conditions at the time of COVID-19 diagnosis was obtained. Additionally, questions used to obtain the method of diagnosis, the symptomatology and treatment of COVID-19, and a description of the associated dermatological lesions were included. The opportunity to attach photographs of these lesions was provided. This proposed questionnaire was circulated among a group of experts and then a panel was held to adapt it and their commentaries were added. The final version was uploaded to an online platform for distribution through an electronic link to all dermatological societies and the main dermatological hospitals and services in the region. The

participating countries were Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Granada, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, and Venezuela. The survey was active from June 9 to July 30, 2020. The data were evaluated through a noninferential descriptive statistical analysis. The project was approved by the Ethics Committee of the Universidad Autónoma de Nuevo León, Mexico, with the code DE20-00005.

Results

Demographic information

Although 730 questionnaires were received, only 347 were fully processed due to missing data. In this study, we found a predominance of females: 179/347. The mean age at presentation was 40.87 years, with a median of 41.0 years and a range of 7 to 90 years. In 99.4% (345/347), the Fitzpatrick phototype was reported; the most frequent was III, 45.8%; followed by IV, 39.1%; II, 13%; V, 1.7% and I, with 0.3% (Table 1).

Dermatological manifestations of patients

The attending physicians reported that 92.3% of patients presented signs and symptoms in the skin, hair, nails, or mucous membranes. Regarding the possible etiology of the dermatological manifestations, 82.7% of dermatologists considered these presentations likely to be related to COVID-19, 4.3% considered them likely to be related to treatment, 1.2% said that they were likely related to a drug other than the one used for the treatment of COVID-19, 1.7% considered them related to another virus, 4% considered them likely to be related to postviral eruption, and 2.3% were not sure. The most frequent dermatological manifestations were maculopapular rash (20.5%) and urticarial lesions (20.5%), followed by papulovesicular lesions (9.9%), vesicular lesions (7.8%), pseudo-chilblains (7.8%), papular lesions (7.1%), ecchymosis (5%), petechial purpura (4.7%), pityriasis rosea-like lesions (4%), pruritus (2.8%), palmoplantar dysesthesias (2.8%), transient livedo (2.2%), acral necrosis (2.2%), palpable purpura (1.6%), livedo racemosa (0.6%), and retiform purpura (0.6%). Only 15.3% of patients underwent a biopsy (Figs. 1–3 and Table 2).

Overall context of the patients and outcomes

Regarding evidence of infection by COVID-19, only clinical diagnosis was made in 25% of patients. The rest underwent any diagnostic test; 64.8% had a positive PCR test, 14.4% had positive antibodies, 3.5% had a negative PCR test, and 0.3% had negative antibodies; in 0.23%, it was unknown whether any type of diagnostic test was performed. No patient underwent a metagenomic test for the diagnosis of COVID-19 infection. Only in four cases the type of diagnostic test performed was not

Table 1 Demographic characteristics

Characteristic	Frequency (percentage)
Surveys (<i>n</i> = 730)	
Language	
Spanish	670 (91.78%)
Portuguese	60 (8.22%)
Origin	
Mexico	227 (31.1%)
Argentina	85 (11.6%)
Brazil	59 (8.1%)
Colombia	48 (6.6%)
Peru	38 (5.2%)
Chile	34 (4.7%)
Ecuador	33 (4.5%)
Dominican Republic	27 (3.7%)
Venezuela	27 (3.7%)
Bolivia	24 (3.3%)
Honduras	24 (3.3%)
Guatemala	23 (3.2%)
Nicaragua	15 (2.1%)
Paraguay	14 (1.9%)
No answer	17 (2.3%)
El Salvador	11 (1.5%)
Costa Rica	9 (1.2%)
Panama	5 (0.7%)
Uruguay	4 (0.5%)
Trinidad and Tobago	3 (0.4%)
Suriname	2 (0.3%)
Cuba	1 (0.1%)
Patients (<i>n</i> = 347)	
Gender	
Female	179 (51.6%)
Male	168 (48.4%)
Age	
Mean (\pm standard deviation)	40.87 (\pm 20.47)
Median (interquartile range)	41.0 (28.0 – 58.0)
Minimum–maximum	(7–90)
Phototype (<i>n</i> = 345)	
I	1 (0.3%)
II	45 (13%)
III	158 (45.8%)
IV	135 (39.1%)
V	6 (1.7%)

specified. It is worth mentioning that the health professionals were able to select more than one option for this item.

