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Letter to the Editor

Cutaneous manifestations of COVID-19 in the Franche-Comté region of France: A monocentric study

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Cutaneous manifestations of SARS-CoV-2 infection were described early in the COVID-19 pandemic. In Franche-Comté, a region in Eastern France, dermatologists from the Association of Franche-Comté Dermatologists (ASFODER) collected data on clinical cutaneous manifestations of suspected or confirmed COVID-19 during the COVID-19 outbreak. The inclusion criteria were as follows: cutaneous manifestations associated with symptoms consistent with COVID-19, a swab positive for SARS-CoV-2 or contact with someone testing positive for COVID-19. A standardized questionnaire to collect demographic data, cutaneous manifestations, other symptoms of COVID-19 and exposure to SARS-CoV-2, was completed prospectively. Laboratory results were collected: SARS-CoV-2 polymerase chain reaction (PCR) testing of nasopharyngeal swab samples, blood tests (depending on cutaneous manifestations), and skin biopsy. SARS-CoV-2 serology testing was retrospectively proposed to all patients. Cases were collated from 1 April 2020 to 1 July 2020 either via face-to-face consultations or during telemedicine consultations.

Data were collected from 39 patients, both ambulatory and hospitalized. Mean age was 44 ± 26 years. Twenty-three patients (59%) had been in contact with a confirmed infected patient during the 14 days preceding the onset of COVID-19 symptoms. General symptoms consistent with COVID-19 were found in 30 patients (77%). Nine patients (23%) presented no clinical signs other than cutaneous manifestations. The average time from the initial general symptoms to the onset of cutaneous symptoms was 1 ± 17 days. PCR testing was performed in 22 patients (56%) and was positive in 12 of these (55%). Among these patients with confirmed COVID-19, cutaneous manifestations were as follows: 6 maculopapular rash (50%), 3 superficial or deep urticaria (25%), 2 vesicular eruptions (16%), 1 photo-distributed eruption, and 1 livedo. Serology tests were performed in 20 patients (51%) but were positive in only 8 cases (40%) (anti-SARS-CoV-2 IgG, attesting to a past infection). Blood tests performed for 11 patients (28%) showed elevated CRP ($n = 2$) and moderate liver dysfunction ($n = 1$). Data regarding cutaneous manifestations, SARS-CoV-2 serology and PCR testing are summarized in Table 1. The most frequent cutaneous manifestation described during the COVID-19 outbreak was pseudo-chilblain, reported in 19 patients (49%) with no previous history of chilblains. Mean age was 35 + - 24 years. Pseudo-chilblain was associated with general symptoms in 12 patients (63%) and remained isolated in 7 patients (37%). The average time from onset of general symptoms to cutaneous manifestations was 9 ± 9 days. Seven patients (37%) had other cutaneous manifestations associated with pseudo-chilblain, including vesicular rash ($n = 2$) and photo-distributed rash ($n = 2$). Most patients tested had negative SARS-CoV-2 PCR results (6 of 7; 86%). The patient with a positive PCR test presented pseudo-chilblain and photo-distributed rash. SARS-CoV-2 serology testing was positive in 2 of the 12 patients tested (17%). Five patients with pseudo-chilblain underwent additional blood tests (blood count, CRP, kidney and liver function, antinuclear antibodies, anti-ENA antibodies, anti-neutrophil-cytoplasmic antibodies, antiphospholipid antibodies, anti-cardiolipin antibodies, anti-B2-GP1 antibodies, blood clotting tests, protein electrophoresis, CH50, C3, C4) that were normal. Skin biopsy performed in 3 patients (16%) showed superficial and deep lymphocytic perivascular dermal infiltration consistent with chilblain in all cases. Neither thrombosis nor vasculitis were identified.

The other skin manifestations during the COVID-19 outbreak were non-specific viral rashes found in 24 patients (61%): 9 maculopapular rashes (23%), 6 vesicular rashes (15%), 5 photo-distributed rashes, and 4 cases of purpura of the fingers or toes (10%).

Maculopapular rash (23%) was the second most frequent cutaneous manifestation. It generally involved the trunk with sparing of the face. The mean patient age was 54 ± 16 years, which is higher than that of patients with pseudo-chilblain. The average time between general symptoms of COVID-19 and onset of maculopapular rash was longer than for pseudo-chilblain (20 ± 15 days). All patients had general symptoms suggesting SARS-CoV-2 infection. Most patients had positive SARS-CoV-2 PCR tests (6 of 9; 67%). A SARS-CoV-2 serology test was positive (IgG) in 2 of the 5 patients tested (56%) in whom initial PCR was also positive.

