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Cutaneous manifestations in SARS-CoV-2 infection (COVID-19): a French experience and a systematic review of the literature

Editor

Skin manifestations have been increasingly reported in the setting of COVID-19. However, their incidence and presentation are debated, and the role, direct or indirect, of SARS-CoV-2 in their pathogenesis has yet to be determined.

In this work, we aimed to analyse our experience in a French referral centre and to perform a systematic review of the literature to evaluate the incidence and prognosis of cutaneous lesions observed in COVID-19 patients.

Cutaneous manifestations were assessed in COVID-19 patients admitted to Cochin Hospital (Paris, France) between 16 March and 27 April 2020. Seven hundred and fifty-nine confirmed moderate-to-severe COVID-19 cases were diagnosed in our institution. Eight patients (1%, six males, two females, mean age 55.6) presented with skin lesions, mainly disseminated maculopapular exanthema, but also digitate papulosquamous rash (reported in Ref.1), herpes recurrence, papulovesicular rash and Grover's disease. The mean delay between respiratory/systemic and dermatological signs was 13 days.

Our systematic review of the literature identified 56 articles (including our series) evaluating 1020 patients (Table 1, WHOLE cohort) between 1 December 2019 and 9 of May 2020.[2–10] Diagnosis of COVID-19 infection was confirmed in 47% of patients (Table 1, CONFIRMED cohort). The female-to-male ratio was 1.1 in both cohorts. Mean ages were 42 and 48 in the WHOLE and CONFIRMED cohorts, respectively. Rashes were the most frequent manifestations (54% and 70% in the WHOLE and CONFIRMED cohorts, respectively). These rashes were erythematous maculopapular/morbilliform, urticarial/annular, vesicular/varicelliform or petechial/purpuric by order of frequency. Trunk was the preferential localization of rashes. Other cutaneous manifestations included chilblains in 34% patients in the WHOLE cohort, but in only 11.5% cases in the CONFIRMED cohort. Digital necrosis was more frequently reported in the CONFIRMED cohort (11.5% vs. 5%). Transient livedo was uncommon (1%). About 70% of all patients experienced pruritus. Other symptoms were burning and pain.

The mean delay between the onset of respiratory/systemic symptoms and cutaneous manifestations was around 6.8 days in both cohorts. In some cases, rashes preceded the occurrence of systemic symptoms. When mentioned, chilblains appeared most frequently as a late manifestation. The mean duration of skin lesions was 9 days in both cohorts.

We retrieved six series, including ours, in which the numbers of both infected patients and patients with skin signs were available.[4,6,7,9,10] Cutaneous lesions were observed in 38 patients over 2199 COVID-19 cases. Therefore, the mean incidence of cutaneous manifestations in COVID-19 patients was 1.7% (Fig. 1a).

Besides, we investigated whether cutaneous manifestations could correlate with COVID-19 severity. Therefore, we analysed severity criteria [hospital admission, pneumonia, transfer to Critical Care Unit (CCU), death] in patients of the WHOLE cohort with rashes or chilblains. In patients with rashes, severity was found in 64% of cases and death in 2%, while it was respectively found in 5% and 0% patients with chilblains. We found a statistically significant association between pneumonia, hospitalization, transfer to CCU or death and the occurrence of a rash as compared to chilblains (Fig. 1b).

The incidence of skin signs during COVID-19 is variable in the literature, ranging from 0.2% in China to 20% in North Italy. Our literature analysis indicated that the worldwide incidence is low, around 1–2%, as we observed in our hospital. Skin lesions were dominated by rashes and chilblains, that seem to present opposite prognosis. However, rashes could not always be discriminated with drug-induced exanthema. Likewise, chilblains pathogenesis in the setting of COVID-19 remains poorly understood and its relationship with SARS-CoV-2 is still unclear. Importantly, in our systematic review of the literature,

Table 1 Characteristics of COVID-19 patients with cutaneous manifestations included in the WHOLE and CONFIRMED cohorts

