

Most chilblains observed during the COVID-19 outbreak occur in patients who are negative for COVID-19 on polymerase chain reaction and serology testing*

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Summary

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Background Acral lesions, mainly chilblains, are the most frequently reported cutaneous lesions associated with COVID-19. In more than 80% of patients tested, nasopharyngeal swabs were negative on reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 when performed, and serology was generally not performed.

Methods A national survey was launched on 30 March 2020 by the French Society of Dermatology asking physicians to report cases of skin manifestations in patients with suspected or confirmed COVID-19 by using a standardized questionnaire. We report the results for acral manifestations.

Results We collected 311 cases of acral manifestations [58.5% women, median age 25.7 years (range 18–39)]. The most frequent clinical presentation (65%) was typical chilblains. In total, 93 cases (30%) showed clinical suspicion of COVID-19, 67 (22%) had only less specific infectious symptoms and 151 (49%) had no clinical signs preceding or during the course of acral lesions. Histology of skin biopsies was consistent with chilblains. Overall, 12 patients showed significant immunological abnormalities. Of the 150 (48%) patients who were tested, 10 patients were positive. Seven of 121 (6%) RT-PCR-tested patients were positive for SARS-CoV-2, and five of 75 (7%) serology-tested patients had IgG anti-SARS-CoV-2. Tested/untested patients or those with/without confirmed COVID-19 did not differ in age, sex, history or acral lesion clinical characteristics.

Conclusions The results of this survey do not rule out that SARS-CoV-2 could be directly responsible for some cases of chilblains, but we found no evidence of

SARS-CoV-2 infection in the large majority of patients with acral lesions during the COVID-19 lockdown period in France.

What is already known about this topic?

- About 1000 cases of acral lesions, mainly chilblains, were reported during the COVID-19 outbreak.
- Chilblains were reported to occur in young people within 2 weeks of infectious signs, which were mild when present.
- Most cases did not have COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR), and few serology results were available.

What does this study add?

- Among 311 patients with acral lesions, mainly chilblains, during the COVID-19 lockdown period in France, the majority of patients tested had no evidence of SARS-CoV-2 infection.
- Overall, 70 of 75 patients were seronegative for SARS-CoV-2 serology and 114 of 121 patients were negative for SARS-CoV-2 RT-PCR.

Coronavirus disease 2019 (COVID-19) is a disease resulting from SARS-CoV-2 infection, which was first reported in Wuhan, China and has subsequently spread to the rest of the world.^{1,2} The World Health Organization (WHO) declared a pandemic viral infection on 11 March 2020.

The first cutaneous manifestations were described in mid-March 2020; since then, more than 50 studies reporting more than 1000 cases have been published, mainly from European countries. Cutaneous manifestations possibly associated with COVID-19 are diverse and include different types of exanthema (maculopapular, urticarial and chickenpox-like lesions).^{3,4} Acral lesions, mainly chilblains, are the most frequently reported cutaneous manifestation.^{3,5} The direct causal link between these skin manifestations and SARS-CoV-2 infection is suspected but remains uncertain.

Acral lesions are mainly observed in adolescents and young adults and are clinically described as pseudochilblains, sometimes with bullous lesions or pseudoerythema multiforme, which are two patterns that can overlap. Lesions resolved spontaneously in 1–4 weeks.^{3,6}

Owing to the high number of reported cases, media sources alerted that chilblains are a sign of COVID-19 and that the appearance of such cutaneous manifestations should lead to measures of isolation and COVID-19 testing.

The aim of our study was to describe the clinical characteristics of acral lesions at the time of the COVID-19 outbreak in order to provide evidence of an association or lack of association between SARS-CoV-2 infection and acral manifestations.

Patients and methods

A national survey was launched on 30 March 2020 by the French Society of Dermatology, which asked physicians to

report cases of skin manifestations in patients with clinically suspected COVID-19 or COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR) and/or serology. Here, we report the survey results for acral manifestations, which closed on 4 May 2020. The number of confirmed cases of COVID-19 registered in France increased from 39 642 to 131 863 from 30 March 2020 to 4 May 2020. Lockdown in France lasted from 17 March 2020 to 11 May 2020. The survey is ongoing for other cutaneous manifestations.

