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Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases

Running head: Cutaneous manifestations of COVID-19

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None

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What is already known about this topic?

- Previous descriptions of cutaneous manifestations of COVID-19 were case reports and mostly lacked illustrations.

What does this study add?

- We describe a large, representative, sample of patients with unexplained skin manifestations and a diagnosis of COVID-19; using a consensus method to define morphological patterns associated with COVID-19.
- We describe five clinical patterns associated with different patient demographics, timing, and prognosis and provide illustrations of these patterns to allow for easy recognition.

SUMMARY

Background: Cutaneous manifestations of COVID-19 disease are poorly characterized.

Objectives: To describe the cutaneous manifestations of COVID-19 disease and to relate them to other clinical findings

Methods: Nationwide case collection survey of images and clinical data. Using a consensus, we described 5 clinical patterns. We later described the association of these patterns with patient demographics, timing in relation to symptoms of the disease, severity, and prognosis.

Results: Lesions may be classified as acral areas of erythema with vesicles or pustules (Pseudo-chilblain) (19%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%). Vesicular eruptions appear early in the course of the disease (15% before other symptoms). The pseudo-chilblain pattern frequently appears late in the evolution of the COVID-19 disease (59% after other symptoms), while the rest tend to appear with other symptoms of COVID-19. Severity of COVID-19 shows a gradient from less severe disease in acral lesions to most severe in the latter groups. Results are similar for confirmed and suspected cases, both in terms of clinical and epidemiological findings. Alternative diagnoses are discussed but seem unlikely for the most specific patterns (pseudo-chilblain and vesicular).

Conclusions: We provide a description of the cutaneous manifestations associated with COVID-19 infection. These may help clinicians approach patients with the disease and recognize paucisymptomatic cases.

INTRODUCTION

In December 2019, the first cases of pneumonia with unknown cause were reported in Wuhan, China¹. The new pathogen, called SARS-CoV-2, was isolated from samples of the lower respiratory tract of infected patients² and the resulting disease was called COVID-19 (Coronavirus Disease 2019). SARS-CoV-2 has rapidly spread reaching the level of a pandemic disease.

COVID-19 can affect different organ systems, probably including the skin. There are few descriptions of the cutaneous manifestations of COVID-19. Twenty per cent of patients in an Italian medical ward had cutaneous lesions, described as rash, urticaria or one case of “chickenpox -like” lesions³. Other case reports describe a rash mistaken for Dengue⁴, achroisquemia in children⁵ and critical patients⁶, plaques in the heels⁷, and urticaria^{8,9}. Most of these reports lack clinical images, due to safety concerns¹⁰, and describe few patients in hospital settings.

There is no previous detailed classification nor description of the cutaneous manifestations of COVID-19. This information may prove useful to manage patients, to recognize paucisymptomatic patients, and might provide prognostic information. The recognition of paucisymptomatic patients could also be helpful for epidemiological control especially in areas where diagnostic tests are scarce¹¹.

For all these reasons, we conducted a dermatologist nationwide case collection survey, to quickly describe the cutaneous manifestations of COVID-19 disease and to relate them to other clinical findings.

MATERIALS AND METHODS

Since the start of the study until 8th April (last available data), the World Health Organization considered Spain an area of SARS-Cov-2 local transmission¹². With the support of the Spanish Academy of Dermatology, we asked all Spanish dermatologists (many of them relocated to the acute care of patients during the COVID-19 pandemic) to include patients in this study for two weeks. All patients with an eruption of recent onset (previous 2 weeks) and no clear explanation, plus suspected (patients presenting with compatible symptoms) or confirmed COVID-19 (with laboratory confirmation of SARS-CoV-2, irrespective of clinical signs and symptoms), using the definitions of the European Centre for Disease Control, were included¹³. A standardized questionnaire was used, and pictures taken for most of them. Expecting 4 or 5 patterns of similar incidence, we had assumed that collecting 60 confirmed cases would be adequate for an initial description. In the middle of the recruitment period, we had 120 cases. Their photographs were independently reviewed by a group of 4 dermatologists without knowing about the rest of the clinical information, and a consensus was reached on the cutaneous patterns of disease. These patterns were applied to the whole dataset of pictures and further refined without knowledge of the rest of clinical information. These morphological diagnostic data were later merged with the rest of the clinical information for analysis.