The most frequently reported symptoms were as follows: fever, 59.4%; cough, 47.8%; headache, 35.5%; general malaise, 34.9%; respiratory distress, 27.95%; myalgia, 24.8%; odynophagia, 21%; arthralgia, 18.4%; diarrhea, vomiting, or nausea, 17%; anosmia, 17%; dysgeusia, 12.7%; chest pain, 10.7%; rhinorrhea, 8%; abdominal pain, 5.2%; and irritability or confusion, 3.5%. Ten percent of the cases were reported as asymptomatic. It is important to mention that the health professionals were able to select more than one option; therefore, the frequencies and percentages reflect the number of times the answer was chosen.

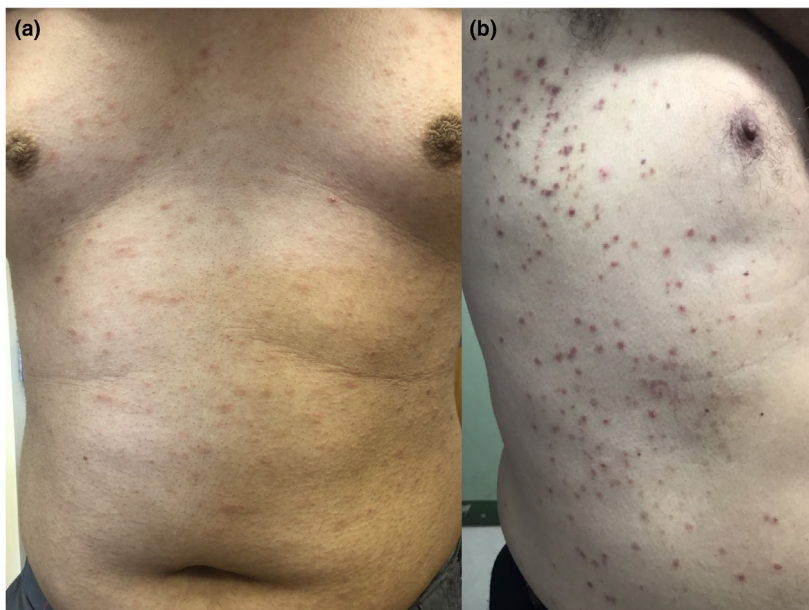


Figure 1 (a) Maculopapular lesions and (b) papulovesicular lesions



Figure 2 (a, b) Urticarial lesions and (c, d) pseudo-chilblains lesions

The treatments administered were as follows: only supportive care in 69.5% of cases, followed by antibiotics (48.4%), glucocorticoids (25.9%), ivermectin (21%), antimalarials (9.5%), IL-6

inhibitors (2.9%), lopinavir/ritonavir (1.7%), JAK inhibitors (1.7%), intravenous immunoglobulin (IVIg, 1.4%), convalescent plasma (0.9%), remdesivir (0.9%), and ciclesonide (0.6%). No



Figure 3 (a, b) Purpuric-necrotic lesions

patient received interferon or bevacizumab, and in 13 (3.8%), the treatment used was unknown. The use of azithromycin was reported in 32.3%, clarithromycin in 1.4%, and other unspecified antibiotic in 16.7%.

Regarding complications associated with COVID-19 infection, 67.4% did not report any complications. However, acute respiratory distress syndrome (ARDS) occurred in 21% of patients, with sepsis in 6.3%, myocarditis or heart failure in 0.9%, concomitant or secondary lung infection in 3.5%, acute kidney injury in 5.5%, and thrombotic events in 2.6%. Regarding the latter, 4% of patients had a personal history of thrombophilia or a state of hypercoagulability; 67.4% hadn't had such history, and in 24.5%, it was unknown.

