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REVIEW

Are the cutaneous manifestations during or due to SARS-CoV-2 infection/COVID-19 frequent or not? Revision of possible pathophysiologic mechanisms

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Abstract

Background SARS-Cov-2 is a single-stranded RNA virus, a Betacoronavirus, composed of 16 non-structural proteins, with specific roles in replication of coronaviruses. The pathogenesis of COVID-19 is not yet fully understood. The virus and host factors interplay among distinct outcomes of infected patients.

Methods Using MeSH (Medical Subject Headings) in PubMed, authors searched for articles cotaining information on COVID-19 and the skin.

Results The pathophysiology of the disease is multifactorial: association with innate immune response, hypercoagulability state, lung tissue damage, neurological and/or gastrointestinal tract involvement, monocytic/macrophage activation syndrome, culminating in exaggerated cytokine secretion, called "cytokine storm", which leads to worsening and death. These systemic conditions may be associated with cutaneous lesions, that have polymorphic aspects, where at histopathological level show involvement in different skin changes. These lesions may be associated with multisystemic manifestations that could occur due to angiotensin-converting enzyme 2 receptor and transmembrane serine protease action, allowing the pulmonary infection and possibly skin manifestation. Several reports in literature show cutaneous lesions similar to chilblain, urticarial eruptions, diffuse or disseminated erythema, livedo racemosa, blue toe syndrome, retiform purpura, vesicle trunk, purpuric exanthema or exanthema with clinical aspects of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) and others.

Conclusions This review describes the complexity of Covid-19, pathophysiological and clinical aspects, dermatological finding and other dermatological conditions associated with SARS-CoV-2 infection or COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Innate immunity · Livedoid vasculitis · Macrophage · Lipoprotein A

Introduction

The 2019 novel beta-coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new worldwide public health crisis has rapidly spread from its origin in Wuhan City of Hubei Province of China, in December 2019 [1]. So far, May 12-2020 a data chart of Coronavirus Resource Center of the John Hopkins University (USA) at 12:34:40 PM has totalized 4,210,079 COVID-19 cases around the world, with 287,156 deaths, and 1,470,598 recovered patients in 187 countries/regions [2].

Cutaneous manifestations reports published in periodicals indexed in PubMed are occasionally rising, but often clinical images and/or histopathological findings of these lesions are not included. Using MeSH (Medical Subject Headings) in PubMed, authors searched for "cutaneous and COVID-19", as well as, "skin and COVID-19", making it possible to retrieve more than 160 articles. Moreover, these papers have published many aspects from patients' cutaneous manifestations with COVID-19 [3–38] to economic impact [40] and protective measures for the cutaneous system during COVID-19 exposure [41–52]. Another aspect are skin damages in healthcare workers [42, 49, 53–58], medical education and telemedicine during the pandemic [59–62], the use

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of immunomodulators [63, 64]; immunosuppressors and immunobiological agents in dermatology [65], as well as, in rheumatology skin conditions [63, 66, 67].

What was reported about cutaneous lesions in COVID-19 patients?

Concerning integumentary clinical manifestations, unfortunately, we cannot access clinical images or histopathological registers of part of such cases reported until now. Some authors described these cutaneous lesions under distinct dermatological terms: erythematous rash [4], urticarial eruptions [18], varicella-like vesicles [4], chilblain-like lesions [7], acrocyanosis [8], retiform purpura [11], livedo [13], among others.

Probably due to lack of adequate personal protective equipment (PPE) for frontline health care workers, including respirators, face shields, gloves, ocular glasses, gowns, and hand sanitizers, dermatologists have not adequately registered the cutaneous findings in COVID-19 patients [18]. Viral infections can produce specific clinical and nonspecific manifestations, due to the direct action in infected human cells or as a phenomenon of immune system hyperactivity. Since some of the associations are considered to be either causal or probably causal whereas others are not, it is useful to consider, through specific case studies, what clinical evidence is well-accepted to establish a causal relation, and which factors may be dispensable [68].

Regarding dermatological manifestations reported until May of 2020, related to COVID-19, we summarized the case studies described in Table 1.