In most areas, viral tests were especially scarce in this period and were rarely done for less severe cases or cases with a clear diagnosis. Due to low sensitivity of some diagnostic tests and their scarcity, we accepted cases with clinical diagnosis of the disease (suspected cases) but performed a sensitivity analysis to check that the results do not change if done only on confirmed patients. Analysis consisted on description of the data and distribution tests (chi-square test for qualitative and ANOVA for quantitative variables) and was done using Stata 16 (Statacorp, 2019).

The study was authorized by an ethics committee (HUGCDN: 2020-172-1- COVID-19), the Spanish Drug Agency (ACG-CLO-2020-01) and included in EnCEPP (EUPAS34469). All patients, or their next of kin in case of minors, gave their informed consent to participate and an explicit consent to use their pictures in publications.

RESULTS

We collected 429 cases from 3rd to 16th of April 2019, during the peak of the epidemic in Spain. Five cases were excluded for being compatible with other diagnosis (3 herpes zoster and 2 psoriasis). 31 patients with cutaneous lesions were excluded for not meeting the definition of confirmed or suspected COVID-19 and 18 for missing information. The overall impression was the majority of excluded patients showed similar lesions, mostly described as acral. Final sample included 375 patients. Case fatality rate in the sample was 1.9%.

Clinical patterns

Consensus following image review lead to the description of five major clinical patterns (see Appendix S1). Nearly all patients could be classified in these groups, and a few unusual cases are highlighted in the description.

- 1.-Acral areas of erythema-oedema with some vesicles or pustules (pseudo-chilblain) (19% of cases). These lesions may resemble chilblains and have purpuric areas, affecting hands and feet. (Fig 1a and 1b). They were usually asymmetrical.
- 2.-Other vesicular eruptions (9%). Some presented on the trunk and consisted of small monomorphic vesicles (unlike polymorphic vesicles in chickenpox) (Fig 1 c). They may also affect the limbs, have haemorrhagic content, and become larger or diffuse.
- 3.- Urticarial lesions (19%)(Fig 1d): mostly distributed in the trunk or disperse. A few cases were palmar.
- 4.- Other maculopapules (47%). Some of them showed perifollicular distribution and varying degrees of scaling (Fig 2a). Some had been described as similar to pityriasis rosea. Purpura may also be present, either punctiform or on larger areas. A few cases showed infiltrated papules in the extremities, mostly dorsum of the hands, that look pseudovesicular (Fig 2b) or resemble erythema elevatum diutinum or erythema multiforme (Fig 2c).
- 5.- Livedo or necrosis (6%). These patients showed different degrees of lesions suggesting occlusive vascular disease, including areas of truncal or acral ischemia. (Fig 2d)

A few patients showed other manifestations such as enanthem or purpuric flexural lesions. Dermatologists also perceived an increased number of herpes zoster cases in COVID-19 patients.

Characteristics associated with each clinical pattern

The different clinical patterns were associated with differences in demographics and in other clinical manifestations (Table 1).

Pseudo-chilblain affected younger patients, lasted for a mean of 12.7 days, took place later in the course of the COVID-19 disease and was associated with less severe disease (in terms of hospital admission, pneumonia, intensive care unit admission or mortality). They could cause pain (32%) or itch (30%).

Vesicular lesions appeared in middle aged patients, lasted for a mean of 10.4 days, appeared more commonly (15%) before other symptoms and were associated with intermedium severity. Itching was common (68%).

Urticarial and maculopapular lesions showed a very similar pattern of associated findings. They lasted for a shorter period (6.8 days mean for urticarial and 8.6 for maculopapular), usually appeared at the same time than the rest of the symptoms and were associated with more severe COVID-19 disease (2% mortality in the sample). Itching was very common for urticariform lesions (92%) and 57% for maulopapular.

