



Dermatological aspects of SARS-CoV-2 infection: mechanisms and manifestations

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Abstract

The human infection caused by the novel SARS-CoV-2 is a public health emergency of international concern. Although the disease associated to this virus, named COVID-19, mainly affects the lungs, the infection can spread to extrapulmonary tissues, causing multiorgan involvement in severely ill patients. The broad infective capacity of SARS-CoV-2 is related to the pattern of expression of the viral entry factors ACE2 and TMPRSS2 in human tissues. As such, the respiratory and gastrointestinal tracts are at high risk for SARS-CoV-2 infection due to their high expression of ACE2 and TMPRSS2, which explains the clinical phenotype described in the vast majority of infected patients that includes pneumonia and diarrhea. Recently, preoccupation about the potential of the virus to infect the skin has been raised by dermatologists due to the increasing observations of cutaneous manifestations in patients with SARS-CoV-2 infection. Although there is little evidence of the expression of ACE2 and TMPRSS2 in the normal skin, the dermatological findings observed among COVID-19 patients warrants further investigation to delineate the mechanisms of skin affection after SARS-CoV-2 infection. Here, we provide a summary of the dermatological findings observed among patients with laboratory-confirmed SARS-CoV-2 infection based on recent reports. In addition, we analyze possible mechanisms of skin injury in COVID-19 patients and discuss about the risk of individuals with chronic skin conditions for SARS-CoV-2 infection. The present review constitutes a useful informative tool to improve our understanding of the pathophysiological mechanisms of COVID-19 and the possible implications of the current pandemic in dermatology.

Keywords Skin · SARS-CoV-2 · COVID-19 · Viral skin infections · Cutaneous manifestations · Rash

Introduction

The world is facing a global pandemic of unprecedented features due to the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As on June 1st of 2020 [109], the coronavirus disease 2019 (COVID-19) has caused more than 6 million cases and 371,000 deaths around the world, putting several health care systems at risk of collapse. This new viral infection is clinically characterized by mild respiratory symptoms in the vast majority of affected individuals, including dry cough, fever, nasal

congestion, anosmia, myalgia, and fatigue [18, 37, 45, 82, 107]. These unspecific manifestations appear 4 to 5 days after the initial infection [45], making difficult to detect positive cases during the incubation period and contributing to the inadvertent viral transmission by asymptomatic individuals [40].

In another 15% of the cases, the virus can affect the lung, causing pneumonia with atypical features in radiological studies of the lung, such as bilateral and multilobe consolidations, as well as ground glass opacities [17, 45, 54]. Unfortunately, the disease can progress to severe acute respiratory syndrome (SARS) in about 5 to 30% of infected persons, requiring intensive medical care and mechanical ventilation [18, 37, 45, 82, 107]. This generates high mortality rates, especially among people with comorbidities such as diabetes, obesity, systemic arterial hypertension (SAH), chronic obstructive pulmonary disease (COPD) [46, 61, 64, 82, 91, 108, 110], among others. Current estimations show an overall 4 to 6% mortality, although a recent study

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demonstrated that 8 out of 10 patients requiring mechanical ventilation succumb to the infection [82].

Severely ill patients can also develop multiorgan failure due to the injury of kidney, liver, heart and even pancreas, as demonstrated by high levels of creatinine, urea, AST, ALT, CPK, amylase and lipase in such patients [45, 82]. Furthermore, recent evidence of gastrointestinal symptoms [13, 111], as well as data of olfactory neuropathy [57], peripheral nerve injury, myopathy, stroke [72], encephalitis [77], and Guillain–Barre syndrome [100, 121], strengthen the notion about a broad infective capacity of SARS-CoV-2 to affect multiple organs other than the lungs.

