Lessons from dermatology about inflammatory responses in Covid-19

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Summary  
The SARS-Cov-2 is a single-stranded RNA virus composed of 16 non-structural proteins (NSP 1-16) with specific roles in the replication of coronaviruses. NSP3 has the property to block host innate immune response and to promote cytokine expression. NSP5 can inhibit interferon (IFN) signalling and NSP16 prevents MAD5 recognition, depressing the innate immunity. Dendritic cells, monocytes, and macrophages are the first cell lineage against viruses’ infections. The IFN type I is the danger signal for the human body during this clinical setting. Protective immune responses to viral infection are initiated by innate immune sensors that survey extracellular and intracellular space for foreign nucleic acids. In Covid-19 the pathogenesis is not yet fully understood, but viral and host factors seem to play a key role. Important points in severe Covid-19 are characterized by an upregulated innate immune response, hypercoagulopathy state, pulmonary tissue damage, neurological and/or gastrointestinal tract involvement, and fatal outcome in severe cases of macrophage activation syndrome, which produce a ‘cytokine storm’. These systemic conditions share polymorphous cutaneous lesions where innate immune system is involved in the histopathological findings with acute respiratory distress syndrome, hypercoagulability, hyperferritinaemia, increased serum levels of D-dimer, lactic dehydrogenase, reactive-C-protein and serum A amyloid. It is described that several polymorphous cutaneous...
lesions similar to erythema pernio, urticarial rashes, diffuse or disseminated erythema, livedo racemosa, blue toe syndrome, retiform purpura, vesicles lesions, and purpuric exanthema or exanthema with clinical aspects of symmetrical drug-related intertriginous and flexural exanthema. This review describes the complexity of Covid-19, its pathophysiological and clinical aspects.

KEYWORDS
Covid-19, innate immunity, lipoprotein a, livedoid vasculitis, SARS-CoV-2, skin

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new worldwide public health crisis, that rapidly spread from its origin in Wuhan City of Hubei Province of China, on December 2019 to the rest of the world. At the time of writing, 13 May 2020, the Coronavirus Resource Center of Johns Hopkins University (United States) reported 4 327 288 coronavirus disease 2019 (Covid-19) cases around the world, with deaths, in 188 countries/regions.

Up to now, cutaneous manifestations of Covid-19 reports published in periodicals indexed in PubMed using the terms ‘cutaneous’ or ‘skin’ refer to economic impact, protective measures for the integumentary system during Covid-19 exposure, dermatological medical education and care during this pandemic disease, the use of immunomodulators, immunosuppressors and immunobiological agents in dermatology in rheumatology skin conditions, and skin damage among healthcare workers during the pandemic.

WHAT WAS REPORTED ABOUT CUTANEOUS LESIONS IN COVID-19 PATIENTS UP TO NOW?

Some authors described cutaneous lesions under distinct dermatological terms: (a) erythematous rash, widespread urticaria, chickenpox-vesicles; (b) ‘mottling’; (c) pneumonia with urticaria and pneumonia with AD, and (d) acro-ischemia on finger/toe with cyanosis, and dry gangrene in seven patients, four of them diagnosed as disseminated intravascular coagulation (DIC), besides other two reports, in China and Italy resembling acral characteristics of DIC, and severe perniosis (acute across-ischemia in the child), respectively.

Probably due to the lack of adequate personal protective equipment (PPE) for frontline health care workers, dermatologists have not registered adequately the cutaneous findings in Covid-19 patients.

Viral infections can produce specific clinical and non-specific manifestations, due to the direct action in infected cells or as a phenomenon of immune system hyperactivity. Since some of the associations are considered to be causal, it is instructive to consider by specific cases what evidence is generally accepted to establish a causal relation and which factors may be dispensable.

We would like to highlight some interesting aspects of SARS-CoV-2 infections for allergists and dermatologists and their possible relation with the skin:

1 The SARS-CoV-2 is composed of 16 non-structural proteins (NSP 1-16) with specific roles in the replication of coronaviruses (CoVs). NSP3 prevents host innate immune response and promotes cytokine expression, NSP5 can inhibit interferon (IFN) signalling and NSP16 prevents MDA5 recognition, depressing innate immunity. Four proteins are structural and essential for viral assembly and infection: homotrimers of S proteins (spikes on the viral surface), M protein (three transmembrane domains), E protein (involved in viral pathogenesis) and N protein.

2 Aerosolized uptake of SARS-CoV-2 leads to infection of target cells expressing angiotensin-converting enzyme (ACE) type II (ACE2) such as alveolar type 2 (that produce lung surfactant) or other unknown target cells.

3 Dendritic cells, monocytes, and macrophages are the first line cell lineage against viral infections. Antiviral proteins that are at the front lines of immune defence are the main targets of virus-encoded antagonists. Protein suppressors, or others involved in up-regulation of the innate response, restore the antiviral response and provide an advantage to the host immune defence against a specific viral infection.

4 Immunopathogenesis is associated with an uncontrolled immune response, which may result in pulmonary tissue damage, functional impairment and reduced lung capacity. Chemotactic factors are essential to the immune responses in viral infections and spectral changes in such factors may lead to severely maladjusted immune responses, increased viral replication and tissue damage. In a subset of patients, the disease can progress to pneumonia, respiratory failure and death related to an extreme rise in inflammatory cytokines including interleukin (IL)2, IL6, IL7, IL10, GCSF, IP10, MCP1, MIPI A and TNFα. The increase in pro-inflammatory cytokines is associated with severe pneumonia and it can have deleterious effects on the adaptive immune system. In a subset of patients, overactive immune responses may induce immunopathological conditions, termed cytokine storm, and in some individuals, may proceed to macrophage activation syndrome (MAS), often causing a fatal outcome.
Hammining et al identified in 2004 the metallopeptidase named angiotensin-converting enzyme 2 (ACE2) as the functional receptor for SARS-CoV responsible for an epidemic outbreak during 2003-2004. Using IHC methods, these authors demonstrated that the most remarkable finding was the surface expression of ACE2 protein in pneumocytes, macrophages and enterocytes of the small intestine. Furthermore, ACE2 was present in arterial and venous endothelial cells and arterial smooth muscle cells in all organs studied, including the skin on the basal layer of the epidermis, endothelial cells in the dermis and eccrine adnexal tissue.