Livedoid/necrotic lesions took place in older patients with more severe disease (10% mortality). However, the manifestations of COVID-19 in this group were more variable, including transient livedo, with some suffering COVID-19 that did not require hospitalization.

Severity of associated disease followed a gradient, from less severe disease in pseudo-chilblain to most severe in patients with livedoid presentations, as shown by the increasing percentages of pneumonia, admission, and intensive care requirements.

Of 71 patients with pseudo-chilblain, only one had a previous history of perniosis. The percentage with confirmed presence of SARS-Cov-2 in this group was 41%, lower than in the other morphological groups (Table 1).

Patients in the group with urticarial and maculopapular eruptions were receiving drugs more commonly than those with pseudo-chilblain or vesicular lesions, but less than those with maculopapules or livedoid lesions, in relationship with an increased severity.

We could describe three familiar clusters with lesions. One family had 2 siblings with pseudo-chilblain and other showing a generalized vesicular eruption with suspected COVID-19. Another 2 families showed clusters of lesions but did not have symptoms of respiratory COVID-19 and did not enter the study: each of the two families had two children, that simultaneously developed pseudo-chilblains.

We have reproduced the same analysis using only confirmed cases of COVID-19, and the results were similar (Supplementary material 2, tables 1S and 2S).

DISCUSSION

We have described five cutaneous clinical patterns and several sub-patterns associated with COVID-19 and showed that the large groups appear at different times in the disease, and are associated with different duration, severity and probably prognosis.

Previous publications have described some of these patterns, but based on very few cases, lacking photography, or using inadequate terms (like “chickenpox-like” for monomorphic lesions or “acro-ischemic” for acral areas of erythema-oedema with some vesicles or pustules). No temporal relationship with symptoms or prognosis has previously been described.

One strength of our study is that the description of clinical patterns has been done by experts based only on morphology. The resulting patterns were shown to allow for easy classification of patients and to correlate with differences in demographics and severity.

Given the large number and distribution of participants, the sample is likely to be representative of the overall distribution of cutaneous lesions in COVID-19. However, we cannot define the source population, and, lacking a denominator, we have no measures of the incidence of clinical manifestations, only relative ones. We have omitted patients in the spectrum of severe disease due to the difficulties to obtain consent. This explains the low case fatality rate. However, description of the lesions in these patients are less useful for diagnosis, as their diagnosis is usually obvious. Patients in the general population without clinical or virologic confirmation of COVID-19 disease were also underrepresented. We thought that this restrictive admission of reports was needed to increase specificity of the results. During the study period, testing was not done to most cases of mild disease. As we aimed to describe the lesions in less severe cases, we accepted both confirmed and suspected cases in our study. Results show that both groups showed similar cutaneous lesions (supplementary material 1) and epidemiological results (supplementary material 2, tables). Patients excluded for lack of COVID-19 diagnostic criteria (31) also had similar patterns, confirming that the inclusion of suspected patients did not bias the results.

As the study describes a short period of follow-up, it is better defined as a transversal rather than a cohort. Data on the duration, severity of the disease and the outcome are limited to the time that the patient was observed. It is possible that some of the less severe patients worsen with time. Against this limitation, data shows that the less severe forms were described late in the evolution of the disease, and have a longer duration, so it is unlikely that they worsen over time.

Our study included any unexplained cutaneous lesions in patients with COVID, so it is possible that some of them have alternative causes.

Pseudo-chilblain may look like perniosis, and as they appear later in the evolution and are less commonly associated with virologic confirmation, it is possible that they are not related to the COVID-19. We think that the pseudo-chilblain pattern is linked to COVID-19 because pseudo-chilblain appeared in a warm weather period, dermatologists perceived a greatly increased incidence, and patients frequently had COVID-19 contacts. Only one of the 71 patients had previous history of chilblain. 29 of 71 (41%) had SARS-CoV-2 confirmed and we found three

simultaneous familiar clusters. The late appearance of pseudo-chilblains might explain the frequently negative PCR results¹⁴.

Monomorphic disseminated vesicular lesions and acral vesicular-pustulous lesions are probably quite specific and their appearance is coherent with lesions in other viral exanthemas.

