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UNIVERSITE DE MONTPELLIER
FACULTE DE MEDECINE MONTPELLIER-NIMES

THESE

Pour obtenir le titre de
DOCTEUR EN MEDECINE

Présentée et soutenue publiquement
Par
Léo-Paul SECCO

le 14 septembre 2020

TITRE

Lésions cutanées vasculaires acrales au cours de la pandémie Covid-19 :
caractéristiques cliniques, anatomopathologiques, immunologiques et
virologiques

Directeur de thèse : Professeur Didier Bessis

JURY

Président :

Professeur Thierry Vincent

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Introduction

Les acrosyndromes vasculaires constituent un groupe d'anomalies vasculaires des extrémités, la plupart du temps les mains ou les pieds. Ces anomalies, permanentes ou transitoires, peuvent être déclenchées par plusieurs facteurs comme le froid.

Les engelures constituent un acrosyndrome vasculaire fréquent chez les sujets jeunes, observées pendant les mois froids et humides où la température moyenne journalière n'excède pas douze degrés. Elles se présentent typiquement par des papules oedémateuses, prurigineuses et peu douloureuses, érythémateuses et cyaniques de la face latérale des doigts et des orteils. Ces lésions persistent au moins une journée et guérissent spontanément en quelques semaines, mais tendent à récidiver les années ultérieures. Un autre acrosyndrome est souvent associé aux engelures. Bien que banales, le mécanisme des engelures est mal compris, d'où le nom d'engelure idiopathique. Les hypothèses physiopathologiques reposent sur l'existence d'un vasospasme anormal, une instabilité du tonus neurovasculaire et de la thermorégulation. Une hypoxie locale secondaire à ces phénomènes provoquerait une réaction inflammatoire secondaire. Parfois, les engelures sont liées à une maladie auto-immune sous-jacente, une néoplasie, ou une infection virale.

Le SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2) isolé pour la première fois en Chine en 2019, typiquement responsable de pneumopathies sévères, s'est progressivement diffusé à l'échelle mondiale, donnant lieu à la pandémie de Covid-19 (Coronavirus disease-19). Plusieurs organes peuvent également être lésés par le biais notamment d'une atteinte vasculaire.

Une grande variété de manifestations cutanées a été décrite dans la littérature au cours de cette pandémie : éruption varioliforme, urticaire diffuse, livédos, éruptions cutanées non spécifiques, et des lésions de pseudo-engelures.

Ces lésions de pseudo-engelures ont été rapportées par des cliniciens de pays différents à partir du début du mois d'avril 2020. L'hypothèse d'un lien entre ce type de manifestation cutanée et l'infection à SARS-CoV-2 a été émise sur plusieurs arguments : caractéristiques cliniques différentes des engelures idiopathiques, absence d'exposition au froid du fait de mesures sanitaires restreignant les déplacements en extérieur de populations et de leur survenue à une période de l'année inhabituelle,

symptômes infectieux suggérant une infection à SARS-CoV-2 dans les jours ou semaines précédant les symptômes cutanés.

Par ailleurs, les interféronopathies de type I récemment individualisées comme le lupus-engelures familial ou le SAVI (STING-associated vasculopathy with onset on infancy) sont caractérisées par une production excessive d'interféron de type I, secondaire à une mutation d'un gène codant pour une protéine impliquée dans cette voie de signalisation. Cette production anormale d'interféron peut être détectée par la mesure du score interféron. Ce groupe de maladies présente des caractéristiques sémiologiques analogues à celles des lésions à type d'engelures rapportées pendant la pandémie de Covid-19. Notamment, le SAVI associe des lésions cutanées acrales et pulmonaires, avec des stigmates biologiques d'auto-immunité.

Or, l'on sait que l'un des mécanismes de l'immunité antivirale repose sur la voie de l'interféron de type I, dont la sécrétion est augmentée en cas d'infection virale.

L'hypothèse de cet exposé est que les lésions cutanées à type d'engelure rapportées dans la littérature au cours de la pandémie à Covid-19 sont des lésions singulières et originales, qui présentent des similitudes cliniques avec les interféronopathies de type I car elles sont en lien avec une infection à SARS-CoV-2, qui induit une activation de la voie de l'interféron. Les caractéristiques cliniques, histologiques, immunologiques et virologiques de trente patients ont été étudiées prospectivement afin d'étayer cette hypothèse.

Prolegomena

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is part of the family-coronavirus, mainly reported with single-strand RNA (Ribonucleic Acid), nucleocapsid protein (N), envelop protein (E), membrane protein (M), spike (S) glycoprotein¹. S protein forms the crown-like structure on the outer surface of the virus, and attaches to the human angiotensin converting enzyme-2 (hACE2) receptor with high affinity. The hACE2 receptor is expressed by many epithelial cells, particularly type-2 pneumocytes, by which SARS-CoV-2 enters into the host cell^{2,3,4}. Uncoating and release of genomic RNA in the cytoplasm of host cell is followed by replication, transcription, assembling processes. Virions are finally released either by fusing with the plasma membrane or by the mechanism of exocytosis.

Pathogenesis behind SARS-CoV-2 is not fully understood, but several studies accordingly find the virus can: (i) downregulate ACE2 receptors expression and increase production of angiotensin-2 (AT2) in the lung, leading to pulmonary vascular permeability and lung injury⁵; (ii) escape to antiviral response by limiting type I and type III interferon (IFN-I and IFN-III) pathways^{6,7}; (iii) elicit a strong chemotactic and inflammatory response called “cytokine storm syndrome”⁸, and activate complement pathway, both promoting coagulopathy⁹. Taken together, these features can lead in some genetically predisposed individuals with comorbidities such as diabetes, liver failure, kidney failure, to acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation, and multiorgan failure, with subsequent morbidity and mortality¹⁰.

Clinical symptoms of SARS-CoV-2 infection onset are about a week after contamination, but differ from age and immune system of the person¹¹. Among these symptoms, the most common are fever, cough, fatigue, sputum. Sometimes, patients describe headache, muscle weakness, breathlessness, sore throat, anosmia, ageusia. Many other organs may be involved, secondary to cytokine storm syndrome. On the other hand, many people who develop SARS-CoV-2 infection remain asymptomatic.

Diagnosis at the beginning of the symptoms can be performed by nucleic acid amplification test through a nasal swab using a real-time fluorescence polymerase chain reaction (RT-PCR)¹². However, if the viral load in the nasal swab is low, sensitivity decreases. Therefore, when high suspicion of SARS-CoV-2 infection despite negative RT-PCR performed on nasopharyngeal swab, computed-tomography (CT) imaging is

recommended in patients with moderate-to-severe clinical features¹³. Indeed, chest CT can show multiple ground-glass opacities in the lungs, early in coronavirus disease (Covid-19), since the first days of the respiratory symptoms¹⁴. Later, to assess previous symptoms were linked to Covid-19 if diagnostic testing were not performed or negative, many serological tests have been developed, and some validated by sanitary authorities¹⁵. They have high sensitivity (96%) and specificity (98%) when performed 21 to 35 days after the onset of infectious symptoms suggesting Covid-19, but there were no studies exclusively in asymptomatic patients¹⁶.

Treatment of SARS-CoV-2 infection remains challenging¹⁷. On one hand, pathophysiology remains unclear, and each individual develop a specific clinical course, depending on the immune system of the individual and the timing of immune response against the virus. On the other hand, no specific medical therapy or vaccine is available. Some treatments yet available have been studied (remdesivir, chloroquine, hydroxychloroquine, protease inhibitors) with disparate results, depending on the timing of the drug administration and the severities of the cases of Covid-19.

Regarding on the lack of efficacy treatment and the very high transmission between humans, preventive measures against transmission of the SARS-CoV-2 in order to prevent his spreading have been proposed by the World Health Organization (WHO)¹⁸: social distancing, masks, regular cleaning of hands. Such measures were mandatory in many countries over the world, because health care systems were overwhelmed and subsequent Covid-19 pandemic a public health problem.

Background

During Covid-19 pandemic, many dermatological manifestations have been reported, but their link with the SARS-CoV-2 is unclear, because of the failing of demonstrating markers of SARS-CoV-2 infection. Some authors have proposed different classifications of the cutaneous signs, based on semiology. One of the most described is “chilblain-like lesions”, also called “pseudochilblains”¹⁸, or “Covid toes”¹⁹, with more than 1200 patients (Table 1).

Chilblain-like lesions concerned young people (mean age: 19 years-old), with few or no past medical history nor drug intake. Nine per cent reported history of chilblains and Raynaud’s phenomenon. Dermatological presentation was quite homogeneous, with erythematous macules and papules, sometimes purpuric or edematous. Lesions were located on the feet (82,3%), hands (17,7%), or both (12,6%). Associated symptoms were pruritus (38,6%), burning (61,9%), pain (63,7%). The mean duration of the skin symptoms was 18,3 days, and healed spontaneously without any treatment in the majority of the cases. 41% of the cases reported infectious symptoms suggesting SARS-CoV-2 infection. The mean time between the onset of infectious symptoms and the onset of the skin lesions was 8 days. A close contact with a person who had proven Covid-19 was reported in 8,7% of the cases. Majority of the patients were not admitted in hospital and mortality rate was low. Pathological examination on skin biopsy was done in 9,3%, showing superficial and deep lymphocytic infiltrate with purpura (79,6%), papillary edema (72,6%), and vascular abnormalities like endothelial cell swelling (77,1%) or thrombi (21,8%). Direct immunofluorescence on skin biopsy was performed in 47 cases and showed vascular C3 deposits in 22 cases. Virological testing noted positive RT-PCR for SARS-CoV-2 performed on nasopharyngeal swab in 3,6% of the cases, and positive serology in 6,3% of the cases. Abnormal blood testing results were: D-dimer elevation (5,2%), low fibrinogen concentration in 3 cases, positive antinuclear antibodies in 8 cases, and one case with weak level of anticardiolipin immunoglobulin (Ig) G antibody. No perturbation of classic complement pathway, liver enzymes, serum creatinine, lactate deshydrogenase was observed.

Some authors proposed that chilblain-like lesions during Covid-19 pandemic were secondary to a robust IFN-I response²⁰. Moreover, this hypothesis is supported by clinical similarities with type I interferonopathies, a group of Mendelian disorders characterized by an up-regulation of type I interferon²¹. Indeed, IFN-I is a crucial

pathway for antiviral immunity²². The physiological response to virus infection is generally initiated at the cellular level following replication. After the virus entry, the infected cells detect the presence of the virus replication through any one of a number of pattern recognition receptors (PRRs). PRRs sense aberrant RNA structures of the virus, and downstream interferon regulator factors (IRFs) and nuclear factor kB (NF-kB). These results in the launch of two general antiviral programs: (i) induction of type I and III interferon and subsequent upregulation of IFN-stimulated genes (ISGs); (ii) recruitment of leukocytes and chemokine secretion¹². Evaluation of these ISGs in the blood is possible with a validated ISG score, based on the mean expression of six ISGs defining type I interferon signature²³. The SARS-CoV-2 is sensitive to IFN, but develops several mechanisms to evade from IFN-I pathway, consistent with reduced ISGs expression, low plasma level of interferon alpha-2 (IFN-a2) in critical Covid-19 patients²⁴. Conversely, critical patients have high cytokine and chemokine-related genes expression, with the induction of a unique response to IFN-II⁶.

Diagnosis of SARS-CoV-2 infection may be challenging because of the lack of sensibility of RT-PCR and serological blood testing, despite clinical symptoms consistent with Covid-19. Therefore, searching for mucous antibodies may increase sensibility. Some patients with conventional RT-PCR performed on nasopharyngeal swab and blood serological testing, symptomatic or not, showed antibodies against SARS-CoV-2 in salivary, nasal fluid of tears^{25,26,27}.

Material and methods

Study design and patients

The study design is a monocentric, descriptive, prospective study of patients presenting vascular acral symptoms or lesions during the Covid-19 pandemic. A total of 30 patients were enrolled in this study. Patients were screened and recruited from April to July 2020 at the Department of Dermatology, in Montpellier Hospital Center, France. A dermatologist diagnosed vascular acral injury. Oral and written informed consent was given to each patient or their legal guardians for children. The Institutional Review Board and Center of Biological Resources of Montpellier University Hospital both approved this study.

Clinical evaluation

A standardized case-report form was created, collecting data on demographic characteristics of the patients, medical history including personal and familial autoimmune diseases, medications, infectious symptoms that may suggest a SARS-CoV-2 infection in the past weeks or months.

Clinical characteristics of cutaneous symptoms and lesions were dated and described using elementary lesions, topography, and subjective functional signs (pruritus, pain, burning).

Photographs of cutaneous lesions were taken for each patient at the end of the clinical evaluation, with written signed consent.

Study procedures

After clinical evaluation, patients included in the study underwent: (i) testing for SARS-CoV-2 on nasopharyngeal swab and saliva collection, (ii) skin biopsy in 26 patients, (iii) blood testing for hematological parameters, SARS-CoV-2 serology, and serum interferon level.

Pathological analyses

Two pathologists read hematoxylin-eosin-stained, Periodic Acid Schiff and Alcian Blue sections of formalin-fixed paraffin-embedded skin biopsies of 26 patients. Histopathological features assessed were: (i) epidermal changes (spongiosis, necrotic keratinocytes, basal vacuolar changes, thickening of the basement membrane,

parakeratosis), (ii) papillary edema, (iii) presence of lymphocytic infiltrate and its characteristics (density, lichenoid pattern, superficial or deep location in the dermis), (iv) existence of vessel alterations (fibrin deposition, vascular ectasia, thrombi, mural lymphocytes, thickening of the vessel wall, endothelial cell swelling), (v) extravasation of erythrocytes, (vi) mucin deposition pattern (dermal or around eccrine sweat glands). Direct immunofluorescence on frozen skin biopsies was performed in six patients using human anti-IgG, anti-IgM, anti-IgA, anti-C3c antibodies.

The study of the expression of plasmacytoid dendritic cells was carried out using the anti-CD123 antibody. This immunohistochemistry was performed on skin biopsies using Ventana BenchMark Ultra, with a 3,3'-diaminobenzidine chromogen.

An anti-SARS-Cov Nucleoprotein IgG rabbit antibody (Sino Biological) assessed immunostains for SARS-Cov-2, with a 1:1000 concentration on paraffin-embedded tissue. This immunohistochemistry was performed on skin biopsies using Ventana BenchMark Ultra, with a 3,3'-diaminobenzidine chromogen and OptiView Amplification Kit to increase the staining intensity.

Laboratory testing

Real-time reverse transcriptase polymerase chain reaction (RT-PCR) against SARS-CoV-2 was performed on nasopharyngeal swab in 23 patients, and on skin lesions in 2 patients, using a validated test by the National Reference Center of viruses of respiratory infections in France.

Several methods assessed blood testing for SARS-CoV-2 serology: (i) semi-quantitative indirect enzyme-linked immunosorbent assay (ELISA) targeting IgG antibodies directed against SARS-CoV-2 nucleocapsid (ID Screen, IDvet, Montpellier, France), (ii) semi-quantitative ELISA targeting IgA antibodies of SARS-CoV-2 (IDvet), (iii) chemiluminescent microparticle immunoassay (CMIA) intended for the quantitative detection of IgG antibodies directed against the nucleocapsid protein of SARS-CoV-2 (Abbott Laboratories, USA), (iii) enzyme immunoassay (EIA) intended for the qualitative detection of total antibodies (IgG/IgA/IgM) to SARS-CoV-2 in human serum (IMMY, USA), (iv) ELISA for the determination of IgA against SARS-CoV-2 using the S1 domain of the spike protein (Euroimmun, Germany).

Patients also underwent investigations to screen for autoimmune diseases or coagulopathy: blood cell count, C-reactive protein, serum creatinine, cryoglobulins, cryofibrinogen, cold agglutinins, antineutrophil cytoplasm antibodies (ANCA), antinuclear, anti-desoxyribonucleic acid (DNA), ribonucleic protein, myositis,

antiphospholipid, anticardiolipin antibodies, rheumatoid factor, serum protein electrophoresis, D-dimers, prothrombin time, fibrinogen, activated partial thromboplastin time.