In addition to cases mentioned above, the prospective study conducted by Galván Casas et al. [39] in Spain reported 375 cases of skin lesions associated with COVID-19, classifying them in 5 different patterns. It is important to state that, for the first time, a temporal relationship between skin lesions and other systemic symptoms, and moreover, a severity of the disease was created. The study showed that vesicular eruptions appeared in the early course of the disease, even before other symptoms. Also, that pseudo-chilblain pattern appeared at a later time during the evolution of the disease and in most cases after other symptoms. When associating severity, the authors described a gradient, from less to most severe disease, illustrating pseudo-chilblain with less severe pulmonary disease in contrast to livedoid presentations which were associated with worse pulmonary diagnosis once these patients required intensive care treatment [39].

It is remarkably interesting that PubMed indexed literature, up to now has retrieved not over 600 cutaneous manifestations in COVID-19 cases reported, despite over 4 million COVID-19 patients [1]. Many correlated possibilities are as follows: under cutaneous manifestation notifications, the presence of severe pulmonary COVID-19, and physicians do not take into account that the skin also needs careful observation, lack of dermatologists in hospitals due to social isolation, patients with mild COVID-19 who have not referred cutaneous manifestations to their general practitioners, among others. However, dermatologists should conduct more photograph registrations and cutaneous biopsies for better scientific documentation, as well as, adequate differential diagnosis when assisting such patients.

Recently, Jones et al. [69] described a case of a 6-month-old infant diagnosed with classic Kawasaki disease, at the same time screened positive for COVID-19 with fever and minimal respiratory symptoms believing there may be a potential association between both diseases. Kawasaki disease has previously been associated with other pathogens, including coronaviruses [70–73]. In an article by Principi et al. [70], there was histological evidence suggested that Kawasaki disease has an infectious origin, with persistent intracytoplasmic inclusion bodies and RNA staining which may be a clue of a viral infection that shall persist indefinitely. They also reported that the first site of infection was the respiratory tract, and later dissemination occurred through macrophages to all body sites, including the medium-sized arteries. This can occur by the direct action of SARS-COV-2 on the complement system and generating MAC (C5b-9), ending with endothelial and coronary arteries damage, as well as, thrombosis by the procoagulant surface [11].

Possible actions of SARS-CoV-2 on human skin and the resulting potential dermatological manifestations

We highlight some interesting aspects of SARS-CoV-2 infections for dermatologists and their possible correlation with the skin:

1. SARS-Cov-2 is a single-stranded RNA virus composed of 16 non-structural proteins (named as NSP 1-16) with specific roles in the replication of coronaviruses (CoVs) [74]. One of them, NSP3, has the property to block host's innate immune response and to promote cytokine expression. The other two, NSP5 can inhibit interferon (IFN) signaling and NSP16 avoids MAD5 (melanoma differentiation-associated gene 5) recognition, depressing innate immunity [74]. 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),

Table 1 Case reports or case series described referring cutaneous lesions in patients with SARS-CoV-2 infection or COVID-19

Author(s)	Country	Number of patients	Cutaneous lesions	Photography register	Histopathological studies
Recalcati [3]	Italy	18	Rash (14 patients), widespread urticaria (3 patients) and chickenpox-like vesicles (1 patient) "Erythematous rash" (14 patients), widespread urticaria (3 patients), and chickenpox-like vesicles (1 patient)	No	No
Henry et al. [4]	France	1	Pruritic urticarial rash on face and limbs	Yes	No
Kamali Aghdam et al. [5]	Iran	1	Neonate with sepsis with "mottling on skin". Probably, cutis marmorata-like	No	No
Joob and Wiwanitkit [6]	Thailand	1	Skin rash with petechiae	No	No
Alramthan and Aldaraji [7]	Kuwait	2	Chilblain-like lesions	Yes	No
Zhang et al. [8]	China	7	Acro-ischemia	Yes	No
Taisheng et al. [9]	China	Not described	Ischemic changes such as ecchymosis of the fingers and toes, at the same time as the organ functions of the heart and kidneys became worse. These manifestations are consistent with the diagnosis of the hypercoagulable phase of disseminated intravascular coagulation	Yes	No
Mazzotta and Toccoli [10]	Italy	1	Acro-ischemia as purpuric and bullous lesions on the feet, in a child very similar with chilblains lesions	Yes	No
Magro et al. [11]	United States of America	5	Retiform purpura, livedo racemosa, and perniosis	Yes	Yes
Marzano et al. [12]	Italy (multicenter case series)	22	Papulovesicular exanthema, or papules, and crusts. Distribution predominantly on trunk Lesions described as "varicella-like"	Yes	Yes
Manalo et al. [13]	United States of America	2	Transitory unilateral livedo after sun exposition	Yes	No
Estébanez et al. [14]	Spain	1	Confluent erythematous-yellowish papules in heels	Yes	No
Mahé et al. [15]	France	1	Acute flexural rash similar to symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)	Yes	No
Jimenez-Cauche et al. [16]	Spain	1	Purpuric skin rash with coalescing macules on both peri-axillary regions	Yes	No
Ehsani et al. [17]	Iran	1	Pityriasis rosea-like	Yes	No
Lu et al. [18]	China	1	Urticaria	No	No
Fernandez-Nieto et al. [19]	Spain	1	Urticarial eruption	Yes	Yes
Dong et al. [20]	China	Not described	Pneumonia associated with atopic dermatitis; pneumonia associated with urticaria	No	No
Van Damme et al. [21]	Belgium	2	Urticarial rash	Yes	No