Soler et al studied ACE2 and ACE in acute and chronic rejection after human heart transplant and found both expressions in endothelial and inflammatory cells. Angiotensin-converting enzyme (ACE)-2 is homologous to ACE. In addition, ACE2 protein levels are increased in failing human hearts, suggesting an important role in the negative modulation of the renin-angiotensin system (RAS), leading to the generation and degradation of angiotensin peptides after cardiac damage.

A transmembrane protease, serine 2 (TMPRSS2), a type II transmembrane serine protease (TTPS), plays a critical role in SARS and MERS coronavirus (COV) indicating that it could be a novel antiviral strategy to treat coronavirus and some low pathogenic influenza virus infections. SARS-COV-2 and SARS-COV bind to ACE2 by the protein s (spike) and allow virus to enter and infect cells. In order for the virus to complete entry into the cell, the spike protein has to be primed by TMPRSS2 to complete this process. In order to attach virus receptor (SPIKE) to host cellular ligand (ACE2), activation by TMPRSS2 as a protease is needed. TMPRSS2 gene is located on human chromosome 21, and a significant feature of the TMPRSS2 gene is that several androgen receptor elements (ARES) are located up-stream of the transcription start site and the first intron.

Lukassen et al investigated ACE2 and TMPRSS2 expression levels and their distribution across cell types in lung tissue and in cells derived from subsegmental bronchial branches by single nuclei and single-cell RNA sequencing, respectively. TMPRSS2 is expressed in both tissues, in the subsegmental bronchial branches and ACE2 is predominantly expressed in a transient secretory cell type. Interestingly, these transiently differentiating cells show enrichment for pathways related to RHO GTPase function and viral processes suggesting increased vulnerability for SARS-CoV-2 infection.

Cleavage of the SARS-CoV S protein (SARS-S) by host cell proteases is essential for viral infectivity, and the responsible enzymes constitute potential targets for intervention. The SARS-CoV can hijack two cellular proteolytic systems to ensure adequate processing of its S protein. Cleavage of SARS-S can be facilitated by cathepsin L, a pH-dependent endo-/lysosomal host cell protease, upon uptake of virions into target cell endosomes. Alternatively, TMPRSS2 and human airway trypsin-like protease (HAT) can activate SARS-S, presumably by cleavage of SARS-S at or close to the cell surface, and activation of SARS-S by TMPRSS2 allows for cathepsin L-independent cellular entry. Both TMPRSS2 and HAT are expressed in ACE2-positive cells in the human lung and results obtained with surrogate cell culture systems suggest that TMPRSS2 might play a significant role in SARS-CoV spread in the human respiratory tract via two independent mechanisms: ACE2 cleavage by these proteases increases entry efficiency, while SARS-S cleavage by TMPRSS2 activates the S protein for cathepsin L-independent host cell entry. Meanwhile, HAT and TMPRSS2 are known to cleave the glycoprotein haemagglutinin (HA) of influenza A viruses, a prerequisite for fusion between viral and host cell membranes and viral cell entry.

Hoffmann et al suggested that the serine protease inhibitor Camostat mesylate, which blocks TMPRSS2 activity, has been approved in Japan for human use, but for an unrelated indication. This compound or related ones with potentially increased antiviral activity could thus be considered for controlled clinical trials of treatment for SARS-CoV-2-infected patients.

Interestingly, in lung cancer cell line, A549, and prostate cancer cell line, LnCap, TMPRSS2 exhibits an androgen-dependent pattern and activates protease-activated receptor 2 (PAR2), causing the upregulation of matrix metalloproteinase-2 (MMP-2) and MMP-9, both of which play key roles in the metastatic tumour cells.

SARS-CoV may enter human cells via two distinct pathways, dependent on the availability of human cell proteases required for virus activation. The first pathway is processed if no SARS-S-activating proteases are expressed on the cell membrane. Upon binding of the virus envelope protein S to ACE2, viruses are taken up into endosomes (phagosomes), and in a second step SARS-S is cleaved and activated by pH-dependent cysteine protease cathepsin L (acid pH is necessary). The second pathway of activation can be pursued if the SARS-S activating protease TMPRSS2 is co-expressed with ACE2 on human membrane cells. Binding to ACE2 and processing by TMPRSS2 are recognized to allow fusion at the human cell surface or upon uptake into cellular vesicles, but before transport of viruses into host cell endosomes.

Angiotensin II (Ang II) is the major biologically active molecule of the RAS, which is involved in the homeostasis of blood pressure through its effects on water and electrolyte balance, as well as peripheral vascular resistance. Ang II is produced from Ang I. When bound to the angiotensin type 1 receptor (AT1R) on the vasculature, Ang II initiates vasoconstriction, whereas it elicits nitric oxide (NO)-mediated vasodilation via binding to the endothelium-located AT2R (cardioprotective effects). Alternatively, cleavage of Ang II by ACE2 produces the heptapeptide angiotensin 1-7 (Ang 1-7), which binds to the MAS receptor (MASR) and initiates downstream vasodilator activity that can counteract the hypertensive effects of AT1R signaling. Ang 1-7, therefore, possesses cardioprotective properties through effects that can prevent and/or reverse heart failure and blunt hypertensive cardiac remodeling.