Interferon signature

Interferon score assessment was performed by Immunology Laboratory in Hospices Civils de Lyon, France. RNA was extracted from whole blood contained in Paxgene tubes (Kit PreAnalytix, Qiagen, SW) and quantified by spectrophotometry assay (Nanodrop 2000, Thermo Scientific, MA, USA). RNA integrity was then evaluated by Agilent RNA microarray (Agilent Technologies, Santa Clara, CA, USA). mRNA quantification of 6 ISGs (interferon alpha inducible protein 27 (IFI27), interferon induced protein 44 like (IFI44L), Interferon Induced Protein With Tetratricopeptide Repeats 1 (IFIT1), ISG15 Ubiquitin Like Modifier (ISG15), Radical-S-Adenosyl Methionine Domain Containing 2 (RSAD2), Sialic Acid Binding Ig Like Lectin 1 (SIGLEC1) and three housekeeping genes (Actin Beta (ACTB), Hypoxanthine Phosphoribosyltransferase 1 (HPRT1), RNA Polymerase II Subunit A (POLR2A)), was performed using nanostring technology. Data standardization was obtained using the geometric mean of internal control and housekeeping genes count number. The relative expression was determined for each normalized ISG expression divided by the median normalized expression of each ISG from a control group. The median of these 6 ISG relative expression was used to calculate the IFN score. The threshold was defined as the mean of control group IFN score + 2 standard derivations corresponding to a score of 2,3 (area under the curve of the ROC curve of 0,856; sensitivity of 89,4%, negative predictive value 95,9%; specificity 72,0%).

Results

Clinical characteristics

Fourteen males and sixteen females were studied (Tables 2 and S2). 10/30 reported previous acrosyndrome history, either chilblain, acrocyanosis or acrorrhigosis. 24/30 presented infectious symptoms suggesting a SARS-CoV-2 infection. These symptoms occurred before or at the same time than the onset of skin lesions in all cases. Skin lesions could affect hands, feet or both, but feet were more involved than hands. Although most of the patients presented at consultation with macules and papules resembling chilblains (Figures 1 and 5), it did not represent the predominant clinical feature in several cases. Indeed, some patients only developed acrosyndrome (Figures 2a and 2b), without permanent lesion, such as Raynaud's phenomenon (7/30) or acrocyanosis (12/30). Permanent or transient skin lesions were associated with symptoms in 24/30 cases.

Finally, two different patterns of skin lesions were observed: (i) paroxysmal vasomotor signs, and (ii) permanent vascular lesions. Both were associated in some patients.

Raynaud's phenomenon involved parts of fingers or toes, without cold triggering (Figure 2b). Ears, nose and nipples were not affected. Associated symptoms were not significant. The cyanic and erythematous phases were absent. Acrocyanosis was reported as de novo, or worsening. It was reinforced in the periungueal nail fold. In some patients, wrists or ankles were affected. No patient described associated pain. Cyanic erythema was a vascular erythema, livid, not infiltrated or purpuric, but sometimes with a skin coloration time up to twenty seconds. When standing up, typical semiological presentation of BASCULE syndrome was observed, but without any ichty or feeling of heavy legs complain (Figure 3).

On the other hand, chilblain-like lesions could develop on normal, cyanic, erythematous or livid skin. Vesiculo-bullous lesions were situated on the dorsal or lateral parts of the fingers or the toes, and in two patients on the ankle. One patient displayed maculo-papules and nodules of the limbs associated with chilblain-like lesions. Three unusual features of chilblains were noted: (i) necrotic evolution, sometimes extensive (Figure 4), (ii) purpuric areas on the palmar face of the toes, and (iii) duration of the lesions (at least one month for all cases, more than 4 months for 6 patients) (Table S1).

Pathological features

Standard pathological examination exhibited chilblain-like features in 23 cases (Table 3 and S3): (i) few epidermal changes apart from some isolated necrotic keratinocytes and mild spongiosis, (ii) superficial and deep lymphocytic infiltrate around vessels and eccrine glands (Figure 6), (iii) perieccrine mucin deposition. Sometimes, a lichenoid pattern of the lymphocytic infiltrate was observed. Dermal papillar edema was mild or absent, except for some patients it was prominent. Three patients did not show similar findings: two showed only nonspecific telangiectatic vessels with a slight lymphocytic infiltrate around them and perieccrine mucin deposits insufficient to conclude to a chilblain-like aspect, maybe because of the time between the onset of skin symptoms and skin biopsy performing (37 days and 3 months). The third patient had a too shallow skin biopsy.

Two features were unusual for chilblain-like pattern: (i) vascular damage stigmata in several cases like nuclear dusting (15/26), endothelial cell swelling (16/26), thrombi (10/26), purpura (16/26) (Figure 7) and (ii) vascular deposits of C3 inside the vessel walls in 4/8 cases on direct skin immunofluorescence. However, frank necrosis in the lymphocytic infiltrate was never observed.

Study of CD123 pattern expression within the lymphocytic infiltrate showed a few up to a moderate number of marked cells, without any particular disposition (Figure 8). However, all of the 21 tested cases displayed at least few positive CD123 cells.

Anti-SARS-CoV antibody showed endothelial and epithelial sweat glands discrete microgranular cytoplasmic staining in 18/21 cases (Figure 9). In two cases, it was not possible to conclude due to the exhaustion of the biopsy material. The last case remained negative.

SARS-CoV-2 testing results

Virological testing hardly highlights viral particles of SARS-CoV-2 (Table 4 and S4), with 0/2 positive RT-PCR performed on skin lesions, and 1/23 RT-PCR performed on nasopharyngeal swab. In the same way, SARS-CoV-2 serology remains negative for all patients with IgG, except for the only patient with positive RT-PCR (Table 5). Notably, the patient with positive RT-PCR during infectious symptoms on March 30th 2020 had a first positive serology 25 days after the first infectious symptoms, and subsequent negative serologies. Three patients had transient blood IgA against SARS-CoV-2. Otherwise, an increased number of patients presented positive immunoglobulins

(IgA) against SARS-CoV-2 in saliva samples (14/29) (Table 6). Over an interval of two months, among the patients who had two saliva samples, one patient had an IgA antibody level above the detection threshold at the first sample and below for the second one, whereas a positivity of the second sample was observed for four patients who had a previous negative saliva sample two months earlier.

Immunological findings

Relevant immunological data on standard blood testings were (Table 7 and S5): (i) mild cytopenias, lymphopenia (3/29), thrombopenia (2/29), and neutropenia (3/29), (ii) elevated D-dimer (> 500 ng/mL) for 2/29 patients, (iii) C3 diminution in 1 patients, (iv) positive antinuclear antibodies in 12/28 cases, without any specificity, and significant values in 4 patients.

Antimyositis antibodies were performed on 26 patients and show only weak positivity for anti-NXP2 for one patient, and remained negative on a second blood testing. Anti-DNA antibodies, rheumatoid factor were negative. Hemostasis evaluation showed 2/29 cases with elevated activated partial thromboplastin time, one case with positive antiprothrombin IgG antibodies, one case with positive anti-beta-2-glycoprotein-1 IgA antibodies, and one patient with anticardiolipin IgG antibodies (Table 8).

Concerning the type I interferon pathway study (Table S1 and S4), 17/27 patients presented at least one increased interferon score value (threshold: 2,3), some with high ones (> 10 for 3/27 patients). Kinetics of the values if checking was performed showed either increased or decreased values: case number 3 with a 13,5 initial interferon score increased at 24,9 22 days later and 32,9 44 days after the first blood testing; on the other hand case number 6 show reverse biological pattern with initial interferon score at 39,2, then 6,5 eleven days after, and finally 2,5 forty-six days after the first one. 10/27 patients did not had an interferon signature in the blood. 1/3 cases had differential interferon score between lesional and non lesional skin on biopsy. These biopsies were performed: one month after the first skin symptoms for the patient with differential interferon scoring; 14 and 5 days after the first skin symptoms for the two others.

Discussion

The detailed analysis of these 30 cases confirms the initial hypothesis based on the clinical impression of skin lesions of vascular origin, as evidenced by purpuric areas and the necrosis of the most severe cases. This can be related to number of superficial and deep thrombosis observed in small skin vessels in pathological examination, as well as nuclear dusting in the lymphocytic infiltrate. Although further immunohistochemical studies would have been desirable to confirm this, nuclear dust seems to come from necrosis of endothelial cells on the observation of several cases of thrombosed vessels with destroyed walls, surrounded by a sparse and unaltered lymphoid infiltrate.

Vascular lesions are localized on the distal parts of the fingers and toes in almost all cases, suggesting a circumscribed selective pathophysiological mechanism of small-wall vessels alteration. Indeed, no sign of systemic organ injury was detected in none of the patients, neither by blood testings or urine sediment. Lacking of coagulopathy was evidenced too. These isolated acral vascular lesions then oppose the vascular lesions observed in the course of severe Covid-19, in patients hospitalized in intensive care unit, with severe pulmonary and renal damage, sometimes with thrombosis of large-caliber vessels, and abnormal hemostasis evaluation²⁸. To note, however, one case has been reported of acral vascular skin lesions associated with retinal vasculitis²⁹.

Why mostly feet and hands are involved remains unclear, although a unique case of auricle perniosis was reported³⁰. Most authors who reported similar cases have compared these lesions to chilblains because they mostly affected young to middle-age adults, with low body mass index³¹. Yet, pathophysiology of this acrosyndrome is poorly understood, idiopathic³². The most commonly accepted hypothesis is an abnormal reaction to cold with neurovascular instability. However, cases of chilblain-like lesions during Covid-19 pandemic did not occur in the cooler months, and were clustered in several families (2 families in this study). A clear difference and unusual finding for idiopathic chilblain is the discrepancy between this study and all of the previous studies in the mean duration of symptoms (9 weeks versus 18 days), which could be explained by the follow-up of four months, although the majority of the authors reported rapid and complete self-healing. Perhaps these acral vascular lesions and chilblains share a common pathophysiological mechanism leading to clinically visualized lesions, but the triggering factor is different.

While some authors, for lack of other explanation, have proposed a link with containment³³, others have hypothesized a type I-IFN response²¹. This study argues in favor of his role, on the one hand because of the clinical similarities with type I interferonopathies²², on the other hand with the proof of an interferon signature in 17/27 cases. This interferon atmosphere is consistent with presence of CD123 cells in skin biopsies. Another study compared Covid-19 associated chilblains with chilblain lupus erythematosus³⁴. Authors did not find any significant difference on interferon markers (MxA, CD123) expression on immunohistochemistry. Conversely, there were significant more red blood cell extravasation, lymphocytic vasculitis, and less lichenoid alterations in epidemic chilblain group than in chilblain lupus erythematosus one. All of these previous elements emphasize involvement of interferon pathway. In the absence of type I interferonopathy, since these vascular lesions are acquired, the presence of an interferon blood signature is suggestive of an ongoing viral infection. The other arguments were previous or current non-specific symptoms suggesting viral infection in 24/30 patients, mild cytopenias in 6/29 patients, and the absence of significant elevation of C-reactive protein. Carrying out Epstein-Barr, Parvovirus B19, Human Immunodeficiency, Hepatitis B and C viruses was non contributive.

Concerning the SARS-CoV-2 testings, the results of this study agree with those published previously, with low rate of positive RT-PCR or blood serology. However, the high rate of detection of antibodies against SARS-CoV-2 in the saliva in this study is not reported in the literature to date. Indeed, few data are available on the immune mucosal response in SARS-CoV-2 infection^{25,26,27,35}. There is a humoral response against S glycoprotein, with IgG, IgA and IgM. A study performed on healthcare professionals exposed to SARS-CoV-2, negative with RT-PCR performed on nasopharyngeal swab and asymptomatic, demonstrates combined detection serum and saliva increases probability of detection of individuals who have developed humoral response against SARS-CoV-2. Correlation between the humoral blood and saliva response is contradictory in two studies, but both evidenced some patients were negative with blood IgG and IgA whereas they had IgA in the mucous secretions, and their level was inversely correlated with age. In moderate or mild Covid-19, mucosal antibodies are positive at low levels, with a transient peak of a few days. Forwarded hypothesis is that local mucous plasma cells and memory B cells are capable of reactivating local production of immunoglobulins in case of subsequent contact with the virus. Hence the absence of marked infectious symptoms and the possible under-detection of certain proportion of patients who potentially developed salivary immunoglobulins, due to a

heterogeneous time between the onset of symptoms and the moment of saliva sampling. Interestingly, patients with the highest interferon score in the blood did not show any anti-SARS-CoV-2 antibody in blood or saliva.

The proportion of individuals with blood or saliva antibodies in this study compared to the general population is in favor of a link between acral skin lesions and SARS-CoV-2³⁶. The corollary is to know whether it is rather viro-induced lesions, or a para-viral immunological reaction triggered by SARS-CoV-2. Immunohistochemical staining in endothelial cells and the eccrine epithelium with anti-SARS-CoV antibody in 18/21 cases as previously reported, is consistent with presence of viral particles in these so infected cells, and at least in favor of the first hypothesis. This result should be interpreted with caution in this study for several reasons: (i) unknown specificity of this antibody for SARS-CoV-2. Yet, SARS-CoV has 90% sequence homology with the S2 subunit of N-protein³⁷; (ii) another study with a control group of chilblain before Covid-19 pandemic did not find immunohistochemical detection with an anti-SARS-CoV-2 antibody³⁸; (iii) sensitivity of the antibody due to polyclonal IgG against N-protein used in this study with possible false-positive results; (iv) weak signal detection intensity related to a defect in the development and optimization of the antibody.

It is likely that SARS-CoV-2 infects endothelial cells and eccrine epithelial cells through the ACE2 receptor³⁹. Triggering of IFN pathway leads to necrosis of infected cell. Then, apoptotic bodies or the virus itself activate complement pathway and coagulation pathway which is closely linked, provoking little vessels thrombosis, mirroring what is observed in thrombotic microangiopathies^{40,41}. The role of the complement pathway is illustrated by the demonstration of vascular C3 deposits in 4/8 cases in this study, and 22/47 cases in the literature. Furthermore, C5b9 deposits in the vessels were observed in one reported case⁴². This activation seems to be local, as few abnormal C3 or C4 levels in peripheral blood was measured. Like systemic lupus erythematosus, the expression of apoptotic bodies from endothelial cells damaged via the complement pathway could account for the high level of antinuclear antibodies observed⁴³.

During the course of severe Covid-19, screening for antiphospholipid antibodies was studied because of high rate of thrombotic events⁴⁴. Despite high frequency and wide variety of detected antibodies, their significance remains not elucidated, not knowing if it is an epiphenomenon that can occur during the course of many infections, or participate to Covid-19 related coagulopathy in severe cases. Positivity for these antibodies in 3/28 patients was not associated with clinical signs of thrombosis,

although further investigations were not performed. Likewise, these antibodies could represent stigmata secondary to viral infection, transient, without pathological significance⁴⁵, as antinuclear antibodies found in 12/28 cases. For this, a new sample is necessary to judge the persistence or not, and the qualification of a possible secondary antiphospholipid syndrome.

This study therefore makes it possible to demonstrate that these acral skin lesions that occurred during the Covid-19 pandemic have a vascular substrate, with the involvement of IFN-I pathway. Biphasic evolution of severe cases of Covid-19, both inhibition of the IFN-I by the virus and sensitivity by the virus to IFN highlights the compartmentalization of the immune response, function of the timing in which IFN is secreted⁴⁶. Complement pathway also appears to play a central role in the genesis of the vascular injury. The prospective follow-up of the patients made it possible to highlight a prolonged duration of the evolution of the symptoms, contrasting with no other organ injury. Although a set of arguments previously exposed converge towards a link between skin lesions and viral infection, the design of this study, with in particular the absence of a control group, the limited number of patients, and the descriptive nature, do not allow to affirm causality. Further investigations are warranted and open the way to the study of the neutralizing and protective character of antibodies⁴⁷, the role of mucous humoral response in Covid-19, as well as the long-term follow-up of infected patients in order to determine whether the biological stigmas of autoimmunity give rise to the development of real autoimmune diseases^{48,49}.

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Annexes

Figures



Figure 1. Permanent vascular macules and papules of the distal part of the limbs. (A) Case 10. (B) Case 18. (C) Case 20. (D) Case 16. Red, blue or purple macules and papules of the toes and fingers. These lesions are well-circumscribed in cases 10 and 16, and more diffuse with cyanic, livid coloration of the skin around these lesions in cases 18 and 20.



Figure 2a. Transient vascular acrosyndromes.

(A), (B) Cases 21 and 23 showing diffuse acrocyanosis of the hand involving the wrist in B, with periungueal and periarticular reinforcement. There was neither associated hyperhidrosis nor pain, but extremities were cold. This acrocyanosis was more or less pronounced, depending on the position of the hands, and could disappear.

(C) Case 17. Raynaud's phenomenon of the fourth and fifth fingers of both hands, with cold extremities, associated erythematous and cyanic erythema of the others fingers, without individualisable skin lesion.



Figure 2b. Transient vascular acrosyndromes. Case 18. Patient presenting background of acrocyanosis without any evident lesion (left photograph), and then spontaneous white discoloration of parts of the fingers during examination (right photograph).