In 323 patient records, there was information about the mortality of the disease. A total of 13.3% of the patients died from COVID-19 or associated complications (Table 2).

Comment

We collected a total of 730 questionnaires in both Spanish and Portuguese with information regarding 347 patients from 25 countries in the Latin American region. To the best of our knowledge, it is the largest registry of its kind in the region.

The majority of the patients were female, which coincides with previous reports in the literature.^{2,4} The average age at presentation was 40.87 years, and phototypes III and IV were the most frequent, consistent with the study population (Latin American countries with a high percentage of mestizo population).

Several groups of researchers have gathered information on cutaneous manifestations, describing and categorizing them with the aim of identifying suspected cases of SARS-CoV-2 infection (Table 3).²⁻⁴

A study in Spain (a country that for some time was the epicenter of the pandemic in Europe) included 375 patients from April 3 to April 16, 2020, with recent skin eruptions without apparent explanation.² Five clinical patterns were identified: (1)

pseudo-chilblains (19%): erythema-edema with some vesicles or acral pustules on the hands and feet, usually asymmetrical; (2) vesicular eruptions (9%): monomorphic vesicles with liquid or hemorrhagic content; (3) urticaria (19%), predominantly in the torso and less frequently in the palms; (4) other (47%): macules and papules with peripheral distribution accompanied by desquamation, also described as pseudovesicles, simulating erythema multiforme; (5) livedo or necrosis (6%), which suggests vascular occlusive disease in the torso or acral ischemia. In addition, the surveyed dermatologists reported an increase in herpes zoster in cases of COVID-19.

The Spanish dermatological group of the Hospital Universitario Virgen de las Nieves (Virgen de las Nieves University Hospital),³ described the following patterns: (1) erythematous exanthem/rash, nonspecific, similar to other viral rashes, predominantly in the torso, asymptomatic or with mild pruritus. It appeared at the onset of respiratory symptoms or days later and resolved spontaneously; (2) urticarial rash with erythema and wheals, a nonspecific presentation clinically indistinguishable from acute urticaria, present in 1.4% of patients with COVID-19; (3) vesicular varioliform eruption (only pattern with vesicles); (4) erythematous lesions similar to acroischemic pernio (pseudo-chilblains), initially asymptomatic and can subsequently cause pain and affect acral areas. This pattern was observed more frequently in young oligosymptomatic patients on the dorsolateral aspects and tips of fingers, soles, and heels. After 2 weeks, the lesions became purpuric; (5) other: lesions similar to livedo reticularis on the thighs; follicular petechial purpura on the limbs, torso and, less frequently, the face. The report also described rashes similar to pityriasis rosea, dengue (with low platelet count), infectious erythema, and eruptive pseudoangiomatosis. Some hospitalized patients presented with miliaria crystallina/rubra and folliculitis.

In the United States, a similar study was carried out with patients from 31 countries (the majority from the United States, 89%) and found that among patients with laboratory-confirmed COVID-19, the most common morphologies were morbilliform