Table 1 (continued)

Author(s)	Country	Number of patients	Cutaneous lesions	Photography register	Histopathological studies
Morey-Olivé et al. [22]	Spain	2	Erythematous, confluent, nonpruritic maculopapular rash and urticaria-like rash	Yes	No
Paolino et al. [23]	Italy	1	Erythematous maculopapular rash and urticaria-like lesions	Yes	No
Tosti et al. [24]	Italy	4	Hardened, erythematous plaques of the heels Erythematous plaques of both heels Erythematous plaques of the extensor surface of the toes and both heels showed erythematous confluent papules Acrocyanosis	Yes	No
Bouaziz et al. [25]	France	14	Exanthema, chicken pox like vesicles, cold urticaria, "porcelain-like" appearance, livedo, non-necrotic purpura, necrotic purpura, chilblain appearance with Raynaud's phenomenon, chilblain, eruptive cherry angioma	Yes	No
Amatore et al. [26]	France	1	Erythematous and edematous non-pruritic annular fixed plaques	Yes	Yes
Diaz-Guimaraens et al. [27]	Spain	1	Erythematous macules, papules, and petechiae in asymmetric peri-flexural distribution	Yes	Yes
Tammaro et al. [28]	Italy, Spain	3	Herpetiform lesions (vesicles surrounded by erythematous halos), and vesicular isolated lesions	Yes	No
Avellana Moreno et al. [29]	Spain	1	Pruritic morbilliform rash (petechial and maculopapular lesions on an erythematous base)	Yes	No
Recalcati et al. [30]	Italy	14	Acral eruption of erythematous-violaceous papules and macules, with possible bullous evolution, or digital swelling Erythematous-papular targetoid lesions	Yes	Yes
Zengarini et al. [31]	Italy	1	Moderately itching erythematous confluent rash, with undefined margins, bleaching, mostly located at the neck, trunk, back, and proximal portions of upper and lower limbs	Yes	Yes
Gianotti et al. [32]	Italy	3	Widespread erythematous macules on arms, trunk and lower limbs Exanthem on the trunk and arms; Widespread pruritic eruption of erythematous macules and papules	Yes	Yes
Ahouach et al. [33]	Italy	1	Diffuse fixed erythematous blanching maculopapular lesions were present, asymptomatic over the limbs and trunk, with burning sensation over the palms	Yes	Yes
Piccolo et al. [34]	Italy	63	Erythematous and edematous lesions and/or blistering lesions described as chilblain-like lesions	Yes	Yes

Table 1 (continued)

Author(s)	Country	Number of patients	Cutaneous lesions	Photography register	Histopathological studies
Guan et al. [35]	China	2	Rash	No	No
Zhang et al. [36]	China	1	Ischemia on both lower limbs and digits of the left hand	No	No
Hoelh et al. [37]	Germany	1	Faint rash	No	No
Ma et al. [38]	China	1	Dry gangrene on right index finger	No	No
Galván Casas C et al. [38]	Spain	375	Pseudo-chilblain lesions; vesicular eruptions; urticarial lesions; maculopapular eruptions; livedo or necrosis	Yes	No

and N protein (2 domains, both of which can bind virus RNA genome) [74].

2. Aerosolized uptake of SARS-Cov-2 leads to infection of angiotensin-converting enzyme (ACE) type II (ACE2) expressing target cells such as alveolar type 2 (that produce lung surfactant) or other unknown target cells [75].
3. Dendritic cells, monocytes, and macrophages are the first cellular lineage to fight viral infections. The interferons type I (α and β) are 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 [76]. Enzymes that metabolize or modify endogenous nucleic acids are critical for preventing an upregulation activation of the innate antiviral response [76]. Humans and their primate ancestors have been under intensive selective pressure due to viral infections for tens of millions of years [76]. These events occurred due to viruses like influenza, polio, measles, and smallpox in the recent past of our history [75]. Antiviral proteins that are at the front lines of immune defense are the main targets of virus-encoded antagonists.