A standardized questionnaire was sent to society members on the mailing list and was accessible on the society website (www.sfdermato.org). In addition to completing the questionnaire, recipients were asked to send pictures, results of biological tests including nasopharyngeal swabs for RT-PCR detection of SARS-CoV-2, serology for SARS-CoV-2 IgG detection, and histology of skin biopsies if available.

The following case data were collected using the questionnaire: month and year of birth; sex; previous cutaneous manifestation; known connective tissue disease; previous Raynaud syndrome; chilblains; any other diseases and current treatment; date of first general symptoms; presence or absence of fever, cough, dyspnoea, asthænia, nausea/vomiting, diarrhoea, headache, anosmia/ageusia or pneumonia; date of first cutaneous manifestations; clinical characteristics; date of resolution of general symptoms; date of resolution of cutaneous manifestation; date and results of SARS-CoV-2 RT-PCR testing and serology; date of hospitalization; date of intensive care unit (ICU) hospitalization; cutaneous manifestation treatment; histology and biological examinations.

According to the WHO definition (modified on 29 May 2020) we classified the patients as having no general symptoms; possible case (if the patient had at least one of the following symptoms: fever, cough, dyspnoea, anosmia, ageusia

or dysgeusia) (<https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition>); or patients with less specific symptoms (if the patient had asthaenia, nausea/vomiting, diarrhoea, headache and none of the aforementioned symptoms). The flow of patients in the study is outlined in Figure 1.

Photographs were reviewed consensually by three experienced dermatologists (M.B.-B., L.L.C., H.A.) in order to classify clinical characteristics. We defined typical chilblains as single or multiple lesions, maculopapular, oedematous and erythematous to violaceous (Figure 2).

We classified other lesions into the following three categories:

- Erythema multiforme (EM)-like, characterized by round maculopapular lesions including target lesions (Figure 3).
- Punctiform purpuric lesions (Figure 4).
- Diffuse vascular erythema and oedema of dorsum or sole of foot and/or palms (Figure 5).

Patients (or legal representative for minors) indicated their nonopposition to participation in the survey. A signed authorization for use of photographs was also requested. Information was sent with anonymization. The study was authorized by the Henri Mondor Hospital ethics committee (Créteil, France) and declared to the Commission Nationale de l'Informatique et des Libertés (no. 2217623).

For serology, serum samples were processed for 60 patients on an Abbott Architect instrument using the Abbott SARS-CoV-2 IgG assay following the manufacturer's instructions. The assay is a chemiluminescent microparticle immunoassay for qualitative detection of IgG against the SARS-CoV-2 nucleoprotein in human serum. Qualitative results and index values

reported by the instrument, associated with a 99.9% specificity and 100% sensitivity, were used in the analysis.⁷ For the 10 other patients, the kit used for serology testing was not specified.

Statistical analyses

Continuous data are described using mean ± SD or median [interquartile range (IQR)] depending on whether there was a normal distribution. Categorical data are described as n (%). Our main analysis was descriptive, assessing characteristics of patients with acral manifestations. The characteristics of patients with/without testing and positive/negative on testing were compared using the χ^2 -test or Fisher's exact test for categorical data and the Mann-Whitney U-test for continuous variables. All tests were two-tailed, and the threshold for statistical significance was set to $P < 0.05$. All statistical analyses were performed using Stata version 14.1 (StataCorp LP, College Station, TX, USA).

Results

Population characteristics

We collected 481 cases of cutaneous manifestations including 311 cases of acral manifestations between 30 March 2020 and 4 May 2020 (Figure 1). Most patients were female ($n = 182$, 58.5%) and the median age was 25.7 years (IQR 18–38.3). A total of 150 patients underwent nasopharyngeal-swab RT-PCR and/or serology for SARS-CoV-2 (69 patients had RT-PCR and serology, 58 patients had RT-PCR only and 23 patients had