In addition to the systemic RAS, local RAS has been found in many tissues, including the heart, which functions both independently and in correlation with systemic RAS components. Importantly, in...
the heart, there is an alternate pathway for Ang II synthesis by the endopeptidase chymase, a serine protease that is predominantly found in mast cells located within the tissue interstitium. Mast cells contain granules disposed into cytoplasm with cytokines (TNFα and VEGF) and proteases (including chymase, tryptase, carboxypeptidase) that are released during the inflammatory process, via a classically mediated ligand-dependent pathway. Chymase acts in the same manner as ACE but with a 20-fold higher catalytic activity for the conversion of Ang I to Ang II. In this context, chymase is believed to serve as a major Ang II-forming enzyme in the human heart and is reported to be involved in many pathological processes, such as hypertension, atherosclerosis, vascular proliferation, development of cardiomyopathies, myocardial infarction and heart failure, as well as cardiac fibrosis.

During Covid-19, by the end of the first week, the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines. The median time from onset of symptoms to dyspnea is 5 days, hospitalization 7 days and acute respiratory distress syndrome (ARDS) 8 days. Intensive care admission was needed in 25% to 30% of affected patients in published series. Considering current knowledge, the SARS-CoV-2 may bind to ACE2 in human cell membranes and these receptors are internalized into the human cytoplasm, forming a phagosome. This exposes the ACE/Ang II/ATR1/ROS signalling pattern so contributing to amplification of acute and chronic inflammation, fibrogenesis and cellular proliferation.

However, up to now, the research medical literature was unable to find ACE2 receptor expression in cutaneous mast cells in patients affected by SARS-CoV-2 infections. At the present time, we know that ACE2 is abundantly present in humans in the epithelia of the lung and small intestine, which might provide possible routes of entry for the SARS-CoV. This epithelial expression, together with the presence of ACE2 in vascular endothelium, probably provides a large field of SARS-CoV-2 infection in the skin, and reactive manifestations due to cytokine-induced expression, in some infected patients. Urticarial eruptions, livedo-like lesions, exanthems and vascular lesions, as purpura or true vasculitis, may be found among patients infected by SARS-CoV-2. They may represent manifestations of secondary epiphenomena as many paraviral exanthems, or by direct involvement of innate and/or adaptive human immunity that involves endothelial cells, macrophages, neutrophils or mast cells causing vasodilatation, vascular leakage or procoagulant effects in cutaneous and/or systemic microcirculation.

3 INNATE AND ADAPTATIVE IMMUNE RESPONSE TO VIRAL INFECTIONS

Interferons (IFN) contribute significantly to the host response to virus infections, and impaired interferon production from mononuclear cells has been associated both to asthma and allergic sensitization. Inadequate production of IFN-α1 by airway mononuclear cells has been linked to more severe human rhinovirus (HRV)-induced illness and obstructive patterns on lung function testing in allergic asthmatics compared with non-allergic controls. Moreover, plasmacytoid dendritic cell (pDCs) from allergic patients produce lesser IFN-α upon toll-like receptor (TLR)-9 intracytoplasmic stimulation, as observed during influenza virus infection where pDCs from asthmatic patients produced less IFN-α. In the skin, 20% to 40% of mast cells are in close contact with macrophages in a conformation known as ‘baseball glove and ball’, as an immune sentinel in the dermis (Figure 1).

Diffuse alveolar damage (DAD) is a histological pattern characterized by hyaline membranes, intra-alveolar edema, alveolar epithelial cell injury and neutrophilic inflammation. DAD is a pathological pattern that can occur as a consequence of distinct forms of lung insult, such as bacterial and viral infections, connective tissue diseases and sepsis, and others. Neutrophils and macrophages are the main drivers in the physiopathology of DAD, besides other cells from the innate and adaptive human immune system, such as dendritic cells, lymphocytes and mast cells.

Buttignol et al retrospectively studied lung tissue from 44 autopsies from patients with clinical diagnosis of acute respiratory distress syndrome (ARDS):15 due to H1N1 infection, 13 ARDS due to non-viral infection causes of death and other 16 patients with ARDS due to non-pulmonary cause of death among non-smokers and non-ventilated patients and without previous lung disease (controls). The main finding was that DAD due to influenza A (H1N1) pdm09 virus infection was associated with an inflammatory phenotype different from non-viral causes of DAD, with partially divergent responses in the lung parenchyma relative to the airways. Both DAD groups presented higher alveolar and airway densities of neutrophils and macrophages. However, there was a significantly higher expression of

FIGURE 1 Mast cell during degranulation process (anaphylactic type) in intimal contact with dermal dendrocyte. Mast cell resembles a ball in a baseball glove (dermal dendrocyte). Note that membrane flaps of dermal dendrocyte consistently shrouded mast cell membrane for 50% to 90% of their perimeter. This suggests the presence of functional interactions between these cells. Immunoelectron microscopy (ITM) technique (original magnification ×40 000)
CD4+ and CD8+ T lymphocytes, dendritic cells, granzyme A+, and NK cell density in the parenchyma of patients who died as a consequence of influenza A (H1N1) pdm09 DAD, and there was down cell density of tryptase+ mast cells, dendritic cells+ and an increased number of IL17+ cells in the airways, compared with non-viral DAD cases and the controls.41

Tang et al42 published an article comparing hospitalized patients in two independent single-centre cohorts, with acute respiratory distress syndrome (ARDS) caused by Covid-19 and H1N1. Both diseases had their outbreak during the winter in the Northern hemisphere. There were many differences between Covid-19 and H1N1-induced ARDS patients in clinical presentation, including a lower severity of illness scores at presentation in Covid-19 group.42

Under pathological changes, in addition to diffuse alveolar damage in lungs from Covid-19 patients, there were cellular fibromyxoid exudate, desquamation of pneumocytes and hyaline membrane formation, indicating ARDS, interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, multinucleated syncytial cells with atypical pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli identified in the intra-alveolar spaces, showing viral cytopathic-like changes.43