   Protein suppressors and/or others involved in upregulation of the human immune innate responses can emerge from mutant genes, which appear randomly in each generation, restore the antiviral response and provide an advantage to the host immune defense to a specific viral infection [76]. Inadequate negative or positive regulation of innate immune receptors, may lead to signals that stimulate nucleic acid and subsequent protein transcription, which can occur as monogenic genetic disorders, with gain in function (GOF) or loss of function (LOF). These are known as type I interferonopathies or other autoinflammatory diseases [76–81].

   Some studies have shown direct T cell viral infection by the detection SARS-like viral particles and SARS-CoV RNA in T lymphocytes from peripheral blood sample, spleen, lymph nodes, and lymphoid tissue of various organs [82]. It is questioned whether the alveolar macrophages can internalize the viral particles and then transfer to lymphocytes [82]. However, the direct attack on other organs by disseminated SARS-CoV-2, the immune pathogenesis caused by the systemic cytokine storm, and the microcirculation dysfunctions together lead to viral sepsis [82].
4. In COVID-19, like MERS-CoV, the pathologies are not yet fully understood, moreover viral and host factors play a key role in these infections. However, it should be noted that immunopathogenesis is associated with an out-of-control immune response, which may result in pulmonary tissue damage, functional impairment, and reduced lung capacity [83]. Chemotactic factors are essential to the immune responses against the virus infections, given their regulatory effect on dilations and positions of leukocytes in the host lungs [83]. Therefore, spectral changes in chemotactic factors may lead to severely maladjusted immune responses [83]. Immune insufficiency or misdirection may increase viral replication and cause tissue damages [83]. In a subset of patients, by the end of the first week, the disease can progress to pneumonia, respiratory failure, and death [1]. This progression is related to an extreme rise in inflammatory cytokines including interleukin (IL)2, IL7, IL10, GCSF, IP10, MCP1, MIPI A, and TNFα [1]. The increase in the pro-inflammatory cytokines, in particular, IL6 is associated with severe pneumonia and it can have deleterious effects on the adaptive immune system [8, 84]. In these subsets of patients, overactive immune responses may induce immunopathological conditions, named as "*cytokine storm*" and in some individuals leads to macrophage activation syndrome (MAS)-like, often causing a

fatal outcome [74, 83, 85, 86]. Cytokines could reach the skin and stimulate dermal dendritic cells, macrophages, mast cells and lymphocytes, in addition to polymorphonuclear cells and promote eruptions such as erythema, urticarial lesions, vesicles and others. These have already been reported in situations with cytokine release during similar situations in patients with systemic lupus erythematosus, antiphospholipid syndrome, adult Still's disease [81]. Magro et al. [11] found complement deposition (C5b-9 and C4d) using immunohistochemistry in dermal capillaries of patients with retiform purpura. This may play a role in pathogenicity, as the data present co-localization of products linked to complement activation with SARS-CoV-2 spike glycoproteins. Llamas-Velasco et al. [87] observed endothelial damage not only in kidney, small bowel and lung, but also in the dermo-hypodermal junction. These biological self-aggressive host behaviors run in the same pattern of the monogenic type I interferonpathies, but in COVID-19 is an acquired viral disease, acute and has a faster clinical evolution. An IL6 blockage, with JAK inhibitors, is one of the possible targeted treatments currently in clinical trial studies [88, 89].

5. Hammining et al. [90] 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 on lung alveolar epithelial cells (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 in the basal layer of the epidermis, endothelial cells of dermal blood vessels and eccrine adnexal tissue [90–93].

   With electron microscopy, Varga et al. [91] revealed viral inclusion structures in endothelial cells across vascular beds of different organs in some patients with COVID-19. This showed direct viral infection of the endothelial cell and diffuse endothelial inflammation [91]. The ACE2 receptor is also widely expressed on endothelial cells in multiple organs, suggesting that endotheliitis could occur in several sites as a direct consequence of viral involvement and host inflammatory response [91]. COVID-19-endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19 [91].