Figure 3. BASCULE (Bier anemic spots, cyanosis with urticaria-like eruption) syndrome presentation. (A) Case 27. (B) Case 4. After a 30-second standing, a particular vascular rash consists of three colors: white, red, blue. This was reversible to the elongated position. Case 27 presented associated distal persistent macules and papules, sometimes purpuric and necrotic.



Figure 4. Purpuric and necrotic acral lesions.

(A) Case 6 presenting with purpuric macules of the distal part of the toes, surrounded by white discoloration mimicking Raynaud's phenomenon.

(B) Case 13 showing macules and papules of the fingers with Raynaud's phenomenon and ulcerated, crusted, necrotic painful lesions.

(C) Case 26 showing macules and papules of the dorsal part of the fingers.

(D) Case 30: this patient complained with sudden onset of distal purpuric subungual lesions, with no other skin or systemic symptoms.



Figure 5. Dermoscopic view of the purpuric lesions. (A) Case 18. (B), (C) Case 20. (D) Case 21. Red-to-purple areas, more or less circumscribed, with small red dots and white areas within the macules, suggesting purpura, inflammation, ischemia and focal thrombosis.

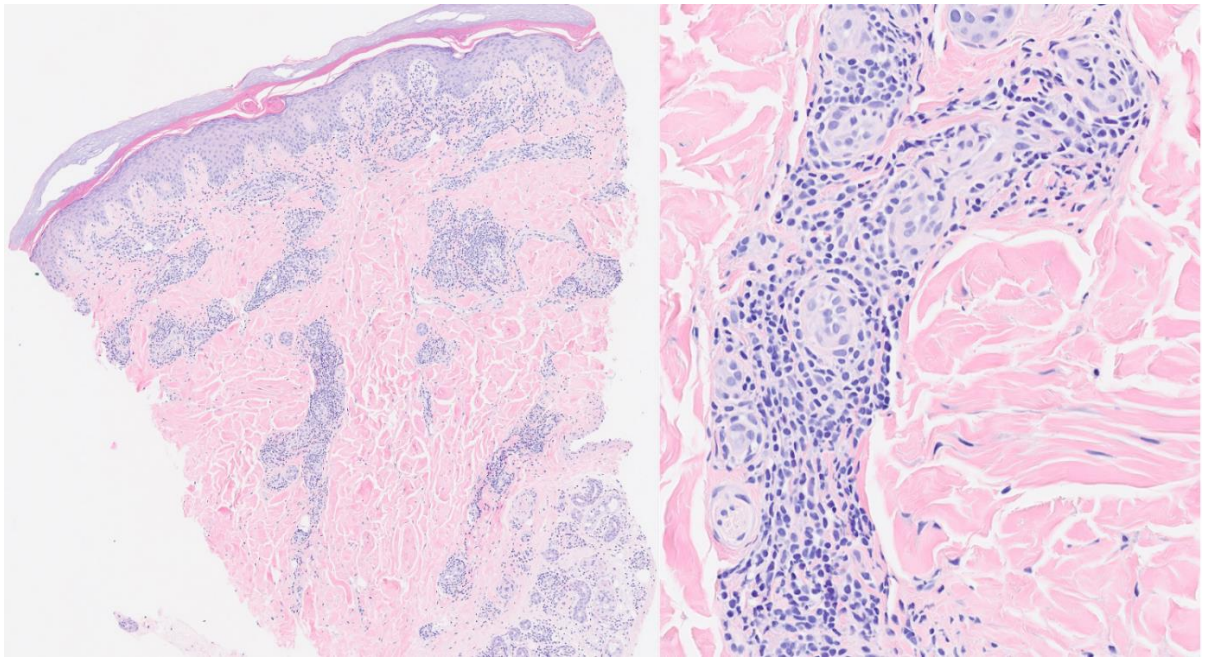


Figure 6. Typical histological features of acral vascular lesions. Same patient (case 8). On the left (hematoxylin-eosin, x 40 magnification), skin biopsy of a finger shows normal epidermis with few papillary edema and a moderate lymphoid infiltrate cuffing superficial and deep vessels, without perieccrine reinforcement. On the right (hematoxylin-eosin, x 200 magnification), the details of the lymphocytic infiltrate show monotonous and small monocytes and lymphocytes, around vessels with prominent endothelium.

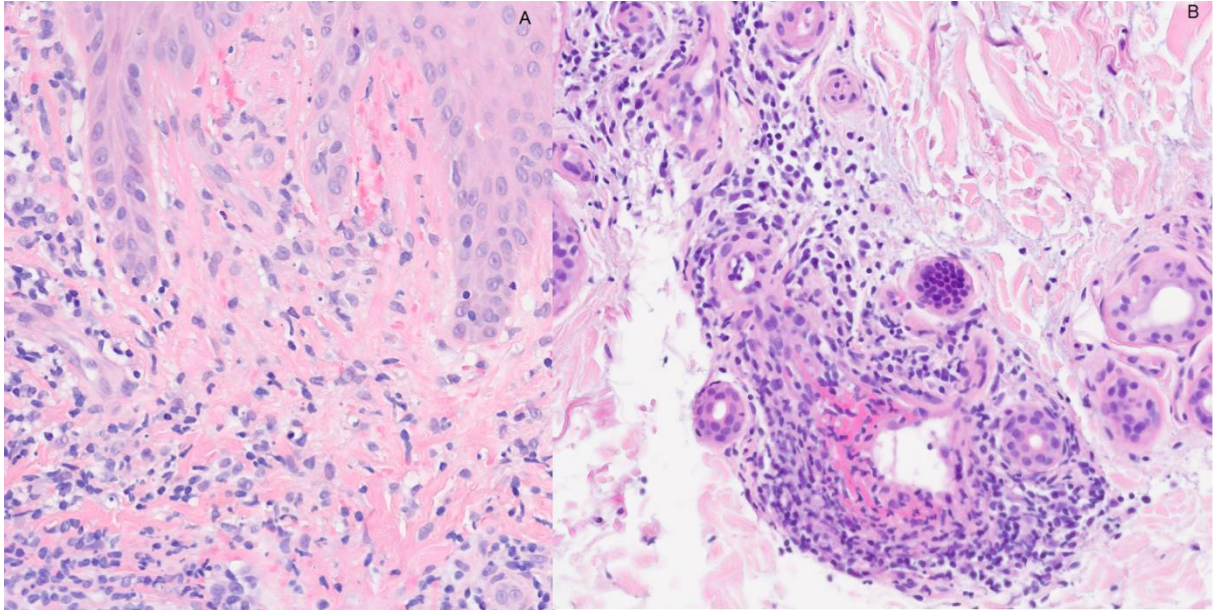


Figure 7. Histological vascular injury on skin biopsies.

(A) Case 2. Lymphocytic infiltrate and extravasated red blood cells in papillary dermis, with no distinguishable wall of the vessels, nuclear dusting. Hematoxylin eosin, magnification x 200.

(B) Case 24. Altered wall of a vessel in the reticular dermis, surrounded by a dense lymphocytic infiltrate, some nuclear dusting, endothelial alteration and purpura. Hematoxylin-eosin, magnification x 200.

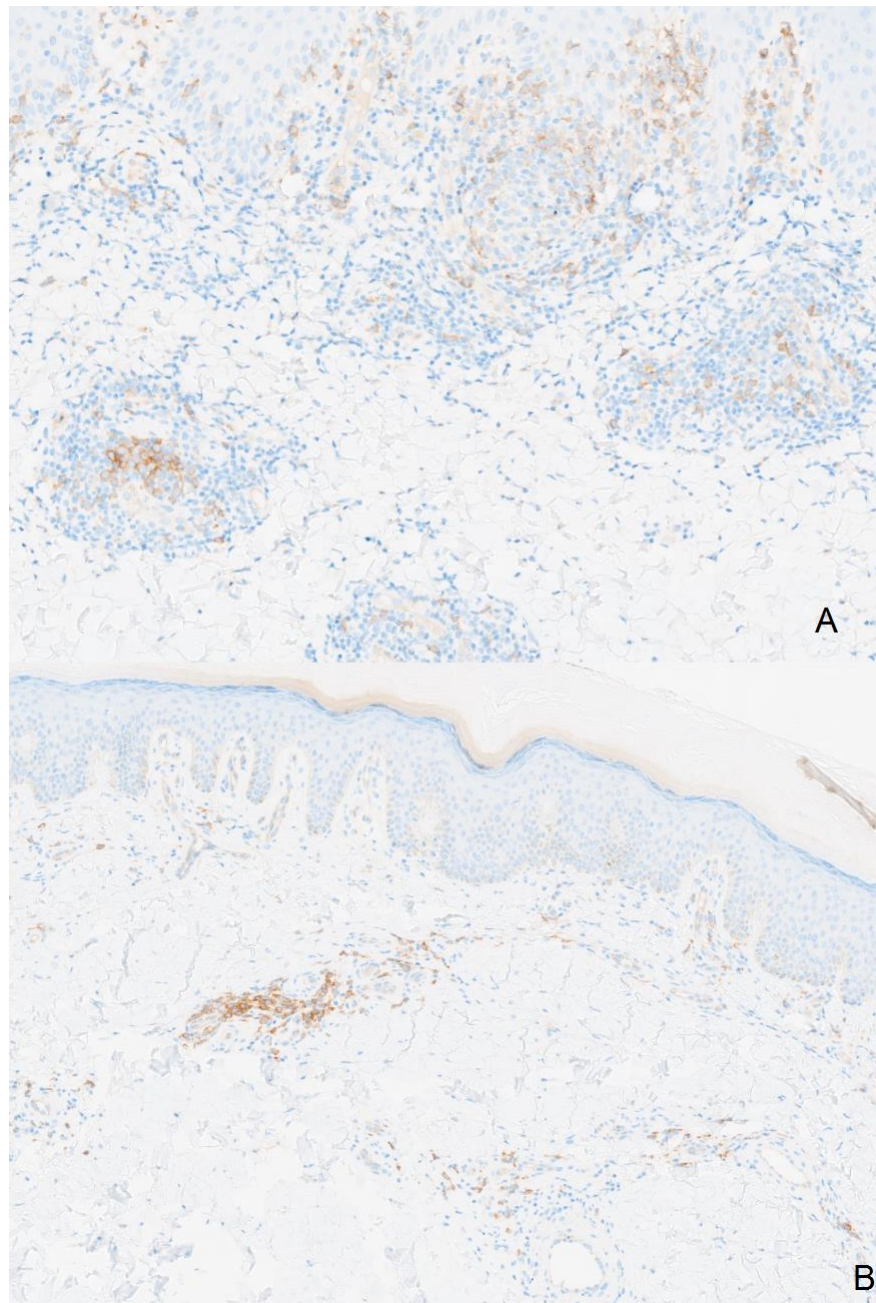


Figure 8. Immunohistochemical staining with anti-CD123 antibody.

(A) Case 14, magnification x 40. Lymphocytic infiltrate is moderate to dense. Marked cells are mainly located in the papillary dermis, or sometimes inside the epidermis (this case displayed an interface dermatitis on hematoxylin-eosin staining), whereas they are not majority in the infiltrate around deeper dermal vessels.

(B) Case 24, magnification x 40. Scattered cells are marked with anti-CD123 antibody around capillaries in the superior dermis. Vessels and epidermis are not altered. On the contrary, lymphocytic infiltrate around deeper vessels in the dermis is mild and most of the cells display a positivity with anti-CD123.

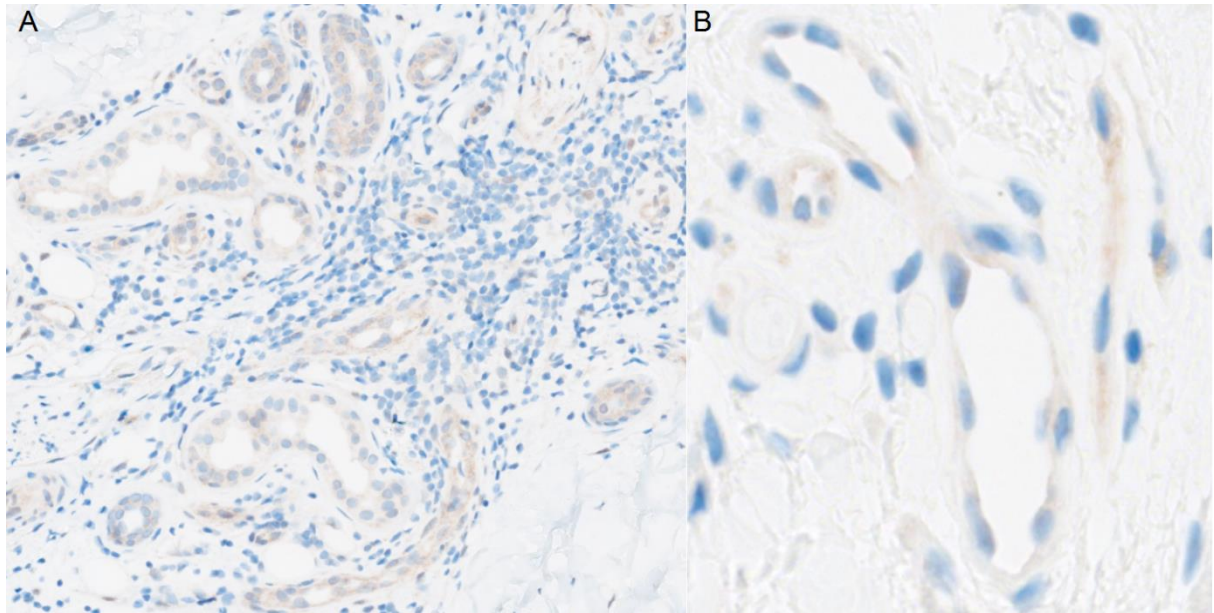


Figure 9. Immunohistochemical staining with anti-SARS-CoV antibody. (A) Case 12 (magnification x 200). (B) Case 22 (magnification x 800). Slight microgranular staining inside the cytoplasm of endothelial cells and eccrine epithelial cells.

Tables

Table 1. Epidemiological, clinical, pathological, biological, virological data of acral vascular skin lesions occurring during COVID-19 pandemic in the previous reported studies or cases report