Table 2 Clinical characteristics of the patients

Characteristics	Frequency (percentage)
Etiology of manifestations (n = 347)	
Most likely related to COVID-19	287 (82.7%)
Most likely related to treatment	15 (4.3%)
Most likely related to a drug other than the ones used to treat COVID-19	4 (1.15%)
Most likely related to another virus	6 (1.72%)
Most likely related to postviral rash	14 (4.03%)
Not sure	8 (2.3%)
Did not answer	6 (1.72%)
Signs or symptoms (n = 322)	
Maculopapular rash	66 (20.5%)
Urticarial lesions	66 (20.5%)
Papulovesicular lesions	32 (9.9%)
Vesicular lesions	25 (7.8%)
Chilblains	25 (7.8%)
Papular lesions	23 (7.1%)
Ecchymosis	16 (5.0%)
Petechial purpura	15 (4.7%)
Pityriasis rosea-like lesions	13 (4.0%)
Pruritus	9 (2.8%)
Palmar or plantar dysesthesias	9 (2.8%)
Transient livedo	7 (2.2%)
Acral necrosis	7 (2.2%)
Palpable purpura	5 (1.6%)
Livedo racemosa	2 (0.6%)
Retiform purpura	2 (0.6%)
Biopsy (n = 347)	
Yes	53 (15.27%)
No	287 (82.71%)
Not known	1 (0.29%)
Did not answer	6 (1.72%)
Preexisting dermatological diseases (n = 347)	
Yes	51 (14.69%)
No	263 (75.79%)
Not known	22 (6.34%)
Did not answer	11 (3.17%)
Diagnostic test for COVID-19 (n = 347)^a	
Clinical diagnosis	87 (25.07%)
PCR positive	225 (64.84%)
Positive antibodies	50 (14.40%)
PCR negative	12 (3.46%)
Negative antibodies	1 (0.28%)
Metagenomic test	0
Not known whether a test was performed for COVID-19	1 (0.28%)
Other	26 (7.49%)
General symptoms (n = 347)^a	
Fever	206 (59.37%)
Cough	166 (47.84%)
Headache	123 (35.45%)
General malaise	121 (34.45%)
Respiratory distress	97 (27.95%)
Myalgia	86 (24.78%)
Odynophagia	73 (21.04%)
Arthralgia	64 (18.44%)
Diarrhea, vomiting, or nausea	59 (17.00%)
Anosmia	59 (17.00%)

Table 2 Continued

Characteristics	Frequency (percentage)
Dysgeusia	44 (12.68%)
Chest pain	37 (10.66%)
None (asymptomatic)	35 (10.09%)
Rhinorrhoea	28 (8.07%)
Abdominal pain	18 (5.19%)
Irritability/confusion	12 (3.46%)
Not known	4 (1.15%)
Other	31 (8.93%)
Treatment received (n = 347)^a	
Supportive care	241 (69.45%)
Antibiotics ¹	168 (48.41%)
Other ²	104 (29.97%)
Glucocorticoids	90 (25.94%)
Ivermectin	73 (21.04%)
Antimalarial	33 (9.51%)
Not known	13 (3.75%)
IL-6 inhibitors	10 (2.88%)
Lopinavir/ritonavir	6 (1.73%)
JAK inhibitors	6 (1.73%)
IVIG	5 (1.44%)
Convalescent plasma	3 (0.86%)
Remdesivir	3 (0.86%)
Ciclesonide	2 (0.58%)
Interferon	0
Bevacizumab	0
Antibiotics used (n = 347)	
Azithromycin	112 (32.28%)
Clarithromycin	5 (1.44%)
Other	58 (16.71%)
Did not use	172 (49.57%)
Complications (n = 347)^a	
None	234 (67.44%)
Acute respiratory distress syndrome	73 (21.04%)
Sepsis	22 (6.34%)
Myocarditis or heart failure	3 (0.86%)
Concomitant lung infection or superinfection	12 (3.46%)
Acute kidney damage	19 (5.48%)
Thrombotic event	9 (2.59%)
It is unknown	14 (4.03%)
Another complication	14 (4.03%)
History of thrombophilia or state of hypercoagulability (n = 347)	
Yes	14 (4.03%)
No	234 (67.44%)
Information not collected	85 (24.50%)
Did not answer	14 (4.03%)
Mortality (n = 347)	
Yes	46 (13.26%)
No	262 (75.50%)
Not known	15 (4.32%)
Did not answer	24 (6.92%)

^aThe respondents could select more than one option.

rash (22%), pseudo-chilblains (18%), urticaria (16%), macular erythema (13%), papulosquamous lesions (9.9%), and retiform purpura (6.4%).⁴ Pseudo-chilblains presentation was more

Table 3 Cutaneous manifestations of suspected and confirmed COVID-19 cases published in European and United States populations