6. A transmembrane protease, serine 2 (TMPRSS2), a type II transmembrane serine protease (TTPS), plays a critical role in SARS and MERS coronavirus (CoV) and in 2003 Asian H7N9 influenza virus and several H1N1 subtype influenza A viruses infections, indicating that TMPRSS2 could be a novel antiviral strategy to treat coronavirus and some low pathogenic influenza virus infections [94]. SARS-Cov-2 (viral agent of the COVID-19) and SARS-CoV bind to ACE2 by the protein S (Spike) and allows the virus to enter and infect cells [95]. In order for the virus to complete entry into the cell following this initial process, the spike protein has to be primed by a protease (TMPRSS2) to complete this process [95]. In order to attach virus receptor (spike protein, S) to host cellular ligand (ACE2), activation by TMPRSS2 as a protease is needed [95]. Bjerregaard et al. [93] studied the expression of ACE2 in various human tissues and it was found on the skin; therefore, for the cleavage protease action of TMPRSS2, it could occur on the skin by the enzyme itself, which has yet to be demonstrated by immunohistochemistry studies, or by other proteases such as human tryptase, that could be released by resident cells of the dermis, such as perivascular mast cells. This may open a window of opportunity for future studies.

   (i) 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 upstream of the transcription start site and the first intron [94]. TMPRSS2 gene encodes a predicted protein of 492 amino acids which anchors to the plasma membrane, and after autocatalytic cleavage, a noticeable portion of them can gain blood circulation [94]. TMPRSS2 is predominantly expressed in the prostate, with a relatively lower level of expression in lungs, colon, liver, kidneys, and pancreas [94].

   (ii) Recently, Wambier and Goren [96] proposed that COVID-19 could affect the male gender more due to this relation between TMPRSS2 and androgen levels, since androgenic hormones stimulate this transmembrane growth. Goren et al. [97] demonstrated a greater prevalence of COVID-19 in male gender among patients in Spain proposing a potential clue to the role of androgens in COVID-19 severity due to the higher prevalence of androgenetic alopecia among patients with COVID-19, both in men and women hospitalized with the disease.

   (iii) Several members of the subfamily of Coronavirinae use peptidases as receptors for host cell entry: most alpha coronaviruses use CD13, and among betacoronavirus' species, the novel coronavirus MERS binds to CD26, and both SARS-CoV and the human coronavirus NL63 engage the carboxypeptidase ACE2. ACE2 expression in human membrane cell protects

against acute respiratory distress syndrome [98]. 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 [99]. The SARS-CoV can hijack two cellular proteolytic systems to ensure the adequate processing of its S protein [99]. 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 [99]. 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 [99]. 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 [99]. Heurich et al. [99] suggested that TMPRSS2 and HAT impact SARS-S-driven entry 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, human airway trypsin-like protease (HAT), and TMPRSS2 (transmembrane protease, serine 2) are known to cleave the glycoprotein hemagglutinin (HA) of influenza A viruses, a prerequisite for the fusion between viral and host cell membranes and viral cell entry [100]. Cleavage of HA is critical for viral infection, with the tissue distribution of proteases determining cell tropism of virus strains [101].

Until the present day, the cardinal points in severe COVID-19 are upregulated innate immune human response; hypercoagulable state; polymorphous clinical manifestations, due to pulmonary tissue damage, neurological and/or gastrointestinal tract involvement; and fatal outcome in severe cases of macrophage activation syndrome-like (MAS) [102].

Additional considerations

Other possibilities in developing ischemic/coagulopathy lesions as livedo racemosa, retiform purpura, and acro-ischemia in COVID-19 patients, besides activation of coagulation system [11] due to viral load, it is the presence in some subjects in selected populations with a background of thrombophilia factors. Coagulopathy is shown to be associated with higher mortality and the use of anticoagulants has been reported with variable outcomes [103]. However, some reports have shown more promising results with the use of soluble thrombomodulin and heparin [104].

Afro-Americans have genetically and increased serum levels of lipoprotein a [Lp(a)] than Caucasians and Asians subjects. Lp(a) is an isolated risk factor for cardiovascular, peripheral arterial and cerebrovascular diseases, and impaired fibrinolysis, because it competes with plasminogen, and has prothrombogenic properties. There are ethnic differences in Lp(a) levels because subjects of African descent have about twice as high levels as Caucasians, Hispanics, and many Asian populations, while intermediate levels are reported for South Asians [105]. This observed interethnic difference could also be due to the apo(a) allele distribution in the subset of the population that presumably left Africa and subsequently gave rise to other population groups [105, 106]. We might make a parallel clinical setting with multi-organ inflammation and hypercoagulability in severe COVID-19, besides complement system activation, and endothelial dysfunction demonstrated by Magro et al. [11]. Enkhmaa et al. [105] suggested a significant association between elevated serum amyloid A, an HDL-associated systemic inflammatory biomarker, and a higher allele-specific Lp(a) level for smaller apo(a) size was found in African and Afro-Americans subjects.