Strikingly, concerns about the potential of the virus to infect the skin have recently been raised by dermatologists due to the increasing observations of cutaneous manifestations in patients with SARS-CoV-2 infection [2, 32, 81]. Despite this, little attention has been put to these dermatological findings, which remain not well characterized until now. Moreover, the mechanisms of skin injury in COVID-19 patients have not been explored. Thus, a better understanding of the characteristics and origin of cutaneous manifestations is urgent to prevent and treat possible dermatological complications in individuals with COVID-19. For this reason, here we aimed to provide a summary of the dermatological findings observed during SARS-CoV-2 infection based on recent reports. In addition, we analyze possible mechanisms of skin injury in COVID-19 patients and discuss about the potential risk of individuals with chronic skin conditions like psoriasis.

Biology of SARS-CoV-2 and mechanisms of infection

SARS-CoV-2 is a novel member of the group of human coronaviruses (HCoVs), which is constituted by HCoV-229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43, SARS-CoV, and MERS-CoV [62]. These are RNA single-stranded viruses belonging to the Coronaviridae family that have caused a variety of respiratory diseases in the past, some of them of high severity as is the case of the 2002–2003 SARS-CoV that infected more than 8000 individuals around the world [58], and MERS-CoV which emerged in Saudi Arabia in 2012 causing high mortality rates [21, 117].

Based on sequence comparisons of viral genomes, HCoVs are grouped in four genera: alpha-, beta-, gamma- and delta-coronaviruses. The novel SARS-CoV-2 is a beta coronavirus genetically related with another bat coronavirus named BatCoV RaTG13, as well as with SARS-CoV [5, 122]. Furthermore, SARS-CoV-2 also shares genetic identity with coronaviruses isolated from pangolins [66, 119]. Hence, it is believed that COVID-19 is a zoonotic disease originated from bats or pangolins. The genome of

SARS-CoV-2 consists of a single RNA strand of 29.903 bp [122] that codifies for the replicase-transcriptase, as well as for the structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N).

The S protein of SARS-CoV-2 is important for the infection of host cells as it mediates the attachment to the receptor angiotensin I converting enzyme 2 (ACE2) [44, 105, 122], which is also recognized by the 2002–2003 SARS-CoV [60]. The S protein has two functional domains: the S1 domain contains the receptor binding domain (RBD) which attaches to ACE2, whereas the S2 domain mediates the fusion of viral and host cell membranes [105]. However, this protein requires to be primed by host proteases to attain a full infective capacity. For this purpose, SARS-CoV and SARS-CoV-2 use the transmembrane serine protease 2 (TMPRSS2), which executes the cleavage of the S protein at the S1/S2 and S'2 sites [34, 44, 73, 105]. Thus, host cells expressing ACE2 and TMPRSS2 are highly susceptible to SARS-CoV-2 infection.

After the entry into host cells, viral replication begins with the translation of the replicase-polymerase gene, and the assembly of the replication-transcription complex. This complex subsequently transcribes the genomic regions that codify for structural proteins. New virions are assembled in the endoplasmic reticulum and Golgi apparatus to finally egress from the cell [62]. Interestingly, SARS-CoV-2 possesses a polybasic furin cleavage sequence in the S1/S2 site, which is absent in other close related coronaviruses [5, 105]. This inserted furin cleavage sequence is processed at the Golgi apparatus during the biosynthesis of the S protein of novel virions inside the host infected cells [105]. Thus, the novel virions of SARS-CoV-2 may contain an S protein primed and ready to infect any other cells expressing the ACE2 receptor, with no further requirement of TMPRSS2 activity. This could expand the transmissibility and tissue tropism of SARS-CoV-2.

SARS-CoV-2 elicits an exuberant immune response which can mediate tissue damage specially among high risk groups [20, 74, 106, 115]. However, the immune receptors that recognize the viral infection and initiate the immune responses against SARS-CoV-2 are unknown. As this virus is genetically related to SARS-CoV, it is presumed that both viruses share mechanisms of infection. In this sense, the 2002–2003 SARS-CoV was shown to be recognized by the toll-like receptors (TLR) TLR3 and TLR4, which induce an immune reaction via MyD88 and TRIF pathways [88, 101]. Furthermore, SARS-CoV was found to be able to induce production of IL-1 β through the activation of the inflammasome [89]. In this regard, the activation of the inflammasome is also possible to occur during SARS-CoV-2 infection, as high levels of IL-1 β has been observed in COVID-19 patients [78]. Collectively, these data indicate

that SARS-CoV-2 can cause damage to different tissues due to the induction of strong inflammatory responses.