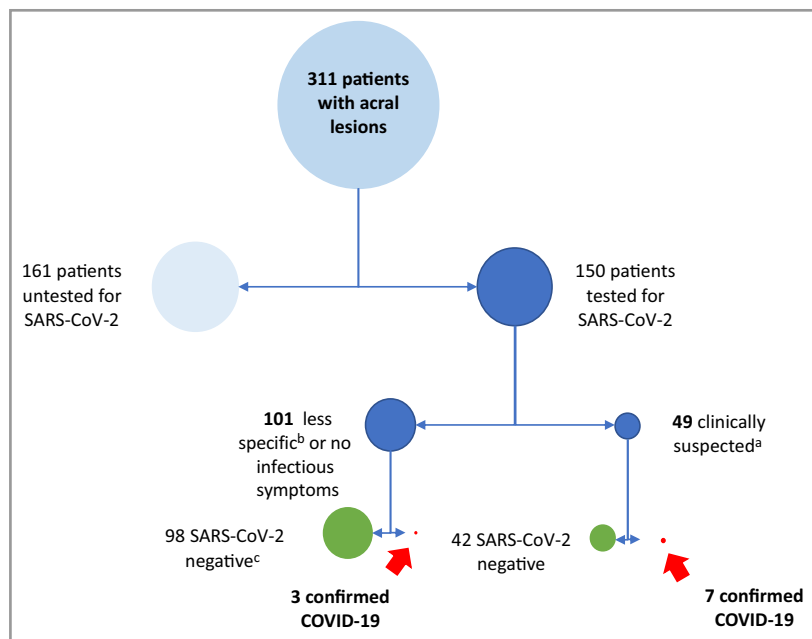


Figure 1 Flow of patients in the study. The size of each circle is proportional to the number of patients. ^aFever and/or cough and/or dyspnoea and/or anosmia/ageusia. ^bAsthaenia, nausea/vomiting, diarrhoea, headache. ^cReverse transcription polymerase chain reaction and/or serology.



Figure 2 Typical chilblains. (a, b) Typical lesions observed in a majority of patients. (c) Typical chilblains with bullae. (d) More severe lesions with purpuric aspect. (e) Chilblains on the toes and lateral side of feet.

serology only). Six (2%) patients had a history of autoimmune disease, 32 (10%) patients had a history of chilblains and 31 (10%) patients had a history of Raynaud syndrome; six of these patients had both Raynaud syndrome and chilblains.

Overall, 93 (30%) patients had fever and/or cough and/or dyspnoea and/or anosmia/ageusia and were classified as suspected COVID-19; three patients had pneumonia, none was admitted to an ICU and none died. A total of 67 (22%) patients had only less specific infectious symptoms (nausea, vomiting and/or diarrhoea and/or odynophagia and/or asthenia and/or myalgia and/or headache) and 151 (49%) patients had no clinical signs preceding or during the course of acral lesions. In most cases, no specific treatment was applied, and topical corticosteroids were prescribed for 54 (17%) patients.

Clinical and histological characteristics

Clinical presentation was classified into four categories after photographic review. Classification was feasible for 245 (79%) patients, for whom photographs were available. The most frequent clinical presentation was typical chilblains (202 of 245, 82%) located mainly on the dorsum of the toes (Figure 2a–e); 22 cases had a severe form with bullae (Figure 2c). Other forms were EM-like lesions, mainly on the lateral part of the feet (Figure 3), in 15 (6%) patients; punctiform purpuric lesions on the dorsum and/or pulps in 11 (4.5%) patients (Figure 4) and diffuse vascular erythema and oedema of the dorsum or soles of the feet and/or palms in 17 (7%) patients (Figure 5).

Acral lesions were localized on the feet in 236 (76%) cases, on the hands in 36 of 311 (12%) cases and on both in 37



Figure 3 Erythema multiforme-like lesion on the hands.



Figure 4 Punctiform purpuric lesions on the toes and feet.

(12%) cases. The median time between infectious symptoms and the appearance of acral lesions was 10.5 days (IQR 1–16) (data available for 148 patients with infectious symptoms) and acral lesions preceded infectious symptoms in 23 cases.

Skin biopsies were obtained for 29 patients (17 patients typical chilblains, two with EM-like lesions, one with punctiform purpuric lesions, nine without photographs). All but three cases (superficial biopsy or unspecific findings) exhibited vacuolization or apoptosis of keratinocytes, superficial and deep infiltrates, mainly of lymphocytes with a perieccrine and



Figure 5 Diffuse vascular erythema and oedema of dorsum of feet.

perivascular reinforcement in most cases and, in some cases, superficial capillary thrombosis and different degrees of dermal oedema.