In patients studied during 2010, with swine H1N1 influenza (S-OIV) infection, there was diffuse alveolar damage associated with necrotizing bronchiolitis and extensive haemorrhage, besides a cytopathic effect in the bronchial and alveolar epithelial cells.43 They reported rotavirus bronchiolitis and extensive haemorrhage, besides a cytopathic OIV infection, there was diffuse alveolar damage associated with necrotizing bronchiolitis and extensive haemorrhage, besides a cytopathic effect in the bronchial and alveolar epithelial cells.43 They reported marked expression of TLR-3, IFN-γ and a large number of CD8+ T cells and granzyme B+ cells within the lung tissue.43 A singular clinical characteristic in patients with Covid-19 is the lymphopenia that might be a critical factor associated with disease severity and mortality, however lymphopenia was described, as well in adult patients with severe pandemic H1N1 influenza A.45

4 | HYPERCOAGULABILITY AND VIRAL INFECTIONS

Zhang et al46 reported three patients admitted in the intensive care unit (ICU) due to severe Covid-19 with ages of 69, 65 and 70 years old, and the first one had evidences of ischemia in lower limbs associated with bilateral cerebral infarcts in multiple vascular territories. All three patients were positive for anticardiolipin (aCL) IgA antibodies, as well as anti-β2-glycoprotein I (anti-β2-GPI) IgA and IgG antibodies.46 However, these antibodies rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia and thrombotic microangiopathy.46

Uthman and Gharavi47 reviewed in 2002 the literature about viral infections and antiphospholipid antibodies (aPL) and found association of these antibodies with hepatitis C virus infection, HIV, cytomegalovirus, Varicella Zoster virus, Epstein-Barr virus, adenovirus and parvovirus B19. These authors emphasized that the clinical significance of finding β2-GPI-dependent aCL and anti-β2-GPI antibodies in the sera of infectious disease remains unknown.47 In some patients, these aPL/anti-β2-GPI antibodies are transient and disappear within 2 or 3 months.47 In some susceptible individuals, they persist and raise the question of whether infections may be a trigger for the development of aPL and anti-β2-GPI antibodies in autoimmune diseases.47

Moreover, Smeeth et al48 and Van Wissen et al49 previously demonstrated that viral acute respiratory infections (VARI) may be associated with thrombotic events, and this association is multifactorial. Acute respiratory tract infections are associated with an increased risk of acute ischemic heart disease, stroke and venous thromboembolism.49 A transient change in local haemodynamic factors, coagulation activation, reduced generation of anticoagulant activated protein C (APC), inhibition of fibrinolysis and endothelial cell perturbation as a result of systemic inflammation might be underlying mechanisms through reduced clotting time, and an increase in the expression of tissue factor and thrombin generation, the latter by reduced levels of protein C (anticoagulation protein).49 Endothelial cell perturbation and increased levels of haemostatic markers, such as von Willebrand factor (VWF), D-dimer, plasmin-α2-antiplasmin complexes (PAP) and plasminogen activator inhibitor-1 (PAI-1), are risk factors for ischemic heart disease, and venous thromboembolism.49 Then, as there is extensive crosstalk between inflammation and coagulation, it is likely the prothrombotic mechanisms in VARI could be further exacerbated in patients suffering from severe forms, as Covid-19.50

Tan et al50 observed in Singapore three Covid-19 patients admitted to ICU with progressive clinical deterioration and higher activated partial thromboplastin time (aPTT)-based clot waveform analysis (CWA) consistent with hypercoagulability. Such patients exhibited a state of hyperinflammation and high level of cytokines (cytokine storm), including TNF-α and IL2, which can upregulate the coagulation system.50

Besides blood hyperviscosity, the hypoxia found in severe Covid-19 can stimulate thrombosis due to hypoxia-inducible transcription factor-dependent signalling pathway.51 The study conducted by Tang et al51 enrolled 449 patients classified as severe Covid-19 and concluded that anticoagulation with heparins [low-molecular weight heparin (LMWH), 40-60 mg enoxaparin/ day or unfractionated heparin (UFH), 10 000-15 000 U/day] was beneficial only for patients

| Item          | ISTH scoring system adopted by Tang et al52 | Score | Range |
|---------------|--------------------------------------------|-------|-------|
| Platelet count (×10^9/L) | 1                      | 100-150 |
| 2                      | <100                                    |
| PT-INR         | 1                      | 1.2-1.4        |
| 2                      | >1.4                                    |
| SOFA score     | 1                      | ≥2       |
| Total score for SIC | ≥4                                    |

Abbreviations: INR, international normalized ratio; ISTH, International Society of Thrombosis and Haemostasis; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment.
meeting SIC score system criteria ≥4 (Tables 1 and 2) or with markedly elevated D-dimer (>3.0 ug/mL, equivalent 6-fold of upper limit of normal, 6 ULN), especially when LMWH used. A similar cut-off for D-dimer >3.0 ug/mL able to take a decision of apply anticoagulant treatment with clinical benefits was found by Yin et al.53

Solaimanzadeh54 reviewed the data published about the pathophysiology of Covid-19 following a characterization of the disease vis-à-vis a similar respiratory illness, the high-altitude pulmonary edema (HAPE), as manifested during the acute hypoxic ventilatory response, and proposed potential treatment options for Covid-19. In severe cases, both Covid-19 and HAPE exhibit a decreased ratio of arterial oxygen partial response pressure to fractional inspired oxygen (PaO₂:FiO₂ ratio) with concomitant hypoxia and tachypnea.54 There was a reported tendency for low carbon dioxide levels, then hypoxia and hypocapnia are seen in both conditions.54 Radiologic findings of ground-glass opacities are present in up to 86% of Covid-19 patients with 76% having bilateral distribution and 33% peripheral. Interestingly, lung cavitation, discrete lung nodules, pleural effusions and