Vesicular rash (15%) was the third cutaneous manifestation and was seen predominantly on the extremities. Mean patient age was 44 ± 27 years. Most patients ($n = 5$, 83%) presented at least one non-dermatological symptom. The average time between the onset of COVID-19 symptoms and vesicular rash was longer than 3 weeks (22 ± 26 days). One patient had pseudo-chilblain associated with a vesicular eruption. SARS-CoV-2 PCR testing was performed in 3 cases and was positive for 2 patients. SARS-CoV2 serology testing was also carried out in 3 patients and was positive in one patient.

Five patients (13%) presented with a photo-distributed rash. No new drug intake or cutaneous application of topical products was reported. Photo tests were not performed.

The results of our study in Franche-Comté match preliminary data gathered in Europe, notably in Spain and Italy [1,2]. Pseudo-chilblain manifestations were predominant and occurred in young patients having no pre-existing peripheral vascular disease and no previous exposure to cold. In these patients, COVID-19 disease was mild to moderate. Seven patients had no manifestations other

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Table 1
Skin manifestations, SARS-Cov2 PCR and serology.

Sex	Age (years)	Skin manifestations	SARS-CoV-2 PCR test	SARS-CoV-2 serology test
F	20	Pseudo-chilblain	NR	NR
M	18	Pseudo-chilblain	NR	+
F	31	Pseudo-chilblain	-	+
M	58	Pseudo-chilblain	NR	-
M	17	Pseudo-chilblain	NR	NR
M	23	Pseudo-chilblain	NR	NR
F	17	Pseudo-chilblain	-	-
M	95	Pseudo-chilblain	-	NR
M	15	Pseudo-chilblain	NR	-
F	48	Pseudo-chilblain	NR	-
F	30	Pseudo-chilblain	NR	NR
M	17	Pseudo-chilblain, purpuric rash, livedo	NR	-
M	15	Pseudo-chilblain, livedo	-	NR
F	47	Pseudo-chilblain, maculopapular rash	-	-
F	64	Pseudo-chilblain, maculopapular rash	+	+
M	18	Pseudo-chilblain, vesicular rash	-	-
F	59	Pseudo-chilblain, vesicular rash, cracks	NR	NR
F	43	Pseudo-chilblain, photodistributed rash	NR	-
F	34	Pseudo-chilblain, photodistributed rash	-	-
F	34	Maculopapular rash	NR	
M	41	Maculopapular rash	+	NR
F	68	Maculopapular rash	+	+
M	60	Maculopapular rash	+	NR
M	70	Maculopapular rash	+	NR
F	41	Maculopapular rash	NR	-
M	81	Maculopapular rash	+	NR
F	43	Vesicular rash	-	-
F	33	Vesicular rash	NR	-
M	51	Photodistributed and vesicular rash	+	+
M	72	Vesicular rash	+	NR
M	3	Photodistributed rash	NR	NR
M	3	Photodistributed rash	NR	NR
F	49	Purpuric rash	-	+
M	39	Purpuric rash	-	NR
F	83	Purpuric rash	+	NR
M	54	Superficial urticaria	+	NR
M	34	Deep urticaria	+	+
F	76	Superficial and deep urticaria	+	+
M	36	Cracks	NR	NR

NR: not reported; M: male; F: female; PCR: polymerase chain reaction test.

than pseudo-chilblain. Blood tests were reassuring; no vasculitis was seen on skin biopsies. SARS-CoV2 swabs were negative in all cases except for one case associated with a photo-distributed rash. These manifestations of late onset (+9 days) and having a very favorable prognosis are most probably indicative of virus-induced endotheliitis. This observation correlates with a recent French survey study in which most patients presenting chilblains during the COVID-19 outbreak were negative for SARS-CoV-2 assessed by PCR and serology testing [3]. Even if no evidence of SARS-CoV-2 infection was proven for most patients with acral lesions during the COVID-19 outbreak, the idea of late manifestation of SARS-CoV-2 remains plausible. Indeed, diagnostic tests for SARS-CoV-2 displayed varying sensitivity according to the time of infection, possibly accounting the high rate of negative tests. Indeed, isolation of these patients should not be recommended but a retrospective search of contact cases could be considered, according to the different situations.

Non-specific rashes such as maculopapular, vesicular, photodistributed and urticarial rashes appear later than pseudo-chilblain and in older patients (> 40 years). They are always accompanied by general symptoms and constitute a differential diagnosis.

Finally, maculopapular rashes appear to be restricted to contagious patients, prompting the use of personal protective equipment and isolation.

To conclude, the skin manifestations described during the COVID-19 outbreak are heterogenous. Further investigations are needed to better understand the mechanisms underlying the skin manifestations of COVID-19.

Disclosure of interest

The authors declare that they have no competing interest.

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