Author, region/country	Year	Number of patients	Dermatological manifestations
Galván-Casas <i>et al.</i> , ² Spain	2020	375	Acral ischemia Pseudo-chilblains Vesicular Urticarial Rash containing macules and papules
Servicio de dermatología MQ y V del Hospital Universitario Virgen de las Nieves de Granada, ³ Spain	2020	Not specified	Rash (erythematous, petechial, morbilliform) Urticarial Vesicular Acral ischemia Other (livedo reticularis, follicular petechial purpura)
Freeman <i>et al.</i> , ⁴ United States of America	2020	716	Retiform purpura Vesicular Rash containing macules and papules Urticarial Pseudo-chilblains
Ocampo-Candiani <i>et al.</i> , Latin America.	2020	347	Maculopapular rash Urticarial lesions Papulovesicular lesions Vesicular lesions Pseudo-chilblains Papular lesions Ecchymosis Petechial purpura Pityriasis rosea-like lesions Pruritus Palmoplantar dysesthesias Acral necrosis Other (transient livedo, palpable purpura, livedo racemosa, and retiform purpura.

The newly described manifestations in this study are bolded.

common in patients with moderate disease, while retiform purpura presented exclusively in severely hospitalized patients.

The vast majority of respondents concluded that the dermatological manifestations of their patients were probably related to COVID-19 infection, and PCR was the most frequently used confirmatory method. In our study, the main dermatological patterns were maculopapular rash, urticarial lesions, papulovesicular rash, vesicular rash, and pseudo-chilblain lesions, which coincides with previous reports in the literature^{2,4} and represents a spectrum of manifestations as broad as that reported by Freeman *et al.*⁴ We also report previously undescribed symptoms: pruritus and palmoplantar dysesthesias. Some hypotheses that could explain the pruritus are the exacerbation of preexisting itchy disorders, secondary reactions to personal protective equipment (PPE), psychological stress-induced itch, and directly related to the dermatoses associated with the COVID-19 infection.⁵ Palmoplantar dysesthesias, without redness or swelling, could be secondary to the already widely recognized occlusive

vasculopathy due to COVID-19 infection or to symptomatic therapy. SARS-CoV-2 is not the only virus that can cause burning sensations on hands and feet as several outbreaks of poxvirus-related burning sensation have been reported in China but accompanied with redness and swelling (erythrodysesthesia).⁶ A histopathological study was performed in a minority of patients, probably due to the transient nature of the clinical manifestation, the overall condition and isolation of the hospitalized patients, and because the vast majority of the patients only required outpatient management. Similar to Suchonwanit,⁷ we consider that the manifestations of COVID-19 could be a response to viral antigens or secondary to phenomena such as vasculitis or thrombotic vasculopathy, which are widely recognized systemic consequences of COVID-19 infection. Regarding this, we found that the majority of our patients (67.4%) did not present any complications; however, ARDS, sepsis, heart failure, concomitant lung infection, acute kidney injury, and thrombotic events were reported as important complications.

The majority of our patients had mild signs and symptoms of the disease, which correlates with the greater frequency of clinical manifestations related to COVID-19, probably associated with hypersensitivity to virus particles.⁷ Most maculopapular rashes occurred during the active phase of the disease, which may correlate to the viremia phase; regarding the prevalence of cutaneous manifestations associated with symptomatic cases of COVID-19 infection, it is suggested that SARS-CoV-2 infection lead to hypercytokinemia and expression of interferon-inducible genes which have multiple immunopathogenic potentials including overexpression of genes involved in inflammation, which can explain most of the cutaneous signs and symptoms.⁸ It is worth noting that no patient received interferon or bevacizumab, the former of which is associated in some case reports with pseudo-chilblain manifestations.⁹⁻¹¹ The majority of the patients recovered and required mostly supportive treatment. However, age and the presence (or absence) of comorbidities are determinants of the implementation of different therapeutic strategies.

Conclusions

The knowledge and identification of dermatological manifestations in patients infected with the SARS-CoV-2 virus can benefit dermatologists and first-contact physicians, who should become familiar with these symptoms. This registry emphasizes skin manifestations as an important criterion for establishing the diagnosis of COVID-19 infection in Hispanic patients. This information will be useful for the early identification of suspected cases by health professionals (nondermatologists), which will allow to make recommendations regarding isolation measures for asymptomatic or paucisymptomatic patients, also allowing contact tracing to mitigate the impact of the disease on the health systems at different levels.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Material Spanish version of the questionnaire used in order to create this registry. Adapted from: Skin signs of Covid-19. Dr. Noufal Raboobe.