Testing for SARS-CoV-2

Among the 311 included patients, 150 had RT-PCR testing or serology for SARS-CoV-2. Seven of 121 patients tested using RT-PCR were positive and five of 75 serology-tested patients were positive (IgG). Of the 69 patients who underwent RT-PCR and serology, results were concordant for 58 patients (56 negatives for both, two positives for both), discordant for two (negative PCR and positive serology) and for nine patients only RT-PCR results (negative) were available (serologies were taken but not processed).

Thus, 10 of 150 (7%) tested patients had confirmed COVID-19 (Figure 1). Serology was performed 21 days (median) (IQR 12–30) after the beginning of infectious symptoms ($n = 45$ patients with symptoms). Results for the following tests were normal or negative in all investigated cases: C-reactive protein level ($n = 20$), activated partial thromboplastin time ($n = 61$), complement ($n = 14$), cold agglutinins ($n = 34$), cryofibrinogen ($n = 30$), coxsackie and parvovirus ($n = 57$). Blood cell count was normal in 57 of 66 patients, with no significant abnormalities.

Overall, 12 patients exhibited significant immunological abnormalities. Detailed characteristics are presented in Table S1 (see Supporting Information).

Comparison between tested and untested patients

Tested and untested patients did not differ in age, sex, history or acral lesion clinical characteristics, nor did they differ in rate of clinically suspected COVID-19 with only nonspecific

Table 1 Comparison between patients with and without RT-PCR testing or serology for SARS-Cov-2

Characteristics	Total population	With PCR testing or serology	Without PCR testing or serology	P-values ^a
Total	311 (100)	150 (48)	161 (52)	
Sex (female)	182 (59)	85 (57)	97 (60)	0.6
Age, years, median (IQR)	25.7 (18–39)	27 (20–38)	24.5 (17–39)	0.1
History				
Connective tissue diseases	6 (2)	2 (1)	4 (2)	0.7
Chilblains	32 (10)	21 (14)	11 (7)	0.06
Raynaud syndrome	31 (10)	15 (10)	16 (10)	1
Extracutaneous clinical manifestations				
Fever	42 (13.5)	21 (14)	21 (13)	0.9
Cough	54 (17)	30 (20)	26 (16)	0.4
Dyspnoea	33 (11)	21 (14)	12 (7)	0.07
Asthma	91 (29)	46 (31)	45 (28)	0.6
Myalgia	31 (10)	18 (12)	13 (8)	0.3
Headache	78 (25)	48 (32)	30 (19)	0.009
Odynophagia	34 (11)	21 (14)	13 (8)	0.1
Anosmia/ageusia	17 (5)	13 (9)	4 (2)	0.02
Fever and/or cough and/or dyspnoea and/or anosmia/ageusia	93 (30)	49 (33)	44 (27.5)	
Asthma and/or myalgia and/or headache and/or odynophagia	67 (22)	28 (19)	39 (24)	0.4
None	151 (49)	73 (49)	78 (48)	
Acral lesion characteristics				
Typical chilblains	201/245 (82)	100/124 (81)	101/121 (83)	0.6

RT-PCR, reverse transcription polymerase chain reaction; IQR, interquartile range. ^aP-values from χ^2 -test or Fisher's exact test for categorical variables or Mann–Whitney U-test for continuous variables. Data are presented as n (%) unless otherwise indicated.

symptoms and no symptoms (Table 1). We observed that headache was significantly more frequent in tested patients compared with untested patients [32% (48 of 150) vs. 19% (30 of 161), $P < 0.009$].

Comparison between patients with positive reverse transcription polymerase chain reaction and/or serology results and patients with negative tests

Patients with/without confirmed COVID-19 did not differ in age, sex, history or acral lesion clinical characteristics (Table 2). Headache and anosmia/ageusia were significantly more frequent in confirmed cases [70% (seven of 10) and 50% (five of 10), respectively] than in unconfirmed cases [29% (41 of 140) and 8% (six of 140), respectively] ($P < 0.013$ and 0.001).

Discussion

We report 311 cases of acral lesions, mainly chilblains, occurring during the COVID-19 outbreak in France. Among the 150 patients who underwent RT-PCR testing and/or serology, only 10 had confirmed COVID-19. Among 75 patients with serology, five (7%) were positive.