References	Gianotti et al. ¹	Herman et al. ²	Kanitakis et al. ³	Le Cleach et al. ⁴	Caselli et al. ⁵	Piccolo et al. ⁶	Galvan Casas et al. ⁷	Rizzoli et al. ⁸	Aguirre et al. ⁹	Troccoli et al. ¹⁰	Locatelli et al. ¹¹
Baseline characteristics											
-Number of patients	14	31	17	311	38	63	71	12	74	1	1
-Mean age (range), years	18 (13-39)	22 (6-72)	32 (15-63)	25,7 (18-38,3)	13,5 (7-18)	14 (12-16)	32,5	13,5 (9-19)	14,5 (3-100)	13	16
-Sex ratio (male/female)	(6/8)	(12/19)	(11/6)	(129/182)	(22/16)	30/33	(23/48)	0,5 (4/8)	(42/32)	1/0	1/0
-Personal autoimmune disease	NA	2/31	0/17	6/311	2/38	6/63	ND	ND	ND	ND	ND
-Familial autoimmune disease	NA	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND
-Other comorbidities	0/14	7/31	ND	ND	1/38	3/63	ND	ND	ND	0/1	ND
-Current smoker	NA	1/31	ND	ND	ND	ND	7/71	ND	ND	ND	ND
-Cold exposure	0/14	ND	ND	ND	ND	ND	ND	ND	ND	ND	0/1
-Hospitalized patients	0/14	0/31	NA	NA	ND	NA	9/71	ND	ND	0/1	ND
-Outpatients	14/14	31/31	NA	NA	ND	NA	62/71	ND	ND	1/1	ND
-Drug intake	0/14	3/31	ND	NA	ND	ND	ND	ND	ND	0/1	ND
-History of chilblains	ND	9/31	ND	32/311	ND	ND	1/71	ND	ND	ND	0/1
-History of acrosyndrome	ND	4/31	ND	31/311	ND	ND	ND	ND	ND	ND	0/1
-BMI (kg/m ²)	ND	19,13 (15,57 - 33,56)	ND	NA	ND	ND	ND	ND	ND	ND	ND
Dermatological presentation											
-Macules	Yes, NA	Yes, NA	Yes, NA	NA	NA	NA	ND	ND	NA	1/1	1/1
-Papules	Yes, NA	Yes, NA	Yes, NA	NA	Yes, NA	NA	ND	ND	76,4%	1/1	1/1
-Purpura	NA	NA	NA	NA	NA	NA	ND	ND	40,54%	1/1	NA
-Vesicles	Yes, NA	Yes, NA	NA	NA	Yes, NA	NA	ND	ND	NA	1/1	NA
-Bullae	Yes, NA	Yes, NA	NA	22/245	Yes, NA	NA	ND	ND	NA	1/1	NA
-Necrosis	NA	Yes, NA	Yes, NA	NA	NA	NA	ND	ND	NA	NA	NA
-Digital swelling	Yes, NA	NA	Yes, NA	NA	NA	NA	ND	ND	NA	NA	1/1
-Livedo	NA	NA	NA	NA	NA	NA	ND	ND	NA	NA	NA
-Acrocyanosis	NA	NA	NA	NA	NA	NA	ND	ND	NA	NA	NA
-Involvement of feet	8/14	1/31	15/17	236/311	NA, Mostly	85,7%	ND	10/12	95,94%	1/1	1/1
-Involvement of hands	4/14	27/31	2/17	36/311	NA, Few cases	6%	ND	3/12	8,1%	0/1	1/1
-Involvement of both feet and hands	2/14	3/31	NA	37/311	NA	7%	ND	1/12	4,05%	0/1	1/1
-Involvement of limbs/head/trunk	NA	NA	NA	ND	NA	NA	ND	ND	NA	NA	0/1
-Mean duration of the skin symptoms	2-4 weeks	13,1 days (3-28 days)	ND	"resolved spontaneously within a few weeks"	25 (3-88 days)	NA but 14% relapsing course, 6,3% fugacious, 79,4% stable	12,7 days	ND	ND	Around 10 days	Several weeks (> 20 days)
-Associated symptoms											
Pruritus	3/14, mild	Yes, NA	ND	NA	ND	ND	21/71	ND	32,4% (24)	1/1	0/1
Burning	NA						8/71		27% (20)	1/1	0/1
Pain	NA						23/71		ND	1/1	0/1
Infectious symptoms											
-Fever	3/14	20/31	5/17	151/311	8/38	NA	NA	NA	NA	1/1	1/1
-Cough	3/14	1/31	NA	NA	6/38	4,8% (3)	44/71	ND	33,33% (25)	1/1	NA
	3/14	7/31	NA	NA	NA	7,9% (respiratory symptoms) (5)	37/71	ND	52,38% (39)	ND	NA
-Rhinitis	ND	12/31	ND	NA	NA	ND	ND	ND	ND	ND	NA
-Dyspnea	ND	6/31	ND	NA	NA	ND	18/25	ND	9,52% (7)	ND	NA
-Fatigue	ND	4/31	NA	NA	NA	ND	37/71	ND	28,57% (asthenia + myalgias) (21)	ND	NA
-Myalgias	ND	ND	ND	NA	NA	ND	ND	ND	19% (diarrhea, nausea, vomiting) (14)	1/1	NA
-Diarrhea	ND	7/31	ND	NA	2/38	11,1% (GI symptoms) (7)	17/71 (diarrhea + vomiting)	ND	19% (diarrhea, nausea, vomiting) (14)	ND	1/1
-Headache	ND	ND	ND	NA	NA	ND	27/71	ND	ND	1/1	NA
-Anosmia/agueusia	ND	ND	ND	NA	NA	ND	13/71	ND	4,76% (3)	ND	1/1
-Close contact with COVID-19 person	0/14	3/31 (possible or confirmed)	6/17	ND	ND	10/63	ND	8/12	24,32% referred close contact with confirmed or clinically diagnosed COVID-19 (18/74)	1/1 Yes (sister, mother)	1/1
Not proved	0/14	NA	NA	NA	NA	8/63	8/63	6/12		1/1	0/1
Proved	ND	NA	2/17	NA	NA	2/63	2/63	2/12		0/1	1/1 (mother)

Mean time onset infectious symptoms and skin symptoms (range)	ND	ND	ND	10,5 days (1-16), data available for 148 patients. In 23 cases, skin preceded infectious symptoms	ND	ND	All : Before 5/71 Same time 24/71 After 42/71	ND	16,15 days (skin after infectious symptoms for 66,7%)	2 days (infectious after skin symptoms)	3 days (infectious symptoms before skin)
Treatment for skin							Confirmed cases : Before 1 Same time 15 After 13				
-None	14/14	NA	ND	NA	ND	ND	33/71	ND	ND	NA	ND
-Hydroxychloroquine	0/14	NA	ND	NA	ND	ND	6/71	ND	ND	NA	ND
-Dermocorticoids	0/14	NA	ND	NA	ND	ND	ND	ND	ND	NA	ND
-Other	0/14	NA	ND	NA	ND	ND	-Paracetamol 32/71 -NSAIDs 11/71 -Lopinavir/ritonavir : 3/71 -Tocilizumab : 2/71 -Corticoids : 1/71 -Azithromycin : 3/71	ND	ND	"Oral macrolide and topical therapy"	ND
Histological features	4/14	22/31	17/17	17/17	ND	ND	ND	ND	ND	ND	1/1
-Spongiosis	NA	NA	2/17	NA	ND	ND	ND	ND	ND	ND	NA
-Necrotic keratinocytes	1/4	NA	7/17	17/17	ND	ND	ND	ND	ND	ND	NA
-Basal vacuolar changes	NA	4/22	3/17	17/17	ND	ND	ND	ND	ND	ND	NA
-Thickening of the basement membrane	ND	NA	NA	NA	ND	ND	ND	ND	ND	ND	NA
-Parakeratosis	NA	NA	12/17	NA	ND	ND	ND	ND	ND	ND	NA
-Papillary edema	1/4	NA	13/17	NA	ND	ND	ND	ND	ND	ND	1/1
-Superficial lymphocytic infiltrate	2/4	NA	NA	17/17	ND	ND	ND	ND	ND	ND	1/1
-Deep lymphocytic infiltrate	2/4	NA	NA	17/17	ND	ND	ND	ND	ND	ND	1/1
-Density of the lymphocytic infiltrate		NA		NA	ND	ND	ND	ND	ND	ND	NA
Light	0/4		5/17								
Mild	2/4		10/17								
Marked	2/4		2/17								
-Pattern of lymphocytic infiltrate				NA	ND	ND	ND	ND	ND	ND	
Perivascular	4/4	22/22	17/17								1/1
Perieccrine	NA	17/22	8/17								1/1
-Type of infiltrate	Prevalence of cytotoxic CD8+ lymphocytes	NA	-Lymphocytes: 13/17 -Ly + eo: 4/17	NA	ND	ND	ND	ND	ND	ND	lymphocytic
-Nuclear dusting	ND	NA	NA	NA	ND	ND	ND	ND	ND	ND	NA
-Lichenoid infiltrate/interface dermatitis	ND	NA	NA	NA	ND	ND	ND	ND	ND	ND	NA
-Extravasation of erythrocytes	1/4	NA	14/17	NA	ND	ND	ND	ND	ND	ND	NA
-Fibrin deposition	NA	NA	5/17	NA	ND	ND	ND	ND	ND	ND	NA
-Vascular ectasia	NA	NA	NA	NA	ND	ND	ND	ND	ND	ND	NA
-Thickening of the vessel walls	2/4	NA	NA	NA	ND	ND	ND	ND	ND	ND	NA
-Thrombi	"some cases"	6/22	3/17	NA, "some cases"	ND	ND	ND	ND	ND	ND	NA
-Endothelial cell swelling	2/4	NA	11/17	NA	ND	ND	ND	ND	ND	ND	"no sign of endothelial damage"
-Mural lymphocytes	NA	NA	NA	NA	ND	ND	ND	ND	ND	ND	NA
-Perieccrine mucin deposition	ND	ND	7/17	NA	ND	ND	ND	ND	ND	ND	ND
-Deposits on direct immunofluorescence on skin lesions (type of deposits)	ND	7/15 -IgG : 0/15, NS -C3 : 7/15, NS -IgM : 4/15, NS -IgA : 1/15, NS -C1q : 0/15	14/17 : perivascular -IgM : 9/17 -IgA : 5/17 -C3 : 5/17	NA	ND	ND	ND	ND	ND	ND	ND

-Other features	"Many eosinophils involving the secretory portion of the sweat glands"	"lymphocytic vasculitis": 6/22	NA	ND	ND	ND	ND	ND	A skin biopsy was performed : lymphocytic perivascular and perieccrine infiltrate without vascular occlusion nor vascular thrombi. DIF negative	ND	ND
Virological characteristics											
-Positive Sars-CoV-2 RT-PCR performed on nasopharyngeal swab	0/3	0/31	0/17	7/121	0/38	2/11	NA	0/12	1/11	0/1	1/1
-Positive Sars-CoV-2 RT-PCR performed on rectal swab	0/2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-Positive Sars-CoV-2 RT-PCR performed on skin lesions	ND	0/21	0/3	ND	ND	ND	ND	ND	ND	ND	ND
-Positive Sars-CoV-2 blood test serology	ND	0/31 (IgG, IgM)	0/17	5/75 (IgG)	0/38 (IgG, IgA, IgM)	2/6	NA	1/12 (IgG)	ND	ND	ND
-Positive anti-Sars-CoV-2 salivary antibody testing	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Blood testing data											
-Thrombopenia	0/14	No, NA	No, NA	0/57	ND	ND	ND	ND	ND	ND	ND
-Anemia	0/14	No, NA	No, NA	0/57	ND	ND	ND	ND	ND	ND	NA
-Neutropenia	0/14	No, NA	No, NA	0/57	ND	ND	ND	ND	ND	ND	NA
-Lymphopenia	0/14	0/31	No, NA	0/57	ND	ND	ND	ND	ND	ND	NA
-Eosinopenia	0/14	0/31	No, NA	0/57	ND	ND	ND	ND	ND	ND	ND
-High C-reactive protein (> 5 mg/L)	0/14	1/26	ND	0/20	ND	ND	ND	ND	ND	ND	ND
-High aPTT	ND	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND
-D-dimer elevation (> 500 ng/mL)	0/14	3/28	No, NA	ND	ND	ND	ND	ND	ND	ND	ND
-Fibrinogen abnormality	ND	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND
-High LDH	0/14	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND
-Low PT	ND	No, NA	ND	NA	ND	ND	ND	ND	ND	ND	ND
-Positive antinuclear antibodies (> 1/160)	ND	1/28	No, NA	4/NA	1/NA	ND	ND	ND	ND	ND	NA
-Positive native ADN antibodies	ND	ND	ND	1/NA (low titer)	ND	ND	ND	ND	ND	ND	ND
-Complement abnormality CH50 C3 C4	ND	No, NA	No, NA	0/14	ND	ND	ND	ND	ND	ND	ND
-Antimyositis antibodies	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-ANCA	ND	No, NA	ND	1/NA	ND	ND	ND	ND	ND	ND	ND
-Cryoglobulin	ND	No, NA	No, NA	0/NA	ND	ND	ND	ND	ND	ND	NA
-Cryofibrinogen	ND	ND	ND	0/30	ND	ND	ND	ND	ND	ND	ND
-Cold agglutinins	ND	No, NA	ND	0/34	ND	ND	ND	ND	ND	ND	ND
-EBV serology	0/14	ND	ND	NA	ND	ND	ND	0/3	ND	ND	ND
-Parvovirus serology	0/14	ND	ND	0/57	ND	ND	ND	0/2	ND	ND	ND
-CMV serology	0/14	ND	ND	NA	ND	ND	ND	0/3	ND	ND	ND
-Coxsackie serology	0/14	ND	ND	0/57	ND	ND	ND	0/2	ND	ND	ND
-HIV serology	ND	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND
-HCV serology	ND	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND
-HBV serology	ND	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND
-Liver laboratory testing abnormality	ND	No, NA	ND	NA	ND	ND	ND	ND	ND	ND	ND
-Abnormal blood creatinin	ND	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND
-Rheumatoid factor	ND	No, NA	ND	NA	ND	ND	ND	ND	ND	ND	ND
-APL antibodies	ND		NA		ND	ND	ND	ND	ND	ND	ND
Lupus anticoagulant		No, NA		NA							
Anti-B2GPI (IgG, IgM)		No, NA		NA							
Anticardiolipin		No, NA		1/NA low IgG							

References	Cordoro et al. ¹²	Fernandez-Nieto et al. ¹³	Aramthan et al. ¹⁴	Ezsol-Lendvai et al. ¹⁵	Monte Serrano et al. ¹⁶	Dertlioglu ¹⁷	Roca-Ginés ¹⁸	Santonja et al. ¹⁹	Colmenero et al. ²⁰	Kolivras et al. ²¹	Neri et al. ²²
Baseline characteristics											
-Number of patients	6	95	2	1	1	1	20	1	7	1	8
-Mean age (range), years	(12-17)	23,4 (2-56)	27-35	13	17	18	12,3 (1-18)	35	(11-17)	23	(11-15)
-Sex ratio (male/female)	5/1	49/46	1/1	1/0	1/0	1/0	(13/7)	0/1	4/3	1/0	3/5
-Personal autoimmune disease	0/6	ND	ND	ND	0/1	0/1	1/20	0/1	0/7	1/1	0/8
-Familial autoimmune disease	0/6	ND	ND	ND	ND	ND	ND	ND	ND	ND	0/8
-Other comorbidities	0/6	ND	0/2	ND	0/1	0/1	ND	0/1	2/7	0/1	0/8
-Current smoker	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-Cold exposure	0/6	ND	ND	0/1	ND	ND	ND	ND	ND	ND	NA
-Hospitalized patients	0/6	ND	0/2	0/1	0/1	ND	0/20	0/1	ND	0/1	0/8
-Outpatients	6/6	ND	2/2	1/1	1/1	ND	20/20	1/1	7/7	1/1	8/8
-Drug intake	ND	ND	ND	ND	ND	ND	2/20	ND	1/7	1/1	ND
-History of chilblains	0/6	ND	ND	ND	ND	ND	9/20 (Raynaud or chilblains)	ND	0/7	0/1	ND
-History of acrosyndrome	ND	ND	ND	ND	ND	ND		ND	0/7	0/1	ND
-BMI (kg/m2)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	<25th percentile in 50% of the patients
Dermatological presentation											
-Macules	6/6	NA	ND	1/1	1/1	1/1	6/20	1/1	ND	1/1	8/8
-Papules	NA	NA	2/2	ND	1/1	ND	9/20	1/1	ND	1/1	NA
-Purpura	6/6	NA	ND	ND	1/1	ND		1/1	ND	ND	NA
-Vesicles	NA	NA	ND	ND	NA	ND	ND	ND	ND	ND	NA
-Bullae	NA	NA	ND	ND	NA	ND	ND	ND	ND	ND	3/8
-Necrosis	0/6	NA	ND	ND	NA	ND	ND	ND	ND	ND	NA
-Digital swelling	NA	NA	ND	ND	1/1	ND	6/20	1/1	ND	ND	NA
-Livedo	3/6	NA	ND	ND	NA	ND	ND	ND	ND	ND	NA
-Acrocyanosis	NA	NA	ND	ND	NA	ND	ND	1/1	ND	ND	NA
-Involvement of feet	6/6	73/95	ND	1/1	1/1	1/1	18/20	1/1	7/7	1/1	8/8
-Involvement of hands	0/6	33/95	2/2	ND	0/1	ND	6/20	ND	1/7	ND	3/8
-Involvement of both feet and hands	0/6	11/95	ND	ND	0/1	ND	4/20	ND	1/7	ND	3/8
-Involvement of limbs/head/trunk	NA	0/95	ND	ND	ND	ND	ND	ND	ND	ND	ND
-Mean duration of the skin symptoms	ND	9,2 days (3-24)	ND	3 weeks	4 weeks	A few days	13,25 days (4 weeks follow-up)	3 weeks	< 8 weeks in all cases	ND	ND
-Associated symptoms	ND		ND								
Pruritus				1/1	1/1	1/1	ND	ND	3/7	0/1	5/8
Burning				1/1	ND	ND	ND	ND	ND	0/1	1/8
Pain				ND	ND	ND	ND	ND	1/7	1/1	3/8
Infectious symptoms	0/6	ND	ND	1/1	1/1	1/1	0/20	1/1	5/7	1/1	0/8
-Fever	0/6	ND	ND	1/1	ND	1/1	0/20	1/1	NA	1/1	NA
-Cough	0/6	ND	ND	ND	1/1	ND	0/20	1/1	NA	1/1	NA
-Rhinitis	0/6	ND	ND	ND	ND	1/1	0/20	ND	NA	ND	NA
-Dyspnea	0/6	ND	ND	ND	ND	ND	0/20	ND	NA	ND	NA
-Fatigue	NA	ND	ND	1/1	ND	ND	0/20	ND	NA	ND	NA
-Myalgias	NA	ND	ND	ND	1/1	ND	0/20	ND	NA	ND	NA
-GI symptoms (diarrhea, nausea, vomiting)	NA	ND	ND	ND	ND	ND	ND	0/1	NA	ND	NA
-Headache	NA	ND	ND	ND	1/1	1/1	0/20	ND	NA	ND	NA
-Anosmia/agueusia	NA	ND	ND	ND	ND	1/1	0/20	0/1	NA	ND	NA
-Close contact with COVID-19 person	6/6	ND	ND	1/1	1/1	ND	0/20 (6/20 similar skin symptoms)	ND	4/7 "suspected house contact"	ND	0/8
Not proved	6/6			1/1	1/1		NA		NA		NA
Proved	0/6			ND			NA		NA		NA
Mean time onset infectious symptoms and skin symptoms (range)	ND	ND	ND	"few days" (infectious after skin lesions)	0	A few days (infectious then skin symptoms)	ND	0	ND	3 days (infectious then skin symptoms)	ND