The spectrum of mucocutaneous manifestations of COVID-19

The skin is the primary site of infection of different human viruses including the herpes simplex virus 1 (HSV-1) and 2 (HSV-2), the vesicular stomatitis virus (VSV), and the molluscum contagiosum virus (MCV) [59, 76, 99]. In addition, this organ is a mirror of several viral systemic infections that cause indirect cutaneous involvement mainly in the form of rash and urticaria. This is the case of measles virus, parvovirus B19 [69], Epstein Barr virus (infectious mononucleosis) [48], HSV-6, HSV-7, HSV-8 [11], human immunodeficiency virus (HIV) [3], among others. Furthermore, several tropical and emergent viruses have been associated with the occurrence of cutaneous manifestations in the past, as is the case of dengue virus (DENV), chikungunya virus (CHIKV), and zika virus (ZIKV) infection [9, 29, 97]. In this sense, current evidence shows that SARS-CoV-2 can also affect the skin, causing a wide range of cutaneous manifestations. In this section, we summarize the spectrum of dermatological findings in COVID-19 patients. The possible mechanisms of skin injury after SARS-CoV-2 infection are discussed later.

Erythematous rash

In one of the initial descriptions of the clinical characteristics of COVID-19 patients from China, two out of 1099 patients presented rash of unspecified features [37]. This manifestation was later reported in 14 of 88 Italian patients with confirmed SARS-CoV-2 infection [81], two out of 103 French COVID-19 patients [41], as well as in seven isolated cases from France [70], Thailand [52], United States [47], Italy [118], Spain [6], and Mexico [68]. Although the description of the semiology of rash among COVID-19 patients remains incomplete, the phenotype observed in the mentioned cases shows that this is often presented as morbilliform maculopapular rash, mainly affecting the trunk, upper and lower limbs, sparing the face, palms, foot plants, and with no involvement of mucosa and conjunctiva. Rash of COVID-19 patients appears at the same time or during the first days after the onset of fever and respiratory symptoms, heals after a few days, and is not associated with the severity of the disease nor with the intake of drugs [81]. Concomitant itching is not common, but rash can be accompanied by petechia [6, 52]. In a patient from Italy, the rash was followed by the appearance of macular hemorrhagic rash in the lower limbs [84]. Furthermore, another case report also shows that the morphology of the rash associated to COVID-19 can be characterized by erythematous and edematous non-pruritic

annular fixed plaques affecting trunk and limbs but not the face [4].

These data indicate that rash in COVID-19 patients resembles classic characteristics of viral exanthema, thus, SARS-CoV-2 infection should be considered in the differential diagnosis of patients presenting with sudden onset of fever, respiratory symptoms, and rash. However, future studies evaluating the relationship between the temporal dynamics of rash and the kinetics of viral loads are warranted. This might help to inform about the potential of contagiousness of COVID-19 patients according to the timing of their rash appearance [93].

Vesicular eruptions

Vesicular lesions arising in the trunk and limbs have been observed in COVID-19 patients [32, 81, 84]. Their morphology can be monomorphic [32], or they can appear as chickenpox-like polymorphic vesicles [81]. Some of them may have hematic content, and frequently appear preceding respiratory symptoms in young patients with mild severity of disease [32]. These lesions last about a week and are accompanied by itching. In general, their appearance resembles lesions observed in other viral exanthemas. However, they might also look like herpetic lesions, as recently observed in two COVID-19 patients from Italy and one patient from Spain [96].