The characteristics of our population are comparable with those of the 995 patients with acral lesions reported during the COVID-19 outbreak in 14 previously published series or

studies (reporting more than 10 patients) (Table S2; see Supporting Information). These series came from four countries (Italy, Spain, France and USA). It is possible that some cases were reported in more than one series. With regard to the 311 patients in our population, to our knowledge, the histological characteristics of 17 cases had already been reported.⁸ As in our study, in which the median age was 25.7 years (IQR 18–38.3), most patients who were reported in these previous studies were children or young adults (the mean age was 10–20 years in 10 series, 32.5 years in one study and the median age varied from 14 years to 27 years in three studies). The rate of patients who had no general symptoms preceding or concomitant with skin lesions was 30% (207 of 678) based on 10 previously published series (data were missing for four other series), compared with 49% (151 of 311) in our study. When present, symptoms were mild. Skin lesions were generally described as chilblains or pseudo-chilblains and more rarely as EM-like lesions. Overall, 300 patients had laboratory confirmation by RT-PCR using a nasopharyngeal swab, which was positive in 54 (18%) patients based on 13 series. In one study³ the proportion was higher [41% (29 of 71)] than in the 12 others [11% (25 of 229)], which varied from 0% to 21%. By comparison, in our study the proportion of positive RT-PCR results in patients who were tested was 6% (seven of 121). Serology was rarely performed and was positive for IgG in seven of 39 cases and positive for IgA in six of 19 cases in the previously published

Table 2 Comparisons between patients positive on RT-PCR and/or serology and negative on RT-PCR and/or serology for SARS-Cov-2 infection

Characteristics	Positive RT-PCR and/or serology (n = 150 tested)	Negative RT-PCR and/or serology (n = 150 tested)	P-values ^a
Total	10 (7)	140 (93)	
Sex (female)	7 (78)	78 (56)	0.3
Age, years, median (IQR)	34 (26–38)	27 (20–39)	0.3
History			
Connective tissue diseases	0	2 (1)	1
Chilblains	1 (10)	20 (14)	1
Raynaud syndrome	2 (20)	13 (9)	0.3
Extracutaneous clinical manifestations			
Fever	2 (20)	19 (14)	0.6
Cough	2 (20)	28 (20)	1
Dyspnoea	3 (30)	18 (13)	0.1
Asthaenia	5 (50)	41 (29)	0.2
Myalgia	3 (30)	15 (11)	0.1
Headache	7 (70)	41 (29)	0.013
Odynophagia	3 (30)	18 (13)	0.15
Anosmia/ageusia	5 (50)	8 (6)	0.001
Fever and/or cough and/or dyspnoea and/or anosmia/ageusia	7 (70)	42 (30)	
Asthaenia and/or myalgia and/or headache and/or odynophagia	0	28 (20)	
None	3 (30)	70 (50)	0.048
Acral lesion characteristics			
Typical chilblains	5/8 (63)	95/116 (81)	0.2

RT-PCR, reverse transcription polymerase chain reaction; IQR, interquartile range. ^aP-values from χ^2 -test or Fisher's exact test for categorical variables or Mann-Whitney U-test for continuous variables. Data are presented as n (%) unless otherwise indicated.

series, compared with five of 75 (7%) cases positive for IgG in our study.^{3,5,9–20}

Serology was not available at the time of publication of these previous series. Also, RT-PCR negativity was to be expected because chilblains were considered a late manifestation of the infection, occurring 1–5 weeks after signs of infection, with the disappearance of detectable virus after a brief or paucisymptomatic infection in young healthy individuals, possibly owing to an immunological response targeting the cutaneous vessels. Indeed, firstly, the sensitivity of RT-PCR varied from 71% to 98% based on negative RT-PCR tests that were positive on repeat testing. Secondly, the median time from the onset of symptoms to negative SARS-CoV-2 RT-PCR test result in hospitalized patients was 20 days.^{21,22}