	WHOLE cohort	CONFIRMED cohort
Number of COVID-19 patients, *N*	1020	480
Confirmed SARS-CoV-2 infection, *N* (%)	480 (47%)	480 (100%)
Suspected SARS-CoV-2 infection, *N* (%)	540 (53%)	0 (0%)
Age		
Mean, years (range)	42.2 (15 days to 98 years)	48.0 (15 days to 98 years)
Not mentioned, *N*	161/1020	45/480
Sex		
Male, *N* (%)	407 (48%)	174 (48%)
Female, *N* (%)	438 (52%)	189 (52%)
Not mentioned *N*	175/1020	117/480
Country		
Belgium, *N* (%)	3 (0.3%)	3 (0.6%)
China, *N* (%)	10 (1%)	10 (2%)
France, *N* (%)	308 (30%)	57 (12%)
Iran, *N* (%)	2 (0.2%)	2 (0.4%)
Italy, *N* (%)	164 (16%)	85 (17.8%)
Kuwait, *N* (%)	2 (0.2%)	2 (0.4%)
Spain, *N* (%)	518 (51%)	308 (64%)
Thailand, *N* (%)	1 (0.1%)	1 (0.2%)
USA, *N* (%)	9 (0.9%)	9 (2%)
Morocco, *N* (%)	2 (0.2%)	2 (0.4%)
Indonesia, *N* (%)	1 (0.1%)	1 (0.2%)
Cutaneous lesions morphology		
Rash, *N* (%)	555 (54%)	337 (70%)
Vesicular/varicelliform, *N* (%)	114 (11%)	80 (17%)
Erythematous maculopapular/morbilliform, *N* (%)	245 (24%)	169 (36%)
Urticarial/annular/eczematiform, *N* (%)	178 (17%)	76 (14%)
Petechial/purpuric, *N* (%)	18 (2%)	12 (3%)
Vascular lesions, *N* (%)	408 (40%)	112 (24%)
Chilblains, *N* (%)	342 (34%)	53 (11.5%)
Transient/livedo reticularis, *N* (%)	9 (1%)	6 (1%)
Digital necrosis/ necrotic purpura, *N* (%)	57 (5%)	53 (11.5%)
Other findings, *N* (%)	57 (6%)	31 (6%)
Herpes recurrence, *N* (%)	21 (2%)	21 (4%)
Eruptive cherry haemangioma, *N* (%)	8 (1%)	1 (0.2%)
Acral dyshidrosis-like lesions, *N* (%)	20 (2%)	1 (0.2%)
Ecthyma/impetigo, *N* (%)	5 (0.5%)	5 (1%)
Coma blisters, *N* (%)	2 (0.2%)	2 (0.4%)
Acute generalized exanthematous pustulosis (drug reaction), *N* (%)	1 (0.1%)	1 (0.2%)
Cutaneous involvement location		
Trunk, *N* (%)	186 (35%)	125 (53%)
Lower limbs (excluding acral lesions), *N* (%)	102 (19%)	43 (18.4%)
Upper limbs, *N* (%)	56 (10%)	29 (12.4%)
Acral lesions (fingers, toes, hands, heels), *N* (%)	322 (60%)	44 (18.8%)
Buttocks, *N* (%)	2 (0.2%)	2 (0%)
Mucosa (oral, genitalia), *N* (%)	6 (1.3%)	6 (1.3%)
Face/head, *N* (%)	26 (5%)	16 (6.8%)
Widespread, *N* (%)	26 (5%)	23 (9.8%)
Flexural areas/folds, *N* (%)	4 (0.75%)	4 (1.7%)
Not mentioned, *N*	485/1020	246/480
Cutaneous symptoms		
Itching, *N* (%)	347 (73%)	205 (68%)
Burning, *N* (%)	66 (14%)	23 (8%)
Pain, *N* (%)	91 (19%)	37 (12.2%)
Asymptomatic, *N* (%)	62 (13%)	38 (12.5%)
Not mentioned, *N*	472/1020	177/480
Mean delay of onset of cutaneous manifestations, days (range)	6.8 (−15 to 25 days)	6.7 (−15 to 25 days)
Mean duration of cutaneous manifestations, days (range)	9.0 (20 min to 30 days)	9.0 (20 min to 30 days)

only 15% of chilblains cases had a proven SARS-CoV-2 infection.