Urticarial lesions

Urticaria has been reported in 16% to 19% of patients that presented skin manifestations during COVID-19 disease enrolled in two studies conducted in Italy and Spain [32, 81], as well as in other six isolated cases from France, Belgium, Indonesia, and Madrid, Spain [27, 38, 41, 103]. Trunk was the main involved region [32, 81], although these lesions can also affect the face and acral regions [32, 38, 42]. Urticarial lesions usually appear at the same time than the rest of the symptoms. Nonetheless, in one case, the appearance of urticarial eruption preceded the onset of any fever or respiratory symptom [42]. These lesions are accompanied by itching, are more common in severe cases, heal in the first week after symptoms onset, and may respond to antihistamines [32, 38, 42, 103]. Urticarial lesions might not be directly related with the viral infection, and should be differentiated from a drug reaction, because most patients presenting urticaria had history of drug intake [32].

Pseudo-chilblains

Chilblains are acral lesions that occur as a result of skin ischemia frequently associated to cold exposure. These lesions are characterized by inflammatory itching papules on

the dorsal aspect of toes and fingers that are caused by damage to capillaries of skin. Interestingly, a recent paper has described the occurrence of chilblains in two asymptomatic patients with laboratory confirmed COVID-19 [2]. Similarly, asymmetric pseudo-chilblain lesions resembling perniosis were observed in 19% of patients that presented cutaneous manifestations of SARS-CoV-2 infection in a study conducted in Spain [32]. Finally, chilblains were described in two of 14 COVID-19 patients from France [12]. Chilblains were more common in young patients with mild forms of the disease, appeared late, healed in about 13 days, and were associated to pain and itching in approximately 30% of the cases [32].

Acro ischemia and livedoid lesions

Some studies have reported other signs of acral ischemia such as livedo reticularis and gangrene [12, 71, 120]. Livedo reticularis is often associated with reduced blood flow through the skin microvasculature that causes accumulation of deoxygenated blood. Its occurrence in COVID-19 patients might be related to events of micro-thrombosis of cutaneous capillaries [71], especially among patients with severe disease, who display a systemic procoagulant state due to the elevated levels of inflammatory cytokines, endothelial dysfunction, and disseminated intravascular coagulation [53, 92, 112]. Indeed, in a recent study of COVID-19 patients admitted to the intensive care unit, all participants with high levels of D-dimer, fibrinogen and fibrinogen degradation products, developed finger/toe cyanosis, skin bulla, and dry gangrene [120]. Similarly, in three hospitalized patients with pneumonia associated with SARS-CoV-2 infection from Madrid, Spain, acro-ischemia in toes was documented after 17–28 days of admission [94]. Finally, two individuals from a French cohort of COVID-19 patients showed necrotic and non-necrotic purpura [12].

Other manifestations

Maculopapular lesions resembling pityriasis rosea, erythema elevatum diutinum, erythema multiforme, and Grover disease have been described among COVID-19 patients [25, 32, 49, 83, 84]. A case report also documented the appearance of confluent and pruritic erythematous-yellowish papules limited to both heels 10 days after the onset of respiratory symptoms in a female patient with confirmed SARS-CoV-2 infection [26]. Furthermore, other manifestations similar to cutaneous autoimmune vasculitis, including symmetric perimaleolar urticaria and vasculitic purpura have been observed in COVID-19 patients [16]. Also, prodromal erythematous-edematous plaques in elbow and knee joints that latter evolve to urticarial lesions have been reported in a patient from Brazil [22]. Meanwhile, no evidence of mucosal

involvement has been reported so far, although some studies have demonstrated that the incidence of conjunctivitis is an important clinical finding in severely ill patients [67]. The studies describing mucocutaneous manifestations of SARS-CoV-2 infection are summarized in Table 1.

What is the origin of dermatological manifestations of SARS-CoV-2 infection?