Treatment for skin													
-None	ND	ND	ND	ND	0/1	ND	ND	ND	ND	ND	ND	ND	ND
-Hydroxychloroquine	ND	ND	ND	ND	0/1	ND	ND	ND	ND	ND	ND	ND	ND
-Dermocorticoids	ND	ND	ND	ND	1/1	ND	ND	ND	ND	ND	ND	ND	8/8
-Other	ND	ND	ND	ND	0/1	ND	ND	ND	Aspirin, heparin	ND	ND	ND	ND
Histological features	2/6	ND	ND	ND	ND	ND	6/20	1/1	7/7	1/1	2/8		
-Spongiosis	NA	ND	ND	ND	ND	ND	6/6	ND	7/7	ND	ND	ND	ND
-Necrotic keratinocytes	NA	ND	ND	ND	ND	ND	6/6	ND	4/7	ND	ND	ND	ND
-Basal vacuolar changes	2/2	ND	ND	ND	ND	ND	6/6	ND	7/7	ND	ND	ND	ND
-Thickening of the basement membrane	NA	ND	ND	ND	ND	ND	NA	ND	0/7	ND	ND	ND	ND
-Parakeratosis	Yes, NA	ND	ND	ND	ND	ND	NA	ND	4/7	ND	ND	ND	ND
-Papillary edema	NA	ND	ND	ND	ND	ND	3/6	ND	7/7	0/1	2/2		
-Superficial lymphocytic infiltrate	2/2	ND	ND	ND	ND	ND	6/6	ND	7/7	1/1	2/2		
-Deep lymphocytic infiltrate	2/2	ND	ND	ND	ND	ND	0/6	ND	7/7	1/1	2/2		
-Density of the lymphocytic infiltrate	NA	ND	ND	ND	ND	ND	ND			ND			
Light								0/1	5/7				
Moderate								1/1	0/7				
Marked								0/1	2/7		2/2		
-Pattern of lymphocytic infiltrate		ND	ND	ND	ND	ND							
Perivascular	2/2						6/6	1/1	7/7	1/1	2/2		
Perieccrine	2/2						6/6	1/1	6/6	1/1	ND		
-Type of infiltrate	lymphocytic	ND	ND	ND	ND	ND	ND	ND	lymphocytic	lymphocytic	lymphocytic		
-Nuclear dusting	NA	ND	ND	ND	ND	ND	ND	ND	NA	1/1	ND		
-Lichenoid infiltrate/interface dermatitis	Yes, NA	ND	ND	ND	ND	ND	ND	ND	NA	1/1	2/2		
-Extravasation of erythrocytes	Yes, NA	ND	ND	ND	ND	ND	ND	1/1	7/7	0/1	ND		
-Fibrin deposition	NA	ND	ND	ND	ND	ND	3/6	ND	2/7	1/1	0/2		
-Vascular ectasia	NA	ND	ND	ND	ND	ND	ND	ND	3/7	ND	2/2		
-Thickening of the vessel walls	NA	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND		
-Thrombi	0/2	ND	ND	ND	ND	ND	2/6	1/1	1/7	0/1	ND		
-Endothelial cell swelling	NA	ND	ND	ND	ND	ND	6/6	1/1	"often"	1/1	ND		
-Mural lymphocytes	2/2 "lymphocytic vasculitis"	ND	ND	ND	ND	ND	ND	ND	7/7	ND	ND		
-Perieccrine mucin deposition	ND	ND	ND	ND	ND	ND	ND	ND	5/7		ND		
-Deposits on direct immunofluorescence on skin lesions (type of deposits)	0/2	ND	ND	ND	ND	ND	ND	1/1	C5b9, C3, C1q	ND	0/1		
-Other features	ND	ND	ND	ND	ND	ND	"lymphocytic vasculitis" 3/6	Positive anti-Sars-Cov-2 antibody on IHC in eccrine & endothelium cells	-3/7 exocytosis -lymphocytic vasculitis 7/7 -CD30+ 2/7 scattered -CD4+>CD8+ -Scattered CD20+ -TEM: 1 case showed viral particle	ND	ND		
Virological characteristics													
-Positive Sars-CoV-2 RT-PCR performed on nasopharyngeal swab	0/6	2/11	2/2	0/1	0/1	1/1	0/20	0/1	0/6	1/1	0/8		
-Positive Sars-CoV-2 RT-PCR performed on rectal swab	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND		
-Positive Sars-CoV-2 RT-PCR performed on skin lesions	ND	ND	ND	ND	ND	ND	ND	ND	ND	0/1	0/1		

-Positive Sars-CoV-2 blood test serology	0/6 (IgG, IgM)	ND	ND	0/1 (IgG/IgE)	0/1 (IgG, IgA, IgM)	ND	0/20 (IgG, IgM, IgA)	0/1 (IgG, IgM)	ND	0/1	0/8 (IgG, IgM)
-Positive anti-Sars-CoV-2 salivary antibody testing	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Blood testing data	Blood count, autoimmune and coagulopathy panels, urinalysis, metabolic panels : normal	ND	Blood count and complete metabolic profile were normal	ND	0/1	ND		ND			
-Thrombopenia	NA	ND	0/19	ND	0/1	ND	0/20	ND	NA	0/1	0/8
-Anemia	NA	ND	0/19	ND	0/1	ND	0/20	ND	NA	0/1	0/8
-Neutropenia	NA	ND	0/19	ND	0/1	ND	0/20	ND	NA	0/1	0/8
-Lymphopenia	NA	ND	0/19	ND	0/1	ND	0/20	ND	NA	0/1	0/8
-Eosinopenia	NA	ND	ND	ND	0/1	ND	0/20	ND	NA	0/1	0/8
-High C-reactive protein (> 5 mg/L)	ND	ND	ND	ND	0/1	ND	0/20	ND	NA	ND	0/8
-High aPTT	NA	ND	ND	ND	NA	ND	NA	ND	NA	0/1	0/8
-D-dimer elevation (> 500 ng/mL)	NA	ND	ND	ND	0/1	ND	0/20	ND	1/6 (900)	0/1	0/8
-Fibrinogen abnormality	3/6 (low titer)	ND	ND	ND	NA	ND	ND	ND	NA	ND	0/8
-High LDH	ND	ND	ND	ND	0/1	ND	0/20	ND	ND	ND	0/8
-Low PT	NA	ND	ND	ND	NA	ND	ND	ND	ND	0/1	0/8
-Positive antinuclear antibodies (>= 1/160)	NA	ND	ND	ND	ND	ND	2/20 (1/160, 1/1280)	ND	ND	0/1	0/8
-Positive native ADN antibodies	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-Complement abnormality	NA	ND	ND	ND	ND	ND		ND	ND	ND	ND
CH50							ND				
C3							0/20				
C4							0/20				
-Antimyositis antibodies	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-ANCA	ND	ND	ND	ND	ND	ND	0/20	ND	ND	ND	ND
-Cryoglobulin	ND	ND	ND	ND	ND	ND	0/20	ND	ND	ND	ND
-Cryofibrinogen	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-Cold agglutinins	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-EBV serology	ND	ND	ND	ND	0/1	ND	0/20	ND	ND	0/1	0/8
-Parvovirus serology	ND	ND	ND	ND	0/1	ND	0/20	ND	ND	ND	0/8
-CMV serology	ND	ND	ND	ND	0/1	ND	ND	ND	ND	ND	0/8
-Coxsackie serology	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-HIV serology	ND	ND	ND	ND	0/1	ND	ND	ND	ND	ND	ND
-HCV serology	ND	ND	ND	ND	0/1	ND	ND	ND	ND	ND	ND
-HBV serology	ND	ND	ND	ND	0/1	ND	ND	ND	ND	ND	ND
-Liver laboratory testing abnormality	ND	ND	ND	ND	0/1	ND	0/20	ND	ND	0/1	ND
-Abnormal blood creatinin	ND	ND	ND	ND	0/1	ND	0/20	ND	ND	0/1	ND
-Rheumatoid factor	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
-APL antibodies	ND	ND	ND	ND	ND	ND		ND	ND	ND	
Lupus anticoagulant							0/20				0/8
Anti-B2GPI (IgG, IgM)							0/20				0/8
Anticardiolipin							0/20				0/8

References	Mahieu et al. ²³	El Hachem et al. ²⁴	Freeman et al. ²⁵	Docampo-Simon et al. ²⁶	Garcia-Lara et al. ²⁷	Colonna et al. ²⁸	Andina et al. ²⁹	Landa et al. ³⁰	Total	This study
Baseline characteristics										
-Number of patients	10	19	318	58	27	4	22	6	1240	30
-Mean age (range), years	27	14 (11-17)	25 (17-38)	14 (0,25-85)	14	8,25 (5-11)	12 (6-17)	35 (15-91)	19,2 (0,25-100)	31,1 (8-70)
-Sex ratio (male/female)	ND	2,8/1 (14/5)	163/155	29/29	18/9	1/3	(13/9)	3/3	601/629 (0;96)	14/16
-Personal autoimmune disease	ND	0/19	NA	ND	0/28	0/4	0/22	ND	18/578 (2,6%)	2/30
-Familial autoimmune disease	ND	ND	ND	ND	ND	ND	ND	ND	0/14 (0%)	2/30
-Other comorbidities	ND	0/19	41/319	6/58	ND	ND	5/22 (ADHD)	ND	92/592 (15,5%)	6/30
-Current smoker	ND	ND	ND	ND	ND	ND	ND	ND	8/102 (7,8%)	4/30
-Cold exposure	ND	ND	ND	ND	ND	ND	0/22	ND	0/44 (0%)	0/30
-Hospitalized patients	ND	0/19	6/318	ND	ND	0/4	0/22	1/6	14/526 (2,7%)	0/30
-Outpatients	ND	19/19	312/318	ND	ND	4/4	22/22	5/6	517/533 (97%)	30/30
-Drug intake	ND	ND	ND	ND	ND	NA	5/22 (meth.)	ND	12/96 (12,5%)	7/30
-History of chilblains	ND	0/19	ND	1/58	0/27	NA	0/22	ND	52/574 (9,1%)	1/30
-History of acrosyndrome	ND	0/19	ND	ND	0/27	NA	0/22	ND	44/465 (9,5%)	10/30
-BMI (kg/m2)	ND	ND	ND	ND	ND	NA	ND	ND	19,13	ND
Dermatological presentation										
-Macules	NA	18/19	NA	NA	NA	NA	NA	NA	45/60 (75%)	29/30
-Papules	NA	ND	NA	NA	NA	NA	NA	NA	72/101 (71,2%)	23/30
-Purpura	NA	13/19	NA	3/58	NA	NA	NA	NA	63/179 (35,2%)	10/30
-Vesicles	NA	ND	NA	3/58	NA	NA	NA	NA	4/59 (6,7%)	10/30
-Bullae	5/10	ND	NA	NA	NA	NA	NA	NA	34/322 (10,6%)	3/30
-Necrosis	NA	NA	NA	NA	NA	NA	NA	NA	0/6	6/30
-Digital swelling	NA	15/19	NA	NA	NA	NA	NA	NA	24/42 (57,1%)	ND
-Livedo	NA	ND	NA	ND	NA	NA	NA	NA	3/6	3/30
-Acrocyanosis	NA	ND	NA	ND	NA	NA	NA	0/6	1/7	12/30
-Involvement of feet	10/10	19/19	298/318	36/58	NA	2/3	22/22	6/6	907/1101 (82,3%)	25/30
-Involvement of hands	2/10	0/19	48/318	9/58	7/27	1/3	3/22	1/6	199/1126 (17,7%)	14/30
-Involvement of both feet and hands	2/10	0/19	28/318	13/58	21/27	1/3	3/22	1/6	139/1107 (12,6%)	10/30
-Involvement of limbs/head/trunk	NA	ND	NA	NA	1/27	NA	ND	0/6	1/129	1/30
-Mean duration of the skin symptoms	2-4 weeks	No resolution at the end of follow up (26-54 days of evolution)	ND	ND	14,6 days	5 days 19 days 27 days 20 days	3-5 weeks (marked improvement or almost complete resolution)	NA	18,3 days	9 weeks
-Associated symptoms										
Pruritus	"Slightly painful or pruriginous"	14/19	282/318		3/27	ND	9/22	2/6	243/630 (38,6%)	15/30
Burning		7/19	137/318	25/58	ND	ND	NA	NA	244/394 (61,9%)	12/30
Pain		2/19	211/218 (pain + burning)	ND	6/27	2/4	7/22	3/6	282/443 (63,7%)	12/30
5/19				22/58						
Infectious symptoms										
-Fever	2/8	6/19	144/318	11/58	1/27	4/4	10/22	4/6	381/921 (41,4%)	24/30
-Cough	NA	5/19	37/318	ND	NA	4/4	0/10	1/4	134/677 (19,8%)	8/30
-Rhinitis	NA	1/19	67/318	ND	NA	1/4	NA	NA	163/623 (26,2%)	14/30
-Dyspnea	NA	2/19	38/318	ND	NA	1/4	NA	2/4	56/403 (13,9%)	6/30
-Fatigue	NA	NA	29/318	ND	NA	NA	9/10	1/4	70/488 (14,3%)	7/30
-Myalgias	NA	NA	31/318	ND	NA	NA	NA	NA	94/515 (18,3%)	6/30
-GI symptoms (diarrhea, nausea, vomiting)	NA	NA	ND	ND	NA	NA	NA	NA	23/96 (24%)	3/30
-Headache	NA	2/19	ND	ND	1/1	NA	2/10	1/4	54/313 (17,3%)	3/30
-Anosmia/agueusia	NA	1/19	47/318	ND	NA	1/4	NA	1/4	80/439 (18,2%)	6/30
-Close contact with COVID-19 person	NA	NA	ND	ND	NA	NA	NA	NA	18/168 (10,7%)	3/30
Not proved	ND	9/19	68/318	19/58	7/27	4/4	13/22	1/6	179/699 (25,6%)	16/30
Proved		9/19	44/318	7/58	NA	4/4	12/22	1/6	100/546 (18,3%)	6/30
		ND	24/318	12/58	NA	0/4	1/22	0/6	44/508 (8,7%)	10/30
Mean time onset infectious symptoms and skin symptoms (range)	7 days (infectious before skin symptoms)	-1-2 months for 5 patients -1 week for 1 patient	19/318 : skin before 80/318 : skin after 22/318 : same time 21/319 : unknown	7 days (0-42 days)	-0 days for 1/1 patient with infectious symptoms	-weeks -4 days -10 days -10 days	14 days (1-28)	10-20 days	8,15 days	20,8 days