### TABLE 2

| System/Organ | Score |
|--------------|-------|
|              | 0     | 1     | 2     | 3     | 4     |
| Respiration  | PaO₂/FiO₂ mm Hg (kPa) | ≥400 | <400 | <300 | <200 | <100 |
| Coagulation  | Platelets, ×10⁹/μL | ≥150 | 101-150 | 51-100 | 21-50 | ≤20 |
| Liver        | Bilirubin mg/dl μmol/L | <1.2 | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | >12.0 |
| Cardiovascular | MAP | ≥70 mmHg | <70 mmHg | DA < 5 or Db (any doses)b | DA 5.1-15 or E≤0.1 or NE≤0.1b | DA > 15 or E<0.1 or NE > 0.1b |
| CNS          | GCS (3-15) | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Renal        | Creatinine, mg/dl (μmol/L) | <1.2 (110) | 1.2-1.9 (110-170) | 2.0-3.4 (171-299) | 3.5-4.9 (300-440) | >5.0 (>440) |
|              | Urine output, mL/d | or <500 | <200 |

Abbreviations: CNS, Central Nervous System; DA, dopamine; Db, dobutamine; E, epinephrine; FiO₂, Fraction of inspires oxygen; GCS, Glasgow Coma Scale; MAP, Mean Arterial pressure; NE; norepinephrine; PaO₂, partial pressure of oxygen; SOFA, sequential organ failure assessment.

5Adapted from Wehler et al.51

bCatecholamines are givens as μg/kg/min for at least 1 hour.

5GCS ranges from 3 to 15 and higher score indicates better neurologic functions.

### TABLE 3

| Macrophage Activation Syndrome | Catastrophic Antiphospholipid Syndrome |
|-------------------------------|---------------------------------------|
| • The immune hyperactivation in which dysregulation of macrophages and lymphocytes leads to excessive cytokine production (cytokine storm) | • Antiphospholipid antibodies and complement activation are felt to play a central role |
| • These cytokines include but are not limited to interleukin-18 (IL-18) and its downstream effector interferon-γ (IFN-γ) | • During infections, molecular mimicry may provide the trigger that unleashes the thrombotic storm characteristic of this condition |
| • Elevated levels of IFN-γ and its downstream effectors are well documented in patients with HLH and MAS | • Regardless of the trigger, however, antiphospholipid antibodies have been postulated to mediate disease by activating platelets, inhibiting anticoagulants, inhibiting fibrinolysis, and activating the classical complement pathway |
| • Chronic IL-18 elevation, potentially mediated by an epithelial inflammasome source, has been shown to play an important role in the pathogenesis of MAS | • The alternative complement pathway can be activated |
| • A total IL-18 level ≥ 24 000 pg/mL was shown to distinguish MAS from familial HLH with 83% sensitivity and 94% specificity | • Complement activation is expected to contribute to a prothrombotic state through endothelial activation and apoptosis mediated by the release of tissue factor and other prothrombotic substances |
| • The immune dysregulation and severe inflammation that characterize MAS result in tissue infiltration by lymphocytes and histiocytes, leading to organ failure and potentially death | |

Note: Based on descriptions of Gansner and Berliber.62
lymphadenopathy were absent.\textsuperscript{54} It has been shown that widespread ground-glass opacities are most commonly a manifestation of hydrostatic pulmonary edema and this is a central point to consider going forward.\textsuperscript{54}

The virulent properties of Covid-19, as well as upregulated inflammatory responses, and their effects on alveolar integrity require further study.\textsuperscript{52} Autopsy results of a Covid-19 fatality revealed bilateral diffuse alveolar damage associated with pulmonary edema, pro-inflammatory concentrates and indications of early-phase acute respiratory distress syndrome (ARDS).\textsuperscript{54} HAPE itself is initially caused by an increase in pulmonary capillary pressure.\textsuperscript{54} HAPE induces altered alveolar-capillary permeability via high pulmonary artery hydrostatic pressures that lead to a protein-rich and mildly haemorrhagic edema.\textsuperscript{54} Covid-19 and HAPE fibrinogen formation/fibrin formation are increased in both, and these entities discretely converge on ARDS.\textsuperscript{54} Over 70\% of COVID-19 patients have elevated lactate dehydrogenase levels (LDH) due to hypoxia.\textsuperscript{54} There are some drugs effective on HAPE that Solaimanzadeh\textsuperscript{54} suggested could be studied in Covid-19 patients: acetazolamide, nifedipine and phosphodiesterase.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Livedoid vasculopathy. A, Upper left: Livedoid macules on malleolar area of the leg. B, Typical clinical cutaneous lesion of LV demonstrates white scar lesions (Atrophie Blanche), ulcer and residual hyperpigmentation due purpura. B, Upper right: Histopathological exam of the skin biopsy showing thrombosis and fibrin deposition into dermal blood vessels in a patient with LV (Haematoxylin-Eosin, OM ×100). C, Down left: Immunohistochemistry stain using mouse monoclonal antibody [8F6A9.8H5C5,Abcam] to Lipoprotein a (dilution 1:200), revealed by LAB-alkaline phosphatase technique (Sigma, St. Louis, Missouri) showing immunostaining in endothelial cells of upper dermal small blood vessels in a patient with LV, confirming the lipoprotein a deposition on cutaneous blood vessels (OM, ×1000). D, Down right: Detail of dermal blood vessels under immunohistochemistry to Lipoprotein(a) (OM, ×1000). LV, livedoid vasculopathy.}
\end{figure}
SKIN CONDITIONS RELATED TO HYPERCOAGULABILITY THAT SHOW HISTOPATHOLOGICAL SIMILARITIES TO COVID-19 AND SHARE SOME DRUG TREATMENTS

The cardinal points in severe Covid-19 are: (a) upregulated innate immune human response; (b) hypercoagulopathy state; (c) polymorphous clinical manifestations, due to pulmonary tissue damage, neurological and/or gastrointestinal tract involvement; and (d) fatal outcome in severe cases of MAS.