Most of the urticarial and maculopapular lesions might not be very helpful for diagnosis, as these are common and may have many different causes. Drug reactions may be an important and difficult differential diagnosis. These patients had more severe disease and received more drugs. Regarding their relationship with the other manifestations, urticarial and maculopapular lesions may be considered similar.

Livedoid and necrotic lesions were relatively uncommon, and mostly appeared in elderly and severe patients. As the number of patients is lower the information is less precise. In two case reports livedoid lesions were transient¹⁵. These might be primary lesions of COVID-19 or simply indicate complications leading to vascular occlusion, as COVID-19 has been linked to alterations in coagulation and vascular damage^{6,16,17}.

It is unusual, from our previous experience with cutaneous manifestations of viral diseases, that a single virus can lead to several different clinical patterns, especially as different patterns do not coexist on the same patient. Patients that may be classified in more than one pattern are very uncommon. Some hypothesis to explain this polymorphism may be that some of them have alternative causes, or differences in the virus or the host. The fact that some of the lesions, even in confirmed patients, are similar to other viral infections (notably parvovirus¹⁸) and the perceived increased number of zoster cases raises the hypothesis of some of these being the result of coinfection and whether SARS-Cov-2 is responsible for this.

In terms of arising suspicion of COVID-19, we feel that pseudo-chilblain and vesicular lesions may be useful as indicators of disease. They uncommonly (10 cases of 375) precede other symptoms in our sample. Pseudo-chilblain lesions more commonly appear later during the disease and are not associated with severe disease, so they might be more useful as epidemiological markers than for diagnosis. It is possible that the sampling strategy might bias this result, and acral lesions might precede other COVID-19 symptoms more commonly in the general population. Urticarial

lesions may be due to many causes and did not precede other symptoms in our study, so they are unlikely to lead to diagnosis. Regarding maculopapular lesions, they tend to concur with other symptoms and most of them are not specific. A few subtypes, such as the pseudovesicular (Fig 2b) or those resembling erythema elevatum diutinum (supplementary material) or erythema multiforme (Fig 2c), could lead to suspect the diagnosis. Livedoid/necrotic lesions are late in the evolution and probably unhelpful for diagnosis. However, they nicely fit with the idea of COVID-19 vascular damage.

We provide a description of the cutaneous manifestations associated with COVID-19. These may help clinicians approach patients with the disease and recognize paucisymptomatic cases. The usefulness of these patterns for diagnosis should be confirmed in clinical use. We suggest that further research could be improved by having more tests to confirm COVID-19 and to exclude other infections, and by describing clinicopathologic correlation and some of the patterns that have been grouped in our study.

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TABLES

Characteristics	Pseudo-chilblain	Vesicular	Urticarial	Maculopapules	Livedo/necrosis	p-value
N, (row percentage over 375 patients)	71 (19)	34 (9)	73 (19)	176 (47)	21 (6)	
Female, n (%)	48 (68)	19 (56)	47 (64)	98 (56)	10 (48)	0.276
Age, mean (sd)	32.5 (21.8)	45.6 (20)	48.7 (19.9)	55.3 (20.2)	63.1 (17.3)	<0.001
Smoking, n (%)	7 (10)	2 (6)	12 (20)	21 (15)	2 (15)	0.402
Cough, n (%)	37 (52)	25 (74)	48 (66)	135 (77)	14 (67)	0.004
Dyspnoea, n (%)	18 (25)	12 (35)	30 (41)	100 (57)	11 (52)	<0.001
Fever, n (%)	44 (62)	24 (71)	55 (75)	140 (80)	17 (81)	0.068
Asthenia, n (%)	37 (52)	21 (62)	47 (64)	110 (63)	11 (52)	0.486
Headache, n (%)	27 (38)	12 (35)	24 (33)	55 (31)	9 (43)	0.735
Nausea/Vomiting/Diarrhoea, n (%)	17 (24)	8 (24)	18 (25)	58 (33)	6 (29)	0.523
Anosmia/Ageusia, n (%)	13 (18)	10 (29)	21 (29)	40 (23)	6 (29)	0.507
Pneumonia, n (%)	10 (14)	10 (29)	38 (52)	110 (63)	15 (71)	<0.001
Hospital admission, n (%)	9 (13)	11 (32)	32 (44)	107 (61)	18 (86)	<0.001
ICU or non-invasive mechanical ventilation, n (%)	2 (3)	2 (6)	8 (11)	21 (12)	7 (33)	0.004
Covid-19 case, n (%)						<0.001
Suspected case	42 (59)	17 (50)	24 (33)	54 (31)	4 (19)	
Confirmed case	29 (41)	17 (50)	49 (67)	122 (69)	17 (81)	
Duration of cutaneous eruption (days), mean (sd)	12.7 (8)	10.4 (9.3)	6.8 (7.8)	8.6 (6.8)	9.4 (5.4)	<0.001
Presence of cutaneous symptoms, n (%)	52 (73)	28 (82)	69 (95)	112 (64)	6 (29)	<0.001