Treatment for skin											
-None	10/10	NA	ND	ND	27/27	4/4	NA	NA	88/127 (69,2%)	30/30	
-Hydroxychloroquine	ND	NA	ND	ND	NA	0/4	NA	1/6	7/102 (6,9%)	0/30	
-Dermocorticoids	ND	NA	ND	ND	NA	0/4	1/22	NA	10/49 (20,4%)	1/30	
-Other	ND	NA	ND	ND	NA	0/4	1/22	1/6	NA	1/30	
Histological features	3/10	18/19	7/318	ND	ND	1/4	6/22	ND	115/1240 (9,3%)	26/30	
-Spongiosis	NA	13/18	1/1	ND	ND	NA	NA	ND	29/44 (65,9%)	7/26	
-Necrotic keratinocytes	NA	4/18	1/1	ND	ND	NA	NA	ND	40/70 (57,1%)	7/26	
-Basal vacuolar changes	NA	14/18	2/2	ND	ND	NA	6/6	ND	59/97 (60,8%)	3/26	
-Thickening of the basement membrane	NA	ND	NA	ND	ND	NA	NA	ND	0/7	0/26	
-Parakeratosis	NA	ND	NA	ND	ND	NA	NA	ND	16/24	7/26	
-Papillary edema	NA	12/18	NA	ND	ND	NA	6/6	ND	45/62 (72,6%)	3/26	
-Superficial lymphocytic infiltrate	NA	18/18	2/2	ND	ND	NA	NA	ND	58/60 (96,7%)	26/26	
-Deep lymphocytic infiltrate	NA	18/18	2/2	ND	ND	NA	NA	ND	52/60 (86,7%)	18/26	
-Density of the lymphocytic infiltrate	NA		NA	ND	ND	NA	NA	ND			
Light		12/18							24/49 (49%)	5/26	
Moderate		6/18 (moderate + marked)							16/49 (32,7%)	16/26	
Marked									11/49 (22,4%)	5/26	
-Pattern of lymphocytic infiltrate	NA	NA		ND	ND			ND			
Perivascular			NA			1/1	6/6		67/70 (95,7%)	26/26	
Perieccrine			1/1			1/1	6/6		50/64 (78,1%)	14/26	
-Type of infiltrate	NA	NA	NA	ND	ND	lymphocytic	NA	ND	lymphocytic	lymphocytic	
-Nuclear dusting	NA	NA	NA	ND	ND	NA	NA	ND	1/1	15/26	
-Lichenoid infiltrate/interface dermatitis	NA	NA	NA	ND	ND	NA	NA	ND	3/3	3/26	
-Extravasation of erythrocytes	NA	15/18	NA	ND	ND	1/1	NA, "some"	ND	39/49 (79,6%)	16/26	
-Fibrin deposition	1/10	0/18	NA	ND	ND	NA	NA	ND	12/61 (19,7%)	11/26	
-Vascular ectasia	NA	NA	NA	ND	ND	NA	NA "some"	ND	5/9	5/26	
-Thickening of the vessel walls	NA	NA	NA	ND	ND	NA	NA	ND	2/11	2/26	
-Thrombi	NA	2/18	1/3	ND	ND	1/1	NA "some"	ND	17/78 (21,79%)	10/26	
-Endothelial cell swelling	NA	15/18	NA	ND	ND	1/1	NA	ND	37/48 (77,1%)	16/26	
-Mural lymphocytes	NA	2/18	NA	ND	ND	NA	NA	ND	11/27 (40,7%)	18/26	
-Perieccrine mucin deposition	NA	17/18	ND	ND	ND	NA	NA "some"	ND	29/42 (69%)	14/26	
-Deposits on direct immunofluorescence on skin lesions (type of deposits)	ND	-C3 : 9/11 granular vessels -IgM : 4/11 colloid -IgG : 2/11	ND	ND	ND	ND	ND	ND	31/47 + (66%) C3 : 22 IgG : 2 IgM : 8 IgA : 6 C5b9 + C1q : 1	4/6 C3 : 4 IgM : 1	
-Other features	-CD4+ and CD8+ infiltrate -1 patient had CD68+CD163+CD15-MPO+ cells	-3/18 "lymphocytic vasculitis" -TEM: endothelial alteration	-2 patients: "lymphocytic vasculitis"	-	-	-	- "evident signs of vasculitis"	- "some" hidradenitis, exocytosis	-	-	
Virological characteristics											
-Positive Sars-CoV-2 RT-PCR performed on nasopharyngeal swab	0/10	0/19	6/318	1/39	0/2	0/2	1/19	2/6 + 1/6 negative but bilateral pneumonia	26/719 (3,6%)	1/23	
-Positive Sars-CoV-2 RT-PCR performed on rectal swab	ND	ND	ND	ND	ND	ND	ND	ND	0/2	ND	
-Positive Sars-CoV-2 RT-PCR performed on skin lesions	0/4	0/3	ND	ND	ND	ND	ND	ND	0/33	0/2	
-Positive Sars-CoV-2 blood test serology	0/10 (IgG, IgA)	1/19 IgG+ 3/19 IgG dbt 6/19 IgA+	23/318 (IgM, IgG), 2 were PCR-IgM+	ND	0/9 (IgG, IgA, IgM)	ND	ND	ND	36/573 (6,3%)	4/30	

-Positive anti-Sars-CoV-2 salivary antibody testing	ND	3/19 IgA dbt ND	ND	ND	ND	ND	ND	ND	ND	ND	14/29
Blood testing data											
-Thrombopenia	NA	0/19	ND	ND	ND	0/3	0/10	ND	0/133	3/29	
-Anemia	NA	0/19	ND	ND	ND	0/2	0/10	ND	0/132	0/29	
-Neutropenia	NA	0/19	ND	ND	ND	0/2	0/10	ND	0/132	3/29	
-Lymphopenia	NA	0/19	ND	ND	ND	0/3	0/10	ND	0/163	3/29	
-Eosinopenia	NA	0/19	ND	ND	ND	0/2	0/10	ND	0/162	0/29	
-High C-reactive protein (> 5 mg/L)	NA	0/19	ND	ND	ND	0/2	ND	ND	0/91	1/29	
-High aPTT	ND	0/19	ND	ND	ND	NA	0/18	ND	0/46	1/29	
-D-dimer elevation (> 500 ng/mL)	ND	0/19	ND	ND	ND	1/2 (723)	1/16 (900)	ND	6/115 (5,2%)	2/28	
-Fibrinogen abnormality	ND	0/19	ND	ND	ND	0/2	0/18	ND	3/53 (low)	1/29	
-High LDH	ND	ND	ND	ND	ND	ND	0/4	ND	0/33	ND	
-Low PT	ND	0/19	ND	ND	ND	ND	0/18	ND	0/46	1/29	
-Positive antinuclear antibodies (>=1/160)	ND	0/19	ND	ND	ND	ND	ND	ND	3/76 + 5/NA	12/29	
-Positive native ADN antibodies	ND	0/19	ND	ND	ND	0/2	ND	ND	1/NA + 0/21	0/29	
-Complement abnormality	NA		ND	ND	ND	ND	ND	ND	0/53		
CH50		ND							ND	0/15	
C3		0/19							0/53	1/28	
C4		0/19							0/53	0/28	
-Antimyositis antibodies	ND	ND	ND	ND	ND	ND	ND	ND	ND	1/26	
-ANCA	ND	ND	ND	ND	ND	ND	ND	ND	0/20 + 1/NA	1/29	
-Cryoglobulin	NA	0/19	ND	ND	ND	ND	ND	ND	0/39	0/20	
-Cryofibrinogen	ND	ND	ND	ND	ND	ND	ND	ND	0/30	0/20	
-Cold agglutinins	ND	ND	ND	ND	ND	ND	ND	ND	0/34	0/22	
-EBV serology	ND	ND	ND	ND	ND	0/2	ND	ND	0/49	0/27	
-Parvovirus serology	ND	0/19	ND	ND	ND	0/2	ND	ND	0/123	0/27	
-CMV serology	ND	ND	ND	ND	ND	0/2	ND	ND	0/28	ND	
-Coxsackie serology	ND	ND	ND	ND	ND	ND	ND	ND	0/73	ND	
-HIV serology	NA	ND	ND	ND	ND	ND	ND	ND	NA	0/27	
-HCV serology	NA	ND	ND	ND	ND	ND	ND	ND	NA	0/26	
-HBV serology	NA	ND	ND	ND	ND	ND	ND	ND	NA	0/27	
-Liver laboratory testing abnormality	NA	0/19	ND	ND	ND	ND	0/4	ND	0/45	1/29	
-Abnormal blood creatinin	NA	0/19	ND	ND	ND	ND	ND	ND	0/41	0/29	
-Rheumatoid factor	ND	ND	ND	ND	ND	ND	ND	ND	NA	0/28	
-APL antibodies	NA		ND	ND	ND			ND		3/29	
Lupus anticoagulant		ND				0/2	0/1		0/31		
Anti-B2GPI (IgG, IgM)		0/19				ND	ND		0/47		
Anticardiolipin		0/19				0/1	ND				
									0/48 + 1/NA (low IgG)		

Abbreviations: ANCA: antineutrophil cytoplasm nuclear antibodies; APL: antiphospholipid; aPTT: activated Partial Thromboplastin Time; B2GPI: beta-2-glycoprotein-1; BMI: Body Mass Index; CD: cluster differentiation; CMV: Cytomegalovirus; dbt: doubtful; DIF: direct immunofluorescence; eo: eosinophils; EBV: Epstein-Barr Virus; GI: gastro-intestinal; HIV: Human Immunodeficiency Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; IHC: immunohistochemistry; ly: lymphocytes; MPO: myeloperoxidase; NA: not available; ND: not done; PT: Prothrombin Time; TEM: Transmission Electronic Microscopy.

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Table 2. Demographic and clinical features of the patients

Number of patients	30
Sex (male/female)	14/16 (87,5%)
Mean age (range, years)	31,1 (8-70)
Personal autoimmune disorder	2/30* (6,7%)
Familial autoimmune disorder	2/30 (6,7%)
History of chilblain	1/30 (3,3%)
History of acrosyndrome	10/30 (33,3%)
Drug intake	7/30* (23,3%)
Current smoker	4/30 (13,3%)
Infectious symptoms	24/30 (80%)
-Fever	8/30 (26,7%)
-Cough	14/30 (46,7%)
-Rhinitis	6/30 (20%)
-Fatigue	6/30 (20%)
-Myalgias	3/30 (10%)
-Diarrhea	4/30 (13,3%)
-Nausea, vomiting	3/30 (10%)
-Headache	6/30 (20%)
-Dyspnea	7/30 (23,3%)
-Anosmia, agueusia	3/30 (10%)
Semiology of skin lesions	
-Macules	29/30 (96,7%)
-Papules	23/30 (76,7%)
-Vesicles	10/30 (33,3%)
-Bullae	3/30 (10%)
-Crusts	7/30 (23,3%)
-Necrosis	6/30 (20%)
-Purpura	10/30 (33,3%)
-Livedo	3/30 (10%)
-Raynaud's phenomenon	7/30 (23,3%)
-Acrocyanosis	12/30 (40%)
Topography of skin lesions	
-Hands	14/30 (46,7%)
-Feet	25/30 (83,3%)
-Limbs	1/30 (3,3%)
Associated symptoms	24/30 (80%)
-Pruritus	15/30 (50%)
-Pain	13/30 (43,3%)
-Burning	12/30 (40%)

*Hashimoto disease (1), inflammatory bowel disease (1)

*isotretinoin (1), mirtazapine (1), amitryptiline (1), mesalazine-azathioprin-prednisolone (1), atenolol (1), desloratadine (1), levothyroxin (1)

Table 3. Histological characteristics on hematoxylin-eosin, Periodic-Acid Schiff and Alcian Blue sections.

Epidermal changes	
-Spongiosis	7/26 (26,9%)
-Necrotic keratinocytes	7/26 (26,9%)
-Basal vacuolar changes	3/26 (11,5%)
-Thickening of the basement membrane	0/26 (0%)
-Parakeratosis	7/26 (26,9%)
Papillary edema	3/26 (11,5%)
Lymphocytic infiltrate	
-Density	Light: 5/26 (19,2%) Moderate: 16/26 (61,5%) Marked: 5/26 (19,2%)
-Nuclar dusting	15/26 (57,7%)
-Lichenoid pattern	3/26 (11,5%)
-Perivascular, papillary dermis	26/26 (100%)
-Perivascular, reticular dermis	18/26 (69,2%)
-Perieccrine reinforcement	14/26 (53,8%)
Extravasation of erythrocytes	16/26 (61,5%)
Vessels	
-Fibrin deposition	11/26 (42,6%)
-Vascular ectasia	5/26 (19,2%)
-Thickening of the vessel walls	2/26 (7,7%)
-Thrombi	10/26 (38,5%)
-Endothelial cell swelling	16/26 (61,5%)
-Mural lymphocytes	18/26 (69,2%)
Mucin deposition pattern	
-Perieccrine	14/26 (53,8%)
-Dermal	2/26 (7,7%)

Table 4. Virological and immunological characteristics of the patients.

Positive RT-PCR SARS-CoV-2 (nasopharyngeal swab)	1/23 (4,3%)
Positive RT-PCR SARS-CoV-2 (skin lesions)	0/2 (0%)
Positive SARS-CoV-2 serology (number of cases)	
-IgG (ID-VET)	1/30 (3,3%)
-IgA (ID-VET)	0/28 (0%)
-IgT ⁺ (IMMY)	1/28 (3,6%)
-IgA (Euroimmun)	3/29 (10,3%)
Positive anti-SARS-CoV-2 antibodies in saliva (IgG, IgA, ID-VET)	14/29 (48,3%)
Mean blood interferon alpha score (range)	7,27 (0,8 – 39,2)
Positive anti-phospholipid antibodies (number)	3/29 (10,3%)
Anti-SARS-CoV immunohistochemistry*	21/26 (80,8%)

+IgT: IgG + IgA + IgM

*Presence of granular staining with anti-SARS-CoV antibody in the cytoplasm of endothelial cells or epithelial sweat gland cells

Table 5. Main SARS-CoV-2 serologies.

Only a portion of SARS-CoV-2 serologies is presented here. The others serologies performed and not mentioned here have only been studied with the IgG ID-VET test, and all show negative results. Refer to Table S1, which reports all the blood samples for SARS-CoV-2 serology for each patient, regardless of the test.

Cases	Sampling date	IgG (ID-VET)	IgA (ID-VET)	IgG + IgA + IgM (IMMY)	IgA (Euro Immun)
1	23/4/2020	-	-	-	-
	28/4/2020	-	-	-	-
2	28/4/2020	-	-	-	-
3	28/4/2020	-	-	-	-
	7/5/2020	-	-	-	-
	20/5/2020	-	-	-	-
4	17/4/2020	-	-	-	-
	7/5/2020	-	-	-	-
5	8/4/2020	-	-	-	+
	17/4/2020	-	-	-	-
	7/5/2020	-	-	-	-
6	8/4/2020	-	-	-	-
	17/4/2020	-	-	-	-
7	8/4/2020	-	-	-	-
	7/5/2020	-	-	-	-
8	9/4/2020	-	-	-	-
	30/4/2020	-	-	-	-
	7/5/2020	-	-	-	-
9	17/4/2020	-	-	-	-
10	9/4/2020	-	-	-	-
	21/4/2020	-	-	-	-
	20/5/2020	-	-	-	-
11	10/4/2020	+	-	+	dbt
	23/4/2020	-	-	+	ND
	7/5/2020	dbt	-	-	-
	25/5/2020	-	-	-	ND
12	15/4/2020	-	-	-	dbt
	7/5/2020	-	-	-	-
13	15/4/2020	-	-	-	-
	23/4/2020	-	-	-	+
14	14/5/2020	-	-	-	-
	23/4/2020	-	-	-	-
	13/5/2020	-	-	-	-
15	20/5/2020	-	-	-	-
16	17/4/2020	-	-	-	-
	13/5/2020	-	-	-	-
17	20/4/2020	-	-	-	-
	24/4/2020	-	-	-	-
18	17/4/2020	-	-	-	-
	13/5/2020	-	-	-	-
	28/5/2020	-	-	-	-
19	17/4/2020	-	-	-	-
	7/5/2020	-	-	-	-
20	16/4/2020	-	-	-	-
	13/5/2020	-	-	-	-
21	23/4/2020	-	-	-	-
	7/5/2020	-	-	-	-
	20/5/2020	-	-	-	-
22	24/4/2020	-	-	-	+
	6/5/2020	-	-	-	-
23	20/5/2020	-	-	-	-
24	28/4/2020	-	-	-	-
	15/5/2020	-	-	-	-
25	7/5/2020	-	-	-	-
26	7/5/2020	-	-	-	-
27	7/5/2020	-	-	-	dbt
28	20/5/2020	-	-	-	ND
29	12/6/2020	-	ND	ND	ND
30	22/7/2020	-	ND	ND	ND

ND: not done; +: positive result; -: negative result; dbt: doubtful

Table 6. Saliva results of IgG and IgA antibodies against SARS-CoV-2.

This table resumes the results of the search for IgG and IgA antibodies directed against SARS-CoV-2 in saliva, according to the date of the saliva sample. The samples were studied with the ID-VET test. The saliva was diluted to 1/4. The threshold for positive antibody detection signal was established from the mean of twelve saliva samples negative for SARS-CoV-2 + 2 standard derivations.