5.1 | Hyperinflammation states

Systemic immune-mediated diseases (SIDs) include autoimmune and autoinflammatory diseases affecting at least two organ systems. Autoinflammatory diseases refer to a growing family of conditions characterized by episodes of unprovoked inflammation in the absence of high autoantibody titres or autoreactive T lymphocytes, reflecting a primary innate immune system dysfunction. Conversely, autoimmune diseases are characterised by aberrant B, T and dendritic cell responses, leading to a break in tolerance against self-antigens, with predominantly cell-mediated or autoantibody-mediated responses in genetically susceptible individuals.

Inappropriate cytokine upregulation is described in some diseases or syndromes, sharing characteristics of autoinflammatory and/or autoimmune conditions. These include monogenic diseases including cryopyrin-associated autoinflammatory syndromes (CAPS) with upregulation of IL1β and IL18, type I interferonopathies with excessive type I IFN synthesis [STING-associated vasculopathy with onset in infancy (SAVI) and Aicardi-Goutières syndromes] as well as autoimmune polygenic diseases like systemic erythematous lupus (SLE) where IFN is critical for immunopathology of cardiovascular disease or adult-onset Still’s diseases (AOSD).

CAPS are a group of rare inherited inflammatory disorders associated with dominant mutations in the cryopyrin-coding gene NLRP3 (nucleotide-binding domain, leucine-rich repeat containing gene family, pyrin domain-containing protein 3) on chromosome 1q44 which is also known as CIAS1, PYPAF1 or NALP3. Currently, more than 90 mutations involving NLRP3 and associated with CAPS phenotypes have been reported.
| Drug or therapy approach | Livedoid vasculopathy [use:(+), References] | Action’s mechanisms | Reported in Covid-19 [use:(+), References] |
|--------------------------|-------------------------------------------------|---------------------|------------------------------------------|
| ASA or Aspirin           | (+) References 63 and 64                        | Cyclooxygenase inhibitor\(^71\) ASA works by irreversibly inhibiting the COX activity in the prostaglandin synthesis pathway (PGH\(_2\)).\(^71\) Low dose ASA (75-150 mg) can induce complete or near-complete inhibition of COX-1, thus inhibiting the production of TXA\(_2\).\(^71\) | (−) |
| Dipyridamole             | (+) Reference 72                                | Antiplatelet and vasodilating properties and inhibits platelet cyclic nucleotide phosphodiesterase.\(^71\) This enzyme is responsible for the degradation of AMP to 5'AMP, which increases intra-platelet cyclic AMP accumulation and inhibits platelet aggregation. It also blocks the uptake of adenosine by the platelets, which also increase cyclic AMP\(^71\) | (−) |
| Clopidogrel (oral thienopyridines) | (+) Reference 63                              | Selective inhibition of the adenosine diphosphate induced (ADP-induced) platelet aggregation.\(^71\) These drugs convert to an active drug with the help of the hepatic CYP450 system that inhibits the platelet P2Y12 receptor\(^71\) | (−) |
| PTX                      | (+) Reference 73                                | PTX is a methylxanthine that inhibits PDE 4, presenting interesting immunomodulatory and antiviral properties.\(^76\) PDE4 is abundant and the major regulator of cAMP metabolism in almost every proinflammatory and immune cell. Anti-inflammatory effects of PTX are additionally due to the reduction of proinflammatory cytokines production as TNF-alpha or IFN\(\gamma\).\(^74\) PTX also down-regulates the activation of NF kappa B (NF\(\kappa\)B) and NFAT transcription factors (involved in the replication of several viruses).\(^74\) cAMP elevation mediated by PDE 4 inhibition leads to a bronchodilator effect\(^74\) | (+) References 74 and 75 (∗suggested for SARS-CoV) |
| Heparin (UFH or LWMH)    | (+) Reference 76                                | Parenteral heparin has huge medical importance as anticoagulant and anti-thrombotic agent and together with its antidote, protamine sulphate, and fragmented LMWH is listed as essential medicines by the World Health Organization\(^77\) | (+) References 52 and 78 |
| Anti-factor Xa agents—direct oral anticoagulants (DOACs) (eg, rivaroxaban, apixaban) | (+) References 70 | Direct oral inhibitors of the Xa factor, being also a substrate for the P-glycoprotein transporter but mainly for CYP3A4/5 and CYP1A2, 2C8, 2C9, 2C19, 2 J2\(^79\) | (−) |
| Danazol or stanozolol    | (+) Reference 65                                | Danazol or stanozolol has fibrinolytic properties.\(^80\) Danazol increases the levels of protein C, protein S, antithrombin III and plasminogen, whereas the levels of plasma fibrinogen, plasminogen activator inhibitor and the expression of CD62 (P-selectin) on platelets are decreased.\(^80\) This results in a decreased thrombogenesis and enhanced fibrinolysis\(^80\) | (−) |
| Cilostazol               | (+) Reference 81                                | Vasodilatory effect, antiplatelet properties, and antiproliferative effects.\(^71\) It also reduces smooth muscle cell hyperplication and intimal hyperplasia after an injury to the endothelium\(^71\) | (−) |
| HOT                     | (+) Reference 82                                | The microvasculature is the critical interface for oxygen and energy delivery to tissues. Thus, any damage to or obstruction of the microvasculature may have harmful consequences.\(^63\) DIC, diffuse microvascular | (−) |
### Table 4 (Continued)