Expression of ACE2, TMPRSS2 and other viral entry factors determines tropism of SARS-CoV-2

The risk of a specific human tissue/organ for SARS-CoV-2 infection is determined by the presence of the viral entry factors ACE2 and TMPRSS2 in local cells. ACE2 is primarily found in alveolar epithelial cells, explaining the high vulnerability of lungs to infection [39, 124]. Expression of ACE2 has been reported in several tissues, such as endothelium, heart, kidney, lymphoid organs, pancreas, testes, gastrointestinal and urinary tract [13, 28, 39, 65, 113, 124]. Recent studies have also demonstrated high expression of ACE2 along the gastrointestinal tract, including the stomach, small intestine, and colon [13, 95]. Furthermore, this receptor is abundant in the respiratory epithelium of the nasopharynx [95], as well as in the oral mucosa [113]. Meanwhile, TMPRSS2 has been observed mainly at prostate, kidney, salivary gland, lung, and pancreas, as well as along different parts of the gastrointestinal tract [19, 63, 102]. The expression of TMPRSS2 is upregulated by androgens [63], which could explain the higher severity and mortality of COVID-19 in men [51].

Despite these data, the multiorgan infection pattern of SARS-CoV-2 does not completely match the tissue distribution of ACE2 and TMPRSS2 [24, 36]. For instance, co-expression of these receptors in the lung is low under normal conditions, even when this is the most affected organ in COVID-19 patients. Nonetheless, both entry factors are present along the gastrointestinal tract [43, 95]. This indicates that the oral route is also important for contagion besides the respiratory route.

Other tissues can also be affected by the virus even when they do not express detectable levels of ACE2 and TMPRSS2. This is the case of lymphoid organs and the brain [7, 24, 36, 98]. The mechanism employed by SARS-CoV-2 to infect these organs is unknown, but it may be related with a possible spread from adjacent tissues. For instance, high expression of ACE2 has been documented in endothelial cells at the vascular niches of different organs [39], and SARS-CoV-2 has demonstrated capacity to infect the endothelium [104]. Thus, it is possible that some tissues might be infected due to the contiguity of their local cells with the endothelium of blood vessels.

Table 1 The spectrum of mucocutaneous manifestations of SARS-CoV-2 infection

Clinical findings	No. of patients	Author	Country	Refs.
Rash	2 / 1099	Guan et al.	China	[37]
	14/88	Recalcati et al.	Italy	[81]
	2 / 103	Hedou et al.	France	[41]
	1 case report	Mahé et al.	France	[70]
	1 case report	Joob et al.	Thailand	[52]
	1 case report	Hunt et al.	United States	[47]
	1 case report	Amatore et al.	France	[4]
	1 case report	Zengarini et al.	Italy	[118]
	1 case report	Avellana-Moreno et al.	Spain	[6]
	1 / 3	Sachdeva et al.	Italy	[84]
	2 / 2	Macedo-Pérez et al.	Mexico	[68]
	Vesicular lesions	9% / 375	Galván-Casas et al.	Spain
1 / 88		Recalcati et al.	Italy	[81]
3 / 130		Tamarro et al.	Italy / Barcelona	[96]
1 / 3		Sachdeva et al.	Italy	[84]
Urticarial lesions	19% / 375	Galván-Casas et al.	Spain	[32]
	3 / 88	Recalcati et al.	Italy	[81]
	2 / 103	Hedou et al.	France	[41]
	1 case report	Henry et al.	France	[42]
	2 / 2	Van Damme et al.	Belgium	[103]
	1 case report	Gunawan et al.	Indonesia	[38]
Chilblains	1 case report	Falkenhain-López et al.	Spain	[27]
	1 case report	Alramthan et al.	Kuwait	[2]
	19% / 375	Galván-Casas et al.	Spain	[32]
Livedo reticularis	1 / 14	Bouaziz et al.	France	[12]
	1 case report	Manalo et al.	United States	[71]
Acral cyanosis/dry gangrene/necrotic purpura	1 / 14	Bouaziz et al.	France	[12]
	7 / 7	Zhang et al.	China	[120]
	3 / 3	Suarez-Valle et al.	Spain	[94]
	1 / 14	Bouaziz et al.	France	[12]