In conclusion, this paper provides a comprehensive overview of cutaneous manifestations reported in COVID-19 patients. However, their relationship with SARS-CoV-2 remains to be specified.

Conflicts of interest

Prof. Dupin, Dr. Matar and Dr. Sohier have nothing to disclose. Dr. Oulès reports personal fees from Novartis, outside the submitted work. Prof. Chosidow is a PI for PSOBIOTEQ. Prof. Beylot-Barry reports personal fees from AbbVie, Celgene, Takeda, Janssen, Novartis, and Lilly, outside the submitted work. Prof. Aractingi reports grants from Novartis and Leo Pharma, and personal fees from Pierre Fabre, BMS and Lilly, outside the submitted work.

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Authors' contributions

N.D. and S.A. designed the study with inputs from O.C. and M.B.B.. S.M. and B.O collected the data and performed the analysis. P.S. performed the pathological analysis. S.M., B.O., N.D. and S.A. wrote the manuscript with inputs from all the other authors.

Data availability statement

All data that support the conclusions, including the complete list of references, are available from the authors upon request.

(a)

Type of study, N, (reference number)	Country	Cutaneous manifestations (n)	Incidence n/N (%)
Case series, N=88, (7)	Italy	Erythematous rash (14), urticaria (3), chickenpox-lik vesicles (1)	18/88 (20%)
Multicentric retrospective study, N=1099, (6)	China	Rash	2/1099 (0.2%)
Prospective study, N=103, (10)	France	Erythematous rash (2), urticaria (2), herpes recurrence (1)	5/103 (5%)
Observational study, N=131, (9)	Italy, Spain	Herpetiform vesicular lesions	3/131 (2.3%)
Retrospective study, N=19 eligible, (4)	Spain	Chilblains	2/19 (10%)
Observational study, N=759, (this study)	France	Rash, digital necrosis, herpes recurrence	8/759 (1%)
			38/2199 (1.7%)

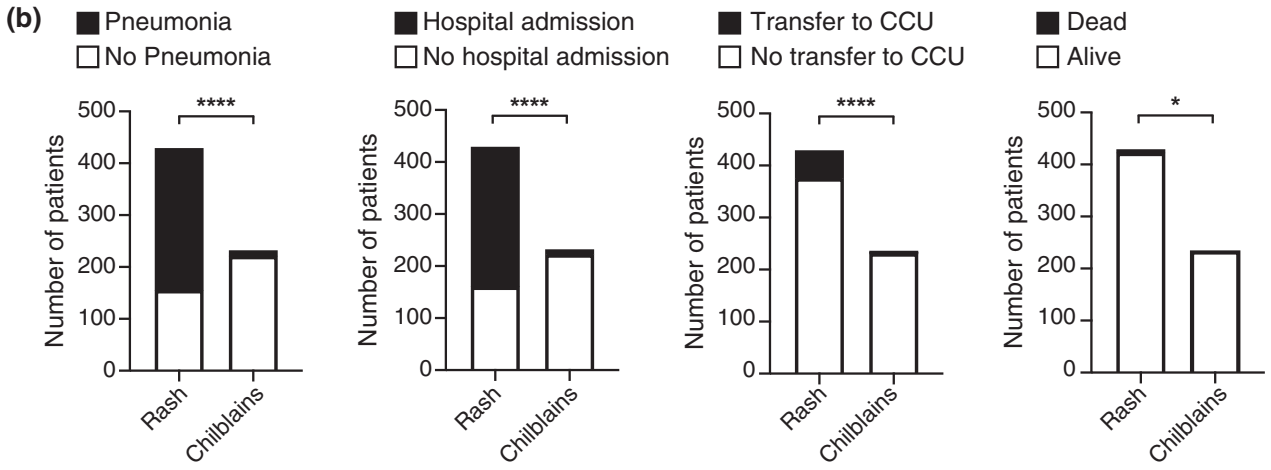

Figure 1 (a) Analysis of the incidence of cutaneous manifestations related to COVID-19. (b) Pneumonia, hospital admission, transfer to CCU and death were analysed in patients of the WHOLE cohort presenting with rash or chilblains. Chi-square test. *P-value < 0.05; ****P-value < 0.0001.