| Drug or therapy approach | Livedoid vasculopathy [use:(+), References] | Action’s mechanisms | Reported in Covid-19 [use:(+), References] |
|--------------------------|----------------------------------------------|---------------------|-------------------------------------------|
| Hydroxychloroquine       | (+) References 84 and 85                     | Useful as immunomodulator, especially in cases with antiphospholipid antibodies. The antithrombotic effect of chloroquine analogues has been attributed to a range of mechanisms, including reduction in red blood cell aggregation, inhibition of platelet aggregation and adhesion, reduction in blood viscosity and enhancement of antiplatelet activity. Hydroxychloroquine and chloroquine were indicated for treating patients with COVID-19, under in vitro effects due to capacity as: (a) an inhibitor of endocytic pathways through an elevation of endosomal pH, and (b) these drugs shown to interfere with the terminal glycosylation of angiotensin-converting enzyme-2 (ACE2), which acts as a plasma membrane receptor for both SARS-CoV and SARS-CoV-2. (+/−) There is limited evidence of in vitro activity of CQ/HCQ against SARS-CoV-2. A number of in vivo clinical trials are underway. The empirical data available from two of these trials reveal conflicting results. Both trials are characterised by small numbers of participants (n = 30 and n = 36) and suffer methodological limitations. No medium or long-term follow-up data is available. |
| Folate (folic acid)       | (+) References 84 and 89                     | Reducing homocysteine serum levels. (−) |
| Alteplase                | (+) Reference 84                             | Intravenous tissue plasminogen activator is recommended in a dose of 10 mg administered intravenously initially six hourly and subsequently once daily for 14 days. Tissue plasminogen activator therapy may be considered especially in patients who have not responded to multiple conventional therapies. After tissue plasminogen activator therapy, maintenance with anti-platelet or anticoagulant agents have to be continued. (+/−) There is evidence in both animals and humans that fibrinolytic therapy in Acute Lung Injury and ARDS improves survival, which also points to fibrin deposition in the pulmonary microvasculature as a contributory cause of ARDS and would be expected to be seen in patients with ARDS and concomitant diagnoses of DIC. |
| Intravenous Immunoglobulin (IVlg) | (+) References 84 and 91-93 | Anti-inflammatory properties it might exert antiagulation effects through: (a) inhibition of thrombogenic effects of antiphospholipid antibodies, (b) inhibitory effects on platelet adhesion, and (c) modulation of endothelial function. (+) Then, the viruses spread through the bloodstream and mainly in the lungs, gastrointestinal tract, and heart, presumably concentrated in the tissues expressing ACE2, the receptor of SARS-CoV-2. This phase occurs around 7-14 after the onset of the symptoms when the virus starts a second attack, which is also the main cause of the aggravation of symptoms. At this time, pulmonary lesions became worse, and chest CT scans show imaging changes consistent with COVID-19. At this stage, the peripheral blood lymphocytes decrease. |
These systemic conditions share polymorphous cutaneous lesions where innate immune cells like macrophages and neutrophils are involved in their histopathological findings, and under extreme exogenous or endogenous stimuli may develop MAS, with ARDS, hyperoagulability, hyperferritinemia, increased serum levels of D-dimer, lactic dehydrogenase (LDH), reactive-C-protein (PCR), serum A amyloid (SAA) very similar to severe cases of Covid-19.

In AOSD, a systemic inflammatory disorder, with intermittent spiking fevers, arthralgias or arthritis, leukocytosis and hyperferritinemia, an evanescent salmon-pink macule often appears on the skin during the evening with mild or without pruritus. However, other authors described polymorphous cutaneous lesions or atypical cutaneous presentations as erythematous eruptions, linear configurations simulating dermographism or flagellate dermatitis, prurigo-pigmentosa-like, urticarial papules, dermatomyositis-like, and lichen amyloidosis-like eruptions. Chamseddin et al reported a 19-year-old woman who developed acute clinical decompensation and atypical annular papules and plaques with purpura on the down extremities. A punch biopsy demonstrated histiocytes with engulfed degenerated erythrocytes and lymphocytes, consistent with hemophagocytic lymphohistiocytosis (HLH). MAS, a variant of secondary HLH occurring in the setting of autoimmune disease, is a life-threatening condition with reported mortality rate of 20% to 50%. It has been reported in 3% to 20% of AOSD cases. MAS is thought to occur because of widespread immune activation with proliferation of cytotoxic CD8+ T-cells and macrophages which develop into hemophagocytosis and cytokotoxic storm. Three cases of MAS secondary to SLE or dermatomyositis have reported skin biopsies with similar histologic findings. Cutaneous hemophagocytosis does not always indicate systemic MAS and may be incidentally found in leukocytoclastic vasculitis, lupus erythematosus, arthropod bites, erysipelas, acne conglobata, and Sweet syndrome.

Early diagnosis and treatment are essential for preventing a suboptimal outcome in MAS. High dose of corticosteroids with or without cyclosporine A was reported as first-line therapy, followed by combinations with anakinra or tocilizumab. The mechanism of action for anti-TNF-α agents in livedoid vasculopathy is still uncertain. However, apart from their anti-inflammatory properties, anti-TNF-α agents act mainly by close interaction between various inflammatory cytokines or pathways and coagulation. Cyclosporin blocks Thrombin-dependent Lymphocyte activation and VEGF induction of Tissue Factor.