Thus, it is possible that in these studies negative RT-PCR test results in some patients could be false-negatives. By contrast, in our study, the absence of SARS-CoV-2 IgG antibodies in 65 of 70 patients tested using a highly sensitive and specific test, 21 days (median) (IQR 12–30) after the onset of symptoms, is strong evidence against a direct causal link between COVID-19 and chilblains. Indeed, performance assessment of the Abbott Architect serology instrument (used in 60 of 75 patients in our study) has found that all patients with positive SARS-CoV-2 RT-PCR had positive serology 17 days after the beginning of symptoms. In a series reporting 19 cases of chilblains in adolescents, serology was negative for IgG using the same kit used in our study (Abbott) and were positive for IgG

in one patient, positive for IgA in six patients and were borderline for three patients using another kit (Euroimmun, Lübeck, Germany).¹⁹ The authors suggested that in asymptomatic children or those who had mild infection, the humoral response could be IgA rather than IgG. However, as the Euroimmun kit is known to provide false-positive results, these results should be interpreted with caution.^{22,23,24}

Four studies reported frequency of cutaneous manifestations in patients with confirmed SARS-Cov-2 infection in 0.2% (N = 1099 patients), 4.9% (N = 103), 20% (N = 88), 10% (N = 125).^{2,18,25,26} Among these patients, only one had chilblains. However, the mean age of these patients was higher.

The lack of difference in sex, age, history of connective tissue disease, and acral lesion characteristics between patients with/without confirmed COVID-19 could also provide evidence against the role of viral infection in chilblains.

Our study has some limitations, mainly that all patients did not undergo the same investigation. However, the characteristics of untested patients did not differ significantly from those of tested patients. We hypothesized that these results could reasonably be extrapolated to the whole population. Photographs were not available for 66 of 311 patients, who could not be classified more precisely other than having chilblains. The strengths of this survey are the large number of included patients and that almost half of the population had a test to confirm COVID-19, including serology for 75 patients. Our study had a different methodology from the study of Galván

Casas *et al.*,³ in which 41% of patients with acral lesions had a positive RT-PCR test and in which criteria for inclusion required a specific clinical sign or RT-PCR confirmation.

The characteristics of our population were similar to those previously reported in patients with chilblains, namely female predominance and adolescents or young adults, with immunological abnormalities found in few patients.^{27,28} Histological findings, when available (deep infiltrates, mainly of lymphocytes with a perieccrine reinforcement associated with dermal oedema and necrotic keratinocytes), were consistent with the classical description of the histological features of chilblains.²⁹

These benign acral chilblain-type lesions occurring in outpatients without severe manifestations of COVID-19 must be distinguished from the acral ischaemic lesions described in seven severely ill patients with COVID-19.³⁰ These severe acrochaemia cases were associated with elevated D-dimer level and fibrinogen degradation products and prolonged prothrombin time with disseminated intravascular coagulation. These thrombotic complications associated with COVID-19 resemble other systemic coagulopathies during severe infections.³¹ When investigated, none of our patients had anomalies of haemostatic markers. Similarly, chilblain-type lesions were not associated with antiphospholipid antibodies, which may be transiently observed in patients with critical infectious diseases.

If chilblains are not directly related to COVID-19, how can we explain the numerous reported cases? Most reported cases occurred between March and April 2020 in Southern Europe. The incidence of chilblains is not known, so affirming an increase is difficult. However, many dermatologists confirmed that this chief complaint was more frequent than in previous years. This situation could be due to the media stating that chilblains were caused by SARS-CoV-2 infection, leading to a higher rate of consultation for benign cutaneous manifestations, or the lockdown leading to increased inactivity and long periods at home barefoot on a cold floor. For March and April, the mean temperature in France was 9 °C (range -5.8–25.2) and 13.7 °C (-6.3–27.1), respectively (<http://www.terre-net.fr>).

The results of this survey did not rule out that SARS-CoV-2 infection could be directly responsible for some cases of chilblains, but we found no evidence of SARS-CoV-2 infection in the large majority of patients with acral lesions during the COVID-19 lockdown period in France. From our results, this usually benign cutaneous manifestation resolved spontaneously in a few weeks and has neither diagnostic nor prognostic value for COVID-19.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1 Characteristics of the 12 patients with immunological abnormalities.

Table S2 Summary of 14 series (> 10 cases) reporting acral lesions during COVID-19 outbreak published on 6 June 2020.

Powerpoint S1 Journal Club Slide Set.