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Recent outbreak of chilblain-like lesions is not directly related to SARS-CoV-2 infection

Editor

Throughout March and April 2020, dermatologists have observed an outbreak of chilblains despite climatic conditions not conducive to their apparition. These lesions have occurred simultaneously to the COVID-19 epidemic, suggesting a relationship between their onset and SARS-CoV-2 infection.

Here we describe a series of 10 patients presenting chilblain-like lesions in whom we have searched for evidence of SARS-CoV-2 infection.

Between 17 and 29 April 2020, we have included patients successively referred to our Department for chilblain-like lesions. Present and past medical history were recorded along with complete skin examination. Blood samples were collected for blood cell count, CRP, liver and renal parameters, antinuclear antibodies (anti-ENA and anti-DNA antibodies if positive immunofluorescence), complement components, ANCA, cryoglobulins, anti-prothrombinase, anticardiolipin antibodies, coagulation factors and D-dimers. Serological status concerning human immunodeficiency virus, hepatitis viruses and SARS-CoV-2 were established using automated assays performed on an Abbott ARCHITECT i2000 (Abbott Diagnostics, Rungis, France). Two biopsies were performed on lesional skin for diagnosis by light microscope examination and for SARS-CoV-2 search by RT-PCR test targeting the RNA-dependent RNA polymerase gene (https://www.who.int/docs/default-source/coronaviruse/real-time-rt-pcr-assays-for-the-detection-of-sars-cov-2-institut-pasteur-paris.pdf). We also searched for SARS-CoV-2 on a nasopharyngeal swab using RT-PCR.

Ten patients were included [median age: 33 years (11–57), sex-ratio 1 : 1]. All had erythematous, livedoid and purplish patches and papules on fingers or toes, evolving towards erosions, pigmentation and scaling (Fig. 1, Table 1). In eight patients, lesions began with a burning pain, which shifted towards pruritus in five patients. Lesions started 26.5 days prior to consultation (14–52) and healed within 35 days (27–45) without sequelae in seven patients. Five patients experienced short-duration viral symptoms without fever, anosmia nor ageusia. None of them had contact with a confirmed COVID infected person. Biopsies showed (Fig. 1) inconstant epidermal lesions (apoptotic keratinocytes, epidermal necrosis, basal layer vacuolation, mild spongiosis and parakeratosis), an upper dermis oedema, and a perivascular and periadnexal lymphohistiocytic infiltrate. Vascular lesions were prominent with angiocentrism, angiotropism and endothelium swelling, capillar ectasia and fibrinoid thrombi. All blood sample examinations were normal except for three patients who had positive antinuclear antibodies with anti-nucleolar or anti-centromere patterns. SARS-CoV-2 research on nasopharyngeal swabs and on skin biopsies was negative, and no SARS-CoV-2-specific IgG was detected in any case.

We present a series of 10 consecutive patients with typical clinical and pathological chilblains occurring during the peak of COVID-19 infection. In our area, the weather was warm at that time and all patients lived under lockdown in well-heated houses. In all patients, we failed to demonstrate neither a current nor recent COVID-19 infection nor SARS-CoV-2 presence in skin. The absence of respiratory symptoms and the known rapid clearance of SARS-CoV-2 in moderate infections could explain the negativity of RT-PCR analysis. The absence of specific IgG suggests that a reaction due to COVID-19 is unlikely even though these patients could have only specific IgM. However, IgM peak between days 5 and 12 after infection[1] whereas IgG reach peak concentrations after day 20 and most patients were