Other cutaneous manifestations reported in COVID-19 patients include maculopapular lesions resembling pityriasis rosea, erythema elevatum diutinum, erythema multiforme, Grover disease, cutaneous vasculitis, and elbow/knee joint erythematous-edematous plaques [16, 22, 25, 32, 49, 83, 84]

Another possibility is that the expression of ACE2 and TMPRSS2 in different organs could be overregulated by circulating inflammatory mediators produced in response to the infection. A recent study shows that the cytokine interferon gamma can induce the overregulation of ACE2 in lung epithelial cells [123], thereby enhancing the capacity of SARS-CoV-2 to infect the respiratory tract. Finally, in the absence of TMPRSS2, SARS-CoV-2 can utilize cathepsin B and cathepsin L as alternative proteases for the priming of the S protein, allowing the infection of other tissues and organs expressing ACE2 but not TMPRSS2 [44]. Taken together, these data indicate that SARS-CoV-2 can affect several organs other than the lungs.

Expression of viral entry factors in the skin and possible mechanisms of cutaneous injury after SARS-CoV-2 infection

The reports of dermatological manifestations in patients with COVID-19 suggest a possible cutaneous tropism of SARS-CoV-2 [2, 32, 81]. However, despite the wide tissue expression pattern of ACE2 and TMPRSS2, the presence of these viral entry factors in the skin has not been comprehensively assessed. Some studies have shown that ACE2 is detectable in the basal layers of epidermis, as well as in hair follicles [35, 39]. Nonetheless, the presence of ACE2 in skin specimens was related to its expression by endothelial cells of cutaneous capillaries but not

in specific subsets of skin cells, such as keratinocytes or melanocytes. Other studies analyzing the expression of ACE2 in skin specimens using single cell RNA-seq technologies have shown that an extremely low proportion of skin cells, mainly represented by keratinocytes, express this receptor [114]. This indicates that, at least under homeostatic conditions, the healthy skin cannot be directly infected by SARS-CoV-2. Hence, mucocutaneous manifestations observed in COVID-19 patients might have an indirect origin (Fig. 1). Indeed, as mentioned before, recent evidence demonstrates that SARS-CoV-2 can infect endothelial cells [104], and clinical findings of skin vasculitis have been observed among COVID-19 patients [16]. This might result in endothelial dysfunction, microthrombosis, and hypoxia in different organs including the skin. Cutaneous lesions reported during SARS-CoV-2 infection are related to skin hypoxia as aforementioned [12, 32]. Endothelial infection and high circulating levels of inflammatory cytokines may also cause vasodilatation and edema, which might lead to the appearance of rash and urticarial lesions [81].

Alternatively, it is possible that ACE2 expression in skin cells could be upregulated by inflammatory mediators produced in response to the virus, since as mentioned before, proinflammatory cytokines overregulate the expression of this receptor in other organs [123]. This might result in an increased risk of patients with chronic inflammatory dermatological conditions to manifest signs of skin viral infection, as well as to present exacerbations of their underlying disease due to local effects driven by the virus. Finally, other potential molecules that could act as alternative receptors for SARS-CoV-2 might be expressed in the skin [50, 90], thus allowing the virus to infect this organ.

Implications of COVID-19 in dermatology

The literature curated in this review remarks the great potential of the current pandemic to impact on dermatology, which is undoubtedly one of the areas of medicine at the front line against SARS-CoV-2. With the increasing number of confirmed cases around the world, it is highly