Taken together, these findings suggest a potential for an additive effect between molecular properties of Lp(a), in particular, small size apo(a) (with elevated serum levels), and inflammation in promoting Lp(a)-associated CVD risk [105]. Furthermore, fibrinogen was positively correlated with Lp(a) levels in Japanese and Caucasians and independently predicted levels [105–108]. Consistent with this finding, fibrinogen was also significantly associated with Lp(a) levels in older Italian subjects [105, 109]. An inflammatory score summarizing the intensity of the pro-inflammatory state based on four different biomarkers (CRP, fibrinogen, IL-6, and IL-1 receptor antagonist) was significantly correlated with Lp(a) concentration in this study [109]. Among Spanish Caucasian subjects with metabolic syndrome, the CRP concentration was two-fold greater in subjects with high Lp(a) concentrations ($\geq$ 30 mg/dl) [110].

Otherwise, Caucasian patients have more prevalence of minor allele frequency for Factor V (Leiden) mutation (rs6025) (0.6–7.3%) among different regions of Europe, than other ethnic groups, as Hispanics (0.4–1.4%), Asians (0.0–3.8%), and Afro-Americans (0.6–0.7%), but almost similar to African subjects (1.0–10.2%) [111]. Thus, in the presence of genetic thrombophilia in a patient with COVID-19, there is theoretically a greater possibility of thrombotic events occurring, both in the macro and microcirculation.

ABO gene polymorphism rs8176719, the insG allele which produces non-O blood group phenotype confers

a 1.5-fold risk of developing venous thromboembolism (VTE), presumably because of a 25% increase levels of von Willebrand factors and factor VIII of coagulation in subjects of non-O blood groups, then in those with O blood group [111–113].

Taking all data together, these thrombophilic genetic conditions might begin to explain the elevated number of fatalities among American, Afro-American, and European populations when compared to Asian subjects in the clinical setting of severe COVID-19.

When discussing possible actions of SARS-CoV-2 on human skin that could result in potential dermatological manifestations, there is still room for more investigation. Excessive activation of inflammatory mediators creating a "cytokine storm", leading to damage to the endothelium; formation of multiple thromboses in the microvasculature of the skin; changes in the cellular component of immunity with activation of the complement system, as well as, the possibility of direct entry of SARS-CoV-2 entry via receptor ACE2 and protease TMPRSS2 in the human endothelial cell in dermal blood vessels cannot be excluded such as possible mechanisms if the possibility of virus circulation in the blood is proved. In any case, the problem of skin manifestations pathogenesis in patients with COVID-19 needs further investigation.

Conclusions

Several viral infections are related to eliciting innate and adaptive human immune responses. In some circumstances, as previous SARS-Cov, MERS-Cov, and SARS-CoV-2 the monocytic–macrophage system may produce an upregulated immune response (sHLH/MAS-like), severe inflammatory systemic state and damage in lungs and other internal organs, often hematological system, gastrointestinal tract, and kidneys. The activation of mast cells and basophils, by direct and/or indirect viral effect, is a possible event and it is important to be alert to skin manifestations such as the onset of urticaria, atopic dermatitis, or the exacerbation of these conditions, rashes, neutrophilic dermatoses and skin manifestations of hypercoagulable states, such as acral ischemia. Considering the cutaneous manifestations described, some aspects of SARS-CoV-2 infection may be caused by cytopathic effects on the endothelium dermal vessels or even stimulated by cytokines in arterioles and capillaries. The direct cytopathic effect of SARS-CoV-2 can occur in the described vesicular or papular–vesicular lesions, which are very similar to those caused by the Herpesviridae family. Rashes may be para-viral due to cytokines or due to drug exposure during treatment of the disease. Photography and anatomopathological studies are critical for the correct diagnosis and for establishing differential diagnosis with other cutaneous or systemic conditions, which may or may not be chronologically and causally related to COVID-19 or be casual events.

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Compliance with ethical standards

Conflict of interest None.

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