<i>Case number</i>	<i>Sampling date</i>	<i>Salivary IgG</i>	<i>Salivary IgA</i>
1	ND		
2	25/5/2020	-	-
	20/7/2020	ND	+
3	07/5/2020	-	+
4	08/6/2020	-	-
	29/7/2020	ND	-
5	08/6/2020	-	-
	29/7/2020	ND	-
6	25/5/2020	-	-
7	7/5/2020	-	+
	22/7/2020	ND	+
8	31/7/2020	ND	-
9	26/5/2020	-	+
	27/7/2020	ND	+
10	20/5/2020	-	-
	22/7/2020	ND	+
11	7/5/2020	-	-
12	7/5/2020	-	-
	23/7/2020	ND	-
13	13/5/2020	-	+
	20/7/2020	ND	-
14	13/5/2020	-	-
	28/7/2020	ND	-
15	15/7/2020	ND	+
16	13/5/2020	-	-
	27/7/2020	ND	-
17	15/7/2020	ND	+
18	13/5/2020	-	-
19	4/5/2020	-	+
20	13/5/2020	-	-
21	7/5/2020	-	-
	29/7/2020	ND	+
22	6/5/2020	-	-
	29/7/2020	ND	-
23	13/5/2020	-	-
	22/7/2020	ND	+
24	13/5/2020	-	-
	29/7/2020	ND	-
25	7/5/2020	-	-
	15/7/2020	ND	-
26	7/5/2020	-	-
27	7/5/2020	-	-
28	20/5/2020	-	+
	27/7/2020	ND	+
29	12/6/2020	ND	+
	21/7/2020	ND	+
30	22/7/2020	ND	+

+: positive result; -: negative result; ND: not done.

Table 7. Main abnormal biological data of the patients

Abnormal full blood count	6/29 (20,7%)
-Neutropenia	3/29 (10,3%)
-Lymphopenia	3/29 (10,3%)
-Thrombopenia	2/29 (6,9%)
Low prothrombin time	1/29 (3,4%)
Elevated activated partial prothrombin time	2/29 (6,9%)
Low fibrinogen in blood	1/29 (3,4%)
Elevated D-dimer (> 500 ng/mL)	2/28 (6,9%)
Elevated C-reactive protein (> 5 mg/L)	1/29 (3,4%)
Elevated blood creatinine (μmol/L)	0/29 (0%)
Elevated liver enzymes	1/29 (3,4%)
Abnormal serum protein electrophoresis	3/28 (10,7%)
Abnormal CH50	0/15 (0%)
Low C3	1/28 (3,6%)
Low C4	0/28 (0%)
Positive rheumatoid factor	0/28 (0%)
Positive antinuclear antibodies	12/29 (41,3%)
Positive anti-DNA antibodies	0/29 (0%)
Positive anti neutrophils cytoplasm antibodies	1/29 (3,4%)
Positive antimyositis antibodies	1/26 (3,8%)

Table 8. Antiphospholipid antibodies' detailed values.

Cases	Anti-B2GPI IgA (ratio*)	Anti-cardiolipin IgA (ratio*)	Anti-cardiolipin IgG (GPL/mL) N<15,00	Anti-PE IgG (U/mL) N<18,00	Anti-PE IgM (U/mL) N<59,00	Anti-PT IgG (ratio*)	Anti-PT IgM (ratio*)
1	0,07	0	1,95	8,60	40,87	0,53	0,28
2	0	0	13,99	14,78	45,31	0,13	0,25
3	0,06	0,18	4,44	5,12	44,01	0,53	0,21
4	0,03	0,18	14,45	17,52	41,44	1,20	0,26
5	0,11	0	5,01	5,15	44,26	0,13	0,21
6	0	0	1,55	2,83	42,04	0,32	0,15
7	0,06	0	2,6	3,06	41,48	0,06	0,74
8	0,09	0	0,43	1,85	44,47	0,11	0,13
9	0,09	0,00	5,43	9,96	41,86	0,15	0,19
10	0,21	0,00	4,36	7,47	42,36	0,49	0,23
11	0,21	0,00	5,15	7,27	44,68	0,21	0,10
12	0,06	0,00	3,10	2,20	41,83	0,09	0,72
13	0,00	0,11	7,18	6,40	42,30	0,09	0,21
14	0,17	0,00	7,11	5,09	39,47	0,15	0,58
15	0,00	0,05	9,19	8,71	44,81	0,17	0,11
16	0,03	0,00	2,46	1,85	46,02	0,11	0,06
17	0,07	0,00	8,84	8,32	45,69	0,23	0,06
18	0,11	0,00	10,41	6,23	44,01	0,09	0,13
19	0,23	0,00	3,12	5,69	43,73	0,15	0,15
20	0,09	0,00	4,69	7,47	42,33	0,34	0,30
21	0,14	0,11	8,86	3,54	41,08	0,32	0,17
22	0,24	0,00	3,86	4,65	43,65	0,26	0,15
23	0,04	0,07	10,42	17,41	45,54	0,17	0,21
24	1,10	0,07	1,91	11,43	46,02	0,28	0,06
25	0,24	0,00	0,00	14,98	44,17	0,21	0,46
26	0,08	0,14	0,56	1,79	40,89	0,08	0,47
27	0,16	0,33	15,09	16,45	43,89	0,10	0,33
28	0,30	0,64	3,07	10,91	9,62	0,13	0,29
29	ND	ND	ND	ND	ND	ND	ND
30	ND	ND	ND	ND	ND	ND	ND

B2GPI: beta-2-glycoprotein-1; N: normal value; ND: not done; PE: phosphatidylethanolamine; PT: prothrombin.

*Results are considered positive if ratio > 1.

Results written in red are considered positive.

Table S1. Temporality of clinical signs and biological testings.

Table showing the dates on which the various biological examinations were carried out for each patient, related to the temporality of the cutaneous and infectious clinical signs presented by each one.

-: absent; DIF: direct immunofluorescence; NA: not available; ND: not done; green: positive result; red: negative result; cAPL: lupus anticoagulant, anti beta-2 glycoprotein-1 IgM and IgG, anticardiolipin IgM and IgG; ncAPL: anticardiolipin IgA, anticardiolipin IgG, antiphosphatidyléthanolamine IgM and IgG, antiprothrombin IgM and IgG; cryo.: cryoglobulinemia; np: nasopharyngeal; Current: no healing of skin lesion on August 1st 2020.

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Onset infectious symptoms	NA	-	NA	16/3/20	16/3/20	-	02/20	14/3/20	27/3/20	26/3/20	20/3/20	28/3/20	01/20	17/3/20	NA	
Onset cutaneous symptoms	02/2020	3/4/20	3/4/20	1/4/20	30/3/20	24/3/20	24/3/20	3/4/20	27/3/20	4/4/20	7/4/20	5/4/20	15/3/20	2/4/20	NA	
Healing of skin signs	06/20	Current	06/20	04/20	04/20	06/20	End 04/20	05/20	05/20	05/20	05/20	05/20	07/20	05/20	ND	
Interferon score blood testing	28/4/20	6/4/20 25/5/20	6/4/20 28/4/20 20/5/20	30/4/20	30/4/20 28/5/20	9/4/20 21/4/20 25/4/20	8/4/20	9/4/20	9/4/20	9/4/20 21/4/20	14/4/20	15/4/20 3/6/20	15/4/20	14/4/20	20/5/20	
Interferon score skin testing	ND	ND	ND	ND	ND	21/4/20	ND	ND	ND	21/4/20	ND	ND	ND	ND	ND	
RT-PCR np testing	ND	16/4/20	6/4/20	8/4/20	8/4/20 17/6/20	8/4/20	8/4/20	9/4/20	9/4/20	9/4/20	30/3/20	15/4/20	14/4/20	ND	ND	
RT-PCR skin testing	ND	ND	ND	ND	ND	8/4/20	8/4/20	ND	ND	ND	ND	ND	ND	ND	ND	
SARS-CoV-2 serological testing	14/4/20 23/4/20 28/4/20 4/5/20 5/6/20	6/4/20 16/4/20 28/4/20 25/5/20 20/7/20	6/4/20 28/4/20 7/5/20 20/5/20	8/4/20 17/4/20 30/4/20 7/5/20 28/5/20 29/7/20	8/4/20 17/4/20 30/4/20 7/5/20 28/5/20 29/7/20	8/4/20 17/4/20 25/5/20	8/4/20 17/4/20 7/5/20 29/5/20 27/7/20	8/4/20 17/4/20 7/5/20 23/5/20 31/7/20	9/4/20 30/4/20 17/4/20 20/5/20 27/7/20	9/4/20 21/4/20 20/5/20 13/5/20 25/5/20	9/4/20 21/4/20 20/5/20 13/5/20 22/7/20	10/4/20 23/4/20 7/5/20 13/5/20 25/5/20	15/4/20 7/5/20 3/6/20 13/5/20 22/7/20	15/4/20 23/4/20 13/5/20 20/7/20	14/4/20 23/4/20 13/5/20 28/7/20	17/4/20 20/5/20 15/7/20
SARS-CoV-2 salivary testing	ND	25/5/20 20/7/20	7/5/20	28/5/20 29/7/20	28/5/20 29/7/20	25/5/20	7/5/20 27/7/20	31/7/20	26/5/20 27/7/20	20/5/20 22/7/20	7/5/20	7/5/20 23/7/20	13/5/20 20/7/20	13/5/20 28/7/20	15/7/20	
Hemostasis evaluation																
-Standard	19/2/20 28/4/20	16/4/20	6/4/20	17/4/20	8/4/20	8/4/20	8/4/20	9/4/20	9/4/20	9/4/20	10/4/20	15/4/20	14/4/20	14/4/20	NA	
-cAPL	19/2/20	16/4/20	6/4/20	8/4/20	8/4/20	8/4/20	8/4/20	23/4/20	9/4/20	11/6/20	10/4/20	15/4/20	14/4/20	14/4/20	NA	
-ncAPL	20/4/20	16/4/20	6/4/20	17/4/20	17/4/20	9/4/20	8/4/20	30/4/20	9/4/20	9/4/20	10/4/20	15/4/20	15/4/20	14/4/20	17/4/20	
-cryo.	28/4/20	29/5/20	8/4/20	ND	14/4/20	17/4/20	ND	30/4/20	17/4/20	11/6/20	7/5/20	ND	14/4/20	15/5/20	17/4/20	
Pathological skin performed	6/3/20	6/4/20	6/4/20	ND	ND	8/4/20	8/4/20 17/4/20 (DIF)	9/4/20	9/4/20	9/4/20	ND	15/4/20	15/4/20	15/4/20	NA	

Case number	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Onset infectious symptoms	3/4/20	-	13/4/20	20/3/20	01/20	13/3/20	30/3/20	13/3/20	12/19	28/2/20	27/2/20	28/2/20	03/20	-	06/20
Onset cutaneous symptoms	9/4/20	15/3/20	13/4/20	10/4/20	Early 03/20	24/3/20	30/3/20	Early 4/20	3/20	17/3/20	17/3/20	17/3/20	03/20	02/20	07/20
Healing of skin signs	05/20	Current	ND	05/20	Current	ND	Current	Current	06/20	06/20	ND	ND	ND	Current	Current
Interferon score blood testing	ND	20/4/20	17/4/20	17/4/20	16/4/20	16/4/20 20/5/20	6/5/20	28/4/20	28/4/20	7/5/20	7/5/20	7/5/20	ND	12/6/20	NA
Interferon score skin testing	ND	ND	ND	ND	ND	ND	ND	ND	28/4/20	ND	ND	ND	ND	ND	ND
RT-PCR np testing	17/4/20	20/4/20	20/4/20	17/4/20	16/4/20	16/4/20	ND	ND	22/4/20	7/5/20	7/5/20	7/5/20	20/5/20	ND	ND
RT-PCR skin testing	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
SARS-CoV-2 serological testing	17/4/20 23/4/20 13/5/20	20/4/20 24/4/20 15/7/20	17/4/20 13/5/20 28/5/20	17/4/20 4/5/20	16/4/20 13/5/20 28/5/20	16/4/20 23/4/20 7/5/20 20/5/20	24/4/20 6/5/20 22/5/20	28/4/20 20/5/20 22/7/20	28/4/20 13/5/20 29/7/20	7/5/20	7/5/20	7/5/20	20/5/20	12/6/20	22/7/20
SARS-CoV-2 salivary testing	13/5/20 28/7/20	15/7/20	13/5/20	4/5/20	13/5/20	7/5/20 29/7/20	6/5/20 29/7/20	13/5/20 22/7/20	13/5/20 29/7/20	7/5/20 15/7/20	7/5/20	7/5/20	20/5/20 27/7/20	12/6/20 21/7/20	22/7/20
Hemostasis evaluation															
-Standard	17/4/20	20/4/20	17/4/20	17/4/20	16/4/20	16/4/20	24/4/20	28/4/20	27/4/20 13/5/20	4/20	4/20	4/20	20/5/20	12/6/20	7/7/20
-cAPL	17/4/20	20/4/20	17/4/20	17/4/20	16/4/20	16/4/20	24/4/20	28/4/20	13/5/20	4/20	4/20	4/20	20/5/20	12/6/20	7/7/20
-ncAPL	17/4/20	20/4/20	17/4/20	17/4/20	16/4/20	16/4/20	24/4/20	28/4/20	13/5/20	7/5/20	7/5/20	7/5/20	20/5/20	12/6/20	22/7/20
-cryo.	ND	20/4/20	13/5/20	ND	28/5/20	ND	ND	ND	28/5/20	4/20	4/20	4/20	ND	12/6/20	ND
Pathological skin performed	17/4/20	20/4/20	17/4/20	17/4/20	16/4/20	16/4/20	7/5/20	28/4/20	28/4/20	4/20	4/20	4/20	20/5/20	15/6/20	ND

Table S2. Demographic and clinical characteristics of each patient in detail.

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Baseline data																														
Sex (M/F)	F	M	F	M	F	M	F	M	F	F	F	F	F	F	M	F	M	M	M	M	F	F	M	M	F	F	M	M	M	F
Age	13	14	23	8	43	25	45	16	27	62	32	13	30	30	14	48	64	18	28	46	18	31	18	70	48	18	16	15	14	38
Personal autoimmune disorder	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No
Familial autoimmune disorder	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
History of chilblain	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
History of acrosyndrome	No	No	No	No	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Yes	Yes	No	No	No	No	No	No	No
Drug intake	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	No	No	Yes	Yes	No
Current smoker	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No
Infectious symptoms																														
-Fever	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
-Cough	No	No	No	Yes	Yes	No	Yes	No	No	No	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No
-Rhinitis	No	No	No	No	No	No	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
-Dyspnea	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	Yes	Yes	No	No	Yes
-Fatigue	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No	No
-Myalgias	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
-Diarrhea	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No
-Vomiting	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No
-Headache	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No
-Anosmia, agueusia	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No
Semiology of skin lesions																														
-Macules	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
-Papules	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
-Vesicles	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No
-Bullae	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
-Crusts	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	No	No	No
-Necrosis	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	No
-Purpura	No	No	No	No	No	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No	No	No	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes
-Livedo	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No
-Raynaud's phenomenon	No	No	No	No	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No
-Acrocyanosis	No	Yes	No	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No
Topography of skin lesions																														
-Hands	No	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	No	No	No	No	No	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
-Feet	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
-Limbs	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No
Associated symptoms																														
-Pruritus	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No
-Pain	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
-Burning	No	No	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	No	No	No

M: male ; F: female

Table S3. Detailed histological features of the patients.