### TABLE 4 (Continued)

| Drug or therapy approach | Livedoid vasculopathy [use: (+), References] | Action’s mechanisms | Reported in Covid-19 [use: (+), References] |
|--------------------------|-----------------------------------------------|---------------------|---------------------------------------------|
| Cyclosporin A            | (+) Reference 95                              | Cyclosporin blocks Thrombin-dependent Lymphocyte activation and VEGF induction of Tissue Factor. |
| Anti-TNF-α biological agent (Etanercept) | (+) Reference 98 | The mechanism of action for anti-TNF-α agents in livedoid vasculopathy is still uncertain. However, apart from their anti-inflammatory properties, anti-TNF-α agents act mainly by close interaction between various inflammatory cytokines or pathways and coagulation. |

Abbreviations: AMP, adenosine monophosphate; ASA, acetylsalicylic acid; COX, cyclooxygenase enzyme; HOT, Hyperbaric oxygen therapy; LMWH, low-molecular weight heparin; PDE 4, phosphodiesterase IV; PTX, Pentoxifylline.
5.2 | Hypercoagulability conditions

In the dermatological setting, there is one condition with pathophysiological and clinical similarities to Covid-19 involving systemic disease: the catastrophic antiphospholipid syndrome.

Catastrophic antiphospholipid syndrome (CAPS) and MAS are both life-threatening hematologic disorders that infrequently afflict patients with rheumatologic disease.62 CAPS is characterized by fulminant multiorgan damage related to small vessel thrombosis in the setting of persistent antiphospholipid antibodies.62 It can occur in patients with rheumatologic diseases, such as SLE, but can also affect patients who do not have rheumatologic disease.62 In contrast, the term MAS is applied when patients with rheumatologic disease develop HLH; therefore, patients with MAS have an underlying rheumatologic disease by definition.62 Similar to CAPS, HLH/MAS can have a fulminant presentation, but the pathogeneis and manifestations are different and these distinct characteristics are listed in Table 3.62 In both CAPS and MAS, management generally includes, but is not limited to, immunosuppression with steroids.62

Livedoid vasculopathy (LV) is another dermatological condition that shares similar clinical, histopathological and therapy aspects to hypercoagulability in Covid-19; however, it is not described that LV presents serious systemic evolution, although around 20% of patients can have mononeuritis. LV is a chronic disorder manifested as recurrent reticulated purpura of the legs associated with painful purpuric, occasionally ulcerative, macules resulting in atrophic, porcelain, stel late scars or atrophie blanche (AB) with peripheral telangiectasis and hyperpigmentation.63

LV is a non-inflammatory thrombotic condition. Among abnormalities in fibrinolysis or coagulation are several factors as lupus anticoagulant, protein C and/or S deficiency, increased anticardiolipin, cryoglobulinemia, factor V Leiden mutation, prothrombin gene mutation, plasminogen activator inhibitor-1 promoter mutation, hyperhomocysteinemia, antithrombin III deficiency, elevated levels of coagulation Factor VIII and/or IX,64 and high serum levels of lipoprotein(a) [Lp(a)]65 (Figure 2) or tissue deposition on cutaneous blood vessels.66 Under histopathological study, LV is compared to primary vasculitis, with mild lymphomononuclear cell perivascular inflammatory infiltrate. Extravasation of red blood cells results from vessel wall damage and there is endothelial proliferation. Neutrophil infiltration and leukocytoclasia are usually absent (unlike in primary vasculitis).

Increased platelet expression of p-selectin is linked to abnormal platelet function. Specifically, high platelet p-selectin levels were noted in LV, in the absence of elevations of the inflammatory cytokines IL1β, IL8 and TNFα, with different pathogenic mechanisms from...
Oral antiplatelet agents, such as aspirin and clopidogrel, have been shown to reduce the risk of cardiovascular events in patients with vascular disease and a history of cardiovascular events. Aspirin works by irreversibly inhibiting COX-1, leading to a decrease in the production of thromboxane A2, a potent vasoconstrictor and aggregator of platelets. Clopidogrel, on the other hand, is a thienopyridine derivative that binds to the platelet ADP receptor P2Y12, preventing the aggregation of platelets by blocking the ADP-dependent signaling pathway. This combination of medications is often used in the management of patients with CV disease due to its synergistic effect in inhibiting platelet aggregation, thereby reducing the risk of thrombotic events.

In the context of this case report, the patient's history of CV disease and his need for antiplatelet therapy is critical. The use of aspirin and clopidogrel in combination is consistent with current guidelines for the management of patients with CV disease, as it provides a comprehensive strategy for reducing the risk of future cardiovascular events. This approach highlights the importance of considering the individual patient's condition and history when selecting appropriate pharmacological treatments, and it underscores the need for ongoing monitoring and adjustment of therapy to optimize outcomes.

Furthermore, this case highlights the potential for drug interactions and the importance of thorough medication review, especially in patients with a history of CV disease. Providers should always be vigilant about the concurrent use of antiplatelet agents and other medications, as well as other potential therapeutic strategies, to achieve the best possible outcomes for their patients.
as high levels of Lp(a), in some genetically predisposed subjects (Figure 4) may trigger this manifestation of the disease, and must, therefore, be considered significant factors in the pathogenesis of viral-induced myocardial ischaemia.\textsuperscript{100}

The interplay among genetic factors, environmental aspects, host immune responses, viral evasive properties and systemic and cutaneous involvement on Covid-19 patients are illustrated in Figure 5.

6 | CONCLUSIONS

Several viral infections are related to elicit innate and adaptative human immune responses. In some circumstances, as previous SARS-CoV, MERS-CoV and SARS-CoV-2, the monocytic-macrophage system may produce an up-regulated immune response (sHLH/MAS-like), severe inflammatory systemic state and damage in lungs and other internal organs, often haematological system, gastrointestinal tract and kidneys. Viral direct and/or indirect mast cell and basophil activation is a possible event and we need to be alert to cutaneous manifestations as onset of urticaria and atopic dermatitis or exacerbation of these conditions, exanthema, neutrophilic dermatosis and cutaneous manifestations of hypercoagulable states. It is very important that photographs and cutaneous biopsies are taken to confirm the correct diagnosis and to make the differential diagnosis from other cutaneous or systemic conditions.

CONFLICT OF INTEREST

The authors have no competing interest.

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