Pain, n (%)	23 (44)	3 (11)	1 (1)	4 (4)	1 (17)	
Burning, n (%)	8 (15)	2 (7)	1 (1)	9 (8)	2 (33)	
Itch, n (%)	21 (40)	23 (82)	67 (97)	99 (88)	3 (50)	
Treatment, n (%)	38 (54)	26 (76)	52 (71)	138 (78)	16 (76)	0.004
With paracetamol or without treatment, n (%)						<0.001
Paracetamol, n (%)	65 (92)	29 (85)	54 (74)	120 (68)	13 (62)	
NSAIDs, n (%)	32 (45)	21 (62)	33 (45)	82 (47)	8 (38)	0.433
Chloroquine/Hydroxychloroquine, n (%)	11 (15)	2 (6)	6 (8)	16 (9)	1 (5)	0.484
Lopinavir/ritonavir, n (%)	6 (8)	7 (21)	23 (32)	79 (45)	11 (52)	<0.001
Tocilizumab, n (%)	3 (4)	2 (6)	13 (18)	54 (31)	6 (29)	<0.001
Systemic corticosteroids, n (%)	2 (3)	1 (3)	4 (5)	9 (5)	3 (14)	0.344
Azithromycin, n (%)	1 (1)	3 (9)	7 (10)	21 (12)	6 (29)	0.004
Patient survival, n (%)	3 (4)	7 (21)	13 (18)	39 (22)	2 (10)	0.005
	71 (100)	34 (100)	73 (100)	172 (98)	19 (90)	0.055

Table 1. Characteristics of the patients, COVID-19, therapy and prognosis of each group.

Percentages are for each column. P-values of chi-square test for qualitative and ANOVA for quantitative variables.

Table 2. Temporal relationship with other manifestations of COVID-19.

Timing of cutaneous signs with respect to other symptoms	Pseudo-chilblain	Vesicular	Urticaria	Maculopapules	Livedo/necrosis	Total
Before, n (%)	5 (7)	5 (15)	3 (4)	8 (5)	1 (5)	22
Same time, n (%)	24 (34)	19 (56)	43 (61)	108 (61)	18 (86)	212
After, n (%)	42 (59)	10 (29)	25 (35)	60 (34)	2 (10)	139
Total	71	34	71	176	21	373

Percentages are for each column. Total numbers are not equal on both tables due to few missing values in this variable. P-value(chi-square) <0.001

Figure legends

Figure 1

All patients in the figures had confirmed COVID-19.

1a.- Acral areas of erythema-edema with vesicles or pustules (pseudo-chilblain).

1b.- Acral areas of erythema-edema with vesicles or pustules (pseudo-chilblain).

1c.-Monomorphic disseminated vesicles

1d.-Urticarial lesions

Figure 2

All patients in the figures had confirmed COVID-19.

2a.-Maculopapular eruption. Some of the lesions are perifollicular

2b.-Acral infiltrated papules (pseudovesicular)

2c.-Acral infiltrated papules (erythema multiforme like)

2d.- Livedoid areas

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SUPPORTING INFORMATION

S1.- Additional images

S2.- Additional tables (sensitivity analysis)

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