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Epidermal changes																														ND	
-Spongiosis	Yes	Yes	No	ND	ND	Yes	No	No	Yes	No	ND	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	ND	
-Necrotic keratinocytes	No	Yes	No	ND	ND	Yes	No	No	Yes	Yes	ND	No	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	ND	
-Basal vacuolar changes	No	No	No	ND	ND	No	Yes	No	Yes	No	ND	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	ND	
-Thickening of the basement membrane	No	No	No	ND	ND	No	No	No	No	No	ND	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	ND	
-Parakeratosis	No	Yes	No	ND	ND	Yes	Yes	No	Yes	No	ND	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	ND	
Papillary edema	Yes	No	No	ND	ND	No	No	No	No	No	ND	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	ND	
Lymphocytic infiltrate																															
-Mild	No	No	No	ND	ND	No	No	No	No	No	ND	No	No	No	No	Yes	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes	ND	
-Moderate	No	No	Yes	ND	ND	Yes	Yes	Yes	Yes	Yes	ND	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	ND	
-Marked	Yes	Yes	No	ND	ND	No	No	No	No	No	ND	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	ND	
-Perivascular, papillar dermis	Yes	Yes	Yes	ND	ND	Yes	Yes	Yes	Yes	Yes	ND	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	ND	
-Perivascular, reticular dermis	Yes	Yes	No	ND	ND	Yes	Yes	Yes	Yes	No	ND	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	No	ND	
-Periecrine reinforcement	No	Yes	Yes	ND	ND	Yes	No	No	Yes	No	ND	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes	NA	No	Yes	Yes	Yes	Yes	No	ND	
Nuclear dusting	Yes	Yes	Yes	ND	ND	No	No	No	No	Yes	ND	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	ND	
Lichenoid pattern	No	No	No	ND	ND	No	Yes	No	No	No	ND	No	No	Yes	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	ND		
Extravasation of erythrocytes	Yes	Yes	Yes	ND	ND	Yes	Yes	No	Yes	No	ND	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes	No	ND	
Fibrin deposition	No	Yes	Yes	ND	ND	No	No	Yes	Yes	No	ND	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes	No	No	ND	
Vascular ectasia	No	No	No	ND	ND	No	Yes	No	No	No	ND	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	Yes	No	No	Yes	No	ND	
Thickening of the vessel walls	No	No	No	ND	ND	No	Yes	No	No	No	ND	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	ND	
Thrombi	Yes	Yes	No	ND	ND	Yes	No	No	Yes	No	ND	Yes	Yes	No	NO	No	No	No	Yes	No	No	No	No	Yes	Yes	Yes	No	No	No	ND	
Endothelial cell swelling	Yes	Yes	No	ND	ND	Yes	No	Yes	No	Yes	ND	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	ND	
Mural lymphocytes	Yes	Yes	Yes	ND	ND	Yes	Yes	Yes	Yes	Yes	ND	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	ND	
Mucin deposition	Yes	No	No	ND	ND	Yes	Yes	No	Yes	Yes	ND	Yes	Yes	Yes	ND	No	Yes	Yes	No	No	Yes	Yes	No	Yes	ND	ND	ND	ND	Yes	Yes	ND
-Periadnexal	Yes	No	No	ND	ND	Yes	Yes	No	Yes	Yes	ND	Yes	Yes	Yes	ND	No	Yes	No	No	No	Yes	Yes	No	Yes	ND	ND	ND	ND	Yes	No	ND
-Dermal	No	No	No	ND	ND	No	No	No	No	Yes	ND	No	No	No	ND	No	No	No	No	No	No	No	No	No	No	ND	ND	ND	No	Yes	ND
Direct skin immunofluorescence	-	ND	ND	ND	ND	ND	-	ND	ND	+ (IgM, epidermis)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	+	+	+	+	ND	-	ND
																									(vascular C3)	(vascular C3)	(vascular C3)	(vascular C3)			

+: positive; -: negative; ND: not done.

Table S4. Virological and immunological features of the patients.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
RT-PCR SARS-CoV-2																														
-Nasopharyngeal	ND	-	-	-	-	-	-	-	-	-	+	-	-	ND	ND	-	-	-	-	-	-	ND	ND	-	-	-	-	-	ND	ND
-Skin lesion	ND	ND	ND	ND	ND	-	-	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
SARS-CoV-2 serology																														
IgG (ID-VET)	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
IgA (ID-VET)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	ND	ND	
IgT (IMMY)	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	ND	ND	
IgA (Euroimmun)	-	-	-	-	+	-	-	-	dbt	-	dbt	dbt	+	-	-	-	-	-	-	-	-	+	-	-	-	-	dbt	-	ND	ND
Salivary antibody (IgA, IgG, ID-VET)	ND	+	+	-	-	-	+	-	+	+	-	-	+	-	+	-	+	-	+	-	+	-	+	-	-	-	-	+	+	+
Interferon alpha score (blood)	3,4	2,7 - 0,9	13,5 - 24,9 - 32,9	1,4	2,6 - 3,1	39,2 -6,5 -2,5	5,8	1,1	3,9	24,1 -5,5	1,3	2,9 - 3,9	5,4	4,3	1,5	ND	1,6	2,4	1,4	9,2	3,5 - 1,6	2,2	3,8	27,7	2,1	0,8	1,8	ND	7,9	ND
Interferon alpha score (skin)																														
-Lesional skin	ND	ND	ND	ND	ND	0,7	ND	ND	ND	1,5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0,6	ND	ND	ND	ND	ND
-Non lesional skin						0,4				1,7															18		ND	ND	ND	ND
Elispot Anti-SARS-CoV	ND	-	-	ND	ND	ND	ND	ND	ND	ND	ND	ND	-	ND	-	-	-	ND	ND	ND	ND	ND	ND	ND	ND	-	ND	ND	ND	ND
IHC	+	-	-	ND	ND	+	+	-	+	+	ND	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	ND
Hemostasis evaluation																														
Anti-cardiolipin Ab IgG and IgM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-
Anti-cardiolipin Ab IgA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-B2GP1 Ab IgG and IgM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-B2GP1 Ab IgA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Lupus anticoagulant	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-PE Ab IgG and IgM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-prothrombin Ab	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

IHC: immunohistochemistry; B2GP1: beta-2-glycoprotein-1; PE: phosphatidylethanolamine; Ab: antibody; dbt: doubtful; IgT: IgG+IgA+IgM; ND: not done; +: positive; -: negative

Table S5. Haematological and immunological data of the patients.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Full blood count	N	N	N	N	N	ly: 0,87 G/L neu: 1,95 G/L	N	N	N	N	N	N	N	N	NA	N	N	pl: 138 G/L	N	ly: 0,88 G/L	N	N	N	neu: 0,7 G/L pl: 144 G/L	N	N	N	neu: 1,36 G/L	N	ly: 0,72 G/L	
Prothrombin time (per cent)	90	76	90	84	100	85	95	84	100	109	100	87	ND	100	NA	100	100	96	95	100	95	81	100	100	106	96	82	91	100	91	
Activated cephalin time (ratio)	1,13	1,02	1,03	1,08	1,02	1,33	1,13	1	1,06	0,9	1,16	1,08	ND	1,13	NA	0,89	0,98	1,06	0,88	1,02	1,09	0,91	1,1	1,06	1	1,07	1	1,38	1,08	1,15	
Fibrinogen (g/L)	2,2	2	2	2,2	3	3,1	3,4	1,9	2,5	2,9	2,1	2,9	ND	2,3	NA	3,2	3,7	2	2,3	3,6	2,3	2,2	2,7	3,5	3,1	3,7	2,9	2,4	3,2	2,7	
D-dimer (ng/mL)	<200	516	<200	272	408	462	<200	<200	297	309	318	365	ND	344	NA	2119	263	<200	<200	215	286	399	ND	<200	351	184	89	445	ND	254	
C-reactive protein (mg/L)	<0,3	<0,3	<0,3	<0,3	<0,3	1,5	0,5	<0,3	1,3	<0,3	0,8	0,7	ND	<0,3	NA	0,4	1,8	<0,3	0,4	0,4	<0,3	<0,3	1,3	6,6	<4	<4	<4	<0,3	0,3	<0,3	
Blood creatinine (µmol/L)	63	75	63	27	55	74	54	71	56	55	59	55	50	75	NA	79	71	84	92	64	69	47	74	65	60	67	76	80	81	62	
Liver enzymes	N	N	N	N	N	N	N	N	N	N	N	N	N	N	NA	N	N	N	N	A (1)	N	N	N	N	N	N	N	N	N	N	N
Serum protein electrophoresis	A	N	N	N	N	N	N	A	N	N	N	N	N	N	NA	N	N	N	N	A (1)	N	N	N	N	N	N	N	N	N	N	ND
CH50 activity (range: 41,68-95,06 U/mL)	ND	59,17	52	ND	ND	65,87	62,15	ND	ND	ND	ND	79,14	NA	71,7	NA	ND	ND	58,47	59,8	80,59	70,96	57,84	ND	ND	50	43	35	60,65	ND	64	
C3 (range: 0,74-1,44 g/L)	ND	1,03	0,82	0,91	0,95	0,93	0,62	0,89	1,02	0,8	0,95	1,36	0,93	0,96	NA	0,88	1,31	1,09	1,29	1,28	0,78	0,91	1,04	1,25	0,82	1,02	1,1	1,1	1,27	1	
C4 (range: 0,13- 0,31 g/L)	ND	0,15	0,18	0,2	0,2	0,24	0,13	0,17	0,18	0,24	0,22	0,19	0,18	0,22	NA	0,22	0,3	0,18	0,26	0,2	0,23	0,21	0,24	0,25	0,18	0,21	0,13	0,22	0,34	0,26	
Rheumatoid factor	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Antinuclear antibodies	1/100 1/640	-	-	-	1/160	-	1/160	-	-	1/160	-	-	-	1/1280	NA	-	-	1/160	-	1/320 (1)	-	1/160	1/1280	1/160	1/80	-	-	-	-	-	1/160
Anti-DNA antibodies	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Antineutrophils cytoplasm antibodies	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Cold agglutinins	-	-	ND	-	-	-	-	-	-	-	-	ND	-	-	-	-	ND	-	-	ND	-	ND	-	ND	-	-	-	ND	-	ND	
DOT myositis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	ND	ND	ND	-	-	-
Virus serologies	-	-	ND	-	-	-	-	-	-	-	-	-	-	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-HIV	-	-	ND	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-HCV	-	-	ND	I	I	-	I	I	-	I	I	-	ND	I	I	I	-	I	I	-	I	-	I	-	I	I	I	-	ND	-	I
-HBV	I	-	I	-	I	-	-	I	I	I	I	ND	ND	I	I	I	-	-	I	I	-	-	-	I	I	-	-	-	-	-	-
-B19	ND	I	I	I	I	-	I	-	-	I	I	ND	I	I	I	I	I	I	I	I	-	I	-	I	I	I	I	I	-	I	I
-EBV	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: negative, absent; +: positive, present; I: immunized; N: normal result; A: abnormal result; ND: not done; NA: not available; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; B19: parvovirus B19; EBV: Epstein-Barr Virus; ly: lymphocytes; neu: neutrophils; pl: platelets
(1) these abnormal results were known, related to a sclerosing cholangitis.

Commentaire

Cette thèse de médecine est celle de l'étude de trente patients présentant des lésions cutanées vasculaires acrales développées au cours de la pandémie de Covid-19, inclus successivement entre avril et juillet 2020 par une équipe avertie de l'histoire naturelle des engelures et des interféronopathies de type I, pour les avoir antérieurement étudiées.

Ce suivi prospectif inédit permet de mettre en exergue une durée d'évolution des symptômes prolongée de plusieurs semaines à mois. Des études statistiques appropriées sont nécessaires pour comparer les caractéristiques détaillées dans ce travail purement descriptif à celles rapportées dans la littérature. Le temps d'écriture de ce travail et la période de réalisation de l'étude sont insuffisamment distanciés pour que des biais incidents ne se réfractent pas dans le prisme de la discussion.

La mise en évidence de particules virales en immunohistochimie avec l'anticorps utilisé nécessite des explorations complémentaires avant de considérer cette méthode comme fiable. En effet, même si la qualité du marquage et la localisation au sein des cellules endothéliales sont cohérentes avec la distribution des récepteurs à l'angiotensine qu'utilise le virus pour infecter les cellules pour arguer en faveur de leur présence dans la peau, deux autres études ont rapporté des résultats discordants avec des anticorps différents. De plus, le marquage est faible, malgré l'optimisation de la technique. La mise en évidence de copies du virus à l'amplification par PCR réalisée sur les lésions cutanées chez les deux patients de l'étude montrant par ailleurs un marquage en immunohistochimie avec l'anticorps dirigé contre le SARS-CoV aurait pu corroborer ce marquage, mais la probable faible quantité de matériel génétique viral au niveau cutané et la méthode de prélèvement utilisée sont les deux écueils ayant rendu cette détection impossible. Davantage de témoins externes positifs et négatifs, voire une étude dédiée sont nécessaires pour évaluer sa reproductibilité.

La pertinence clinique de la présence d'anticorps anti-phospholipides n'a pas été étudiée, afin notamment d'étayer le rationnel d'un traitement anticoagulant ou par antipaludéen de synthèse. L'absence de recherche systématique de signe clinique ou d'imagerie en faveur d'une thrombose de vaisseaux dans les cas décrits ne permet pas d'établir l'existence d'un syndrome des antiphospholipides sur le plan clinique, et l'absence de contrôle des anticorps au cours du suivi pour les patients ayant des valeurs au-dessus du seuil de positivité non plus sur le plan biologique. La recherche

de leur présence est en revanche intéressante à considérer sous l'angle de l'auto-immunité déclenchée par l'infection virale et doit être précisée, comme l'ont souligné d'autres travaux.

Néanmoins, ce travail apporte des arguments en faveur d'un lien entre les lésions cutanées vasculaires acrales et l'infection à SARS-CoV-2 par des données originales : détection d'anticorps salivaires dirigés contre le SARS-CoV-2 au cours du temps chez certains sujets sur deux prélèvements, présence d'une signature interféron chez la majorité des sujets, proposition d'une atteinte vasculaire histologique de l'endothélium congruente avec les mécanismes d'infection du virus. Notamment, il prouve par l'utilisation d'un test validé la présence d'une signature interféron avec une cinétique concordante avec une infection virale en cours et en l'absence de contexte d'interféronopathie de type I, ainsi que le changement du profil d'anticorps au cours du temps pour les patients ayant bénéficié d'un second prélèvement dans une série ayant minimisé le biais d'attrition. Cette démonstration de l'ambiance interféron est renforcée par la présence de cellules positives avec l'anticorps anti-CD123 dans les biopsies cutanées des lésions, et d'un différentiel de score interféron entre la peau saine et la peau lésée chez un patient. Tous ces résultats rendent improbable l'absence de lien affirmé par certains auteurs entre SARS-CoV-2 et lésions cutanées acrales, ou même que ces lésions sont secondaires aux mesures de confinement. Cependant, le faible effectif de la série, son caractère monocentrique, les biais de recrutement incitent à confirmer ce lien avec d'autres études plus larges, notamment avec des groupes témoins de patients ayant présenté des engelures idiopathiques ou s'intégrant dans le cadre d'une interféronopathie avant 2019.

Dans ces études ultérieures, il serait opportun d'étudier les anomalies qui ont été mises en évidence ici, telles que la présence d'anticorps antinucléaires. Par analogie au lupus ou aux interféronopathies de type I, les mécanismes de cette auto-immunité doivent être précisés, de même que leur relation temporelle avec l'infection virale par le SARS-CoV-2 : transitoire et sans signification clinique, ou alors persistante et potentiellement substratum du développement de maladies auto-immunes. Le second axe important à étudier est celui du complément, du fait des hypothèses suggérées dans les articles cités et publiés au cours de la réalisation de cette thèse, et de la présence de dépôts de la fraction C3 dans les parois des capillaires du derme, pouvant constituer un signe histopathologique distinctif entre engelures idiopathiques et lésions vasculaires cutanées acrales au cours de l'infection par le SARS-CoV-2.

Serment

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.

Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

Résumé

Contexte

La pandémie due au Covid-19 a donné lieu à la description de manifestations cutanées disparates survenant pendant la phase aiguë de l'infection. Des lésions vasculaires acrales stéréotypées ont été rapportées dans un même cadre temporel et plusieurs cadres spatiaux, faisant d'elles de nouveaux symptômes suspects d'être en lien avec le virus.

Objectif

Cette étude avait pour objectif de décrire les caractéristiques cliniques et histologiques des manifestations cutanées acrales survenues au cours de la pandémie mondiale de Covid-19, d'argumenter leur lien avec le SARS-CoV-2, en se basant sur des données immunologiques et virologiques.

Matériel et méthodes

Après avoir reçu un consentement éclairé, les patients ont été soumis à : (i) une évaluation clinique, (ii) des tests virologiques pour le SARS-CoV-2, (iii) l'évaluation biologique d'anomalies de la coagulation, de maladies auto-immunes, et la recherche d'une signature interféron, (iv) un prélèvement biopsique cutané pour étude anatomopathologique et dans des cas sélectionnés, une immunofluorescence directe et la recherche d'une signature interféron.

Résultats

Trente patients ont été inclus. Deux types de manifestations cutanées ont été identifiées : des lésions vasculaires paroxystiques, et des lésions permanentes. Les caractéristiques anatomopathologiques évoquaient l'aspect d'engelures idiopathiques, mais avec des atteintes vasculaires inhabituelles. Le score interféron sanguin était augmenté, parfois de manière très importante, chez la majorité des patients, suggérant un processus viral en cours. Alors que les sérologies pour le SARS-CoV-2 étaient souvent négatives, des anticorps dirigés contre le virus étaient détectés dans la salive chez la moitié des patients.

Conclusion

Plusieurs arguments convergent vers un lien entre les lésions vasculaires acrales observées au cours de la pandémie à Covid-19 et le SARS-CoV-2, mais d'autres études doivent le confirmer.

Mots-clés : SARS-CoV-2 ; Covid-19 ; vasculopathie ; lésions cutanées acrales ; engelures