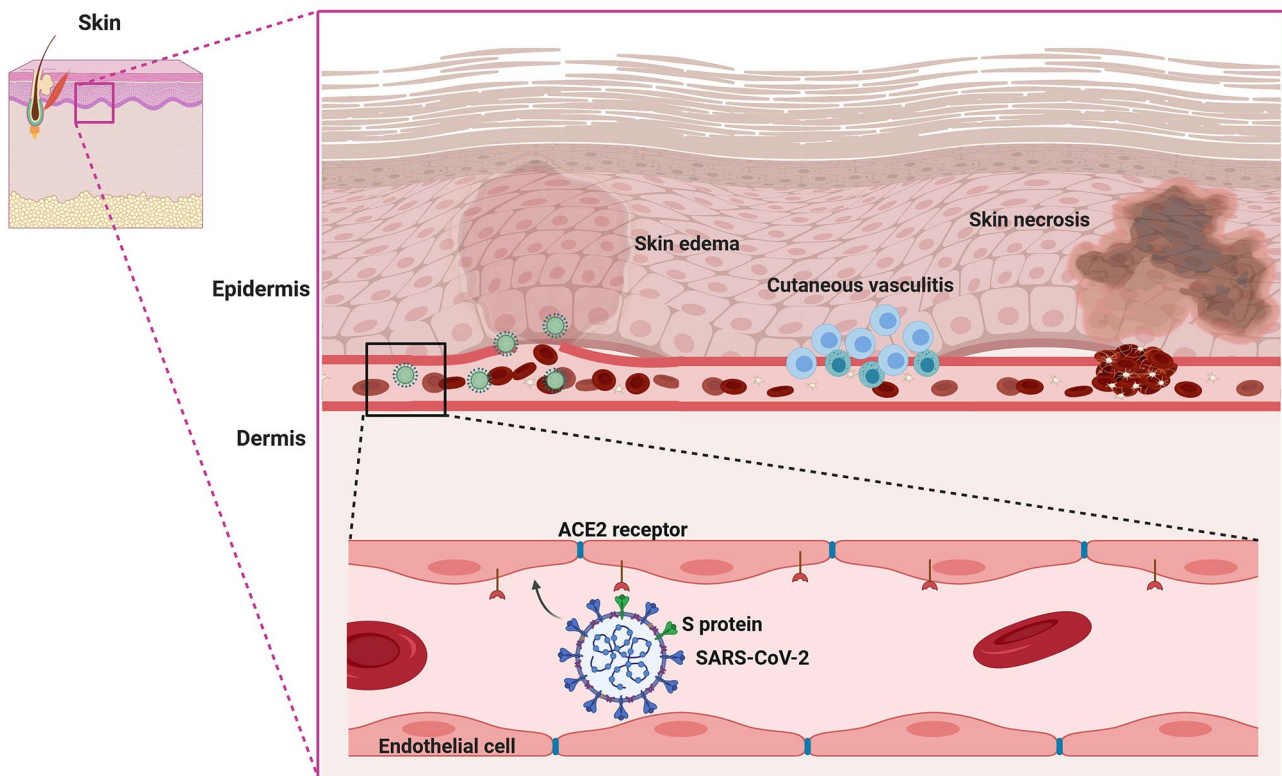


Fig. 1 Possible mechanisms of skin injury after SARS-CoV-2 infection. Lack of expression of the viral entry factors ACE2 and TMPRSS2 in the normal skin suggests an indirect origin of mucocutaneous manifestations of SARS-CoV-2 infection. Nonetheless, ACE2 expression has been detected in endothelial cells from the cutaneous microvasculature at the dermoepidermal junction. Furthermore, SARS-CoV-2 can directly infect the endothelium of different

organs, causing endothelial dysfunction. This might lead to edema in the skin, explaining rash and urticarial lesions observed among COVID-19 patients. Furthermore, infection of the endothelium can cause cutaneous vasculitis. Finally, endothelial dysfunction could result in micro-thrombosis, ischemia, and necrosis of the skin, which explains the observation of acral chilblains, toe/finger cyanosis, and dry necrosis in severely ill COVID-19 patients

likely that dermatologists will be in contact with COVID-19 patients, some of which might present mucocutaneous manifestations of the disease. Thus, it is mandatory to improve our knowledge about the mechanisms of SARS-CoV-2 infection, as well as about the clinical picture of COVID-19 patients that develop cutaneous manifestations. Although little literature exists about the dermatological aspects of COVID-19 so far, available data show a wide range of possible cutaneous manifestations that must be timely recognized to establish an opportune treatment and avoid dermatological complications among patients with laboratory-confirmed infection. In addition, it is crucial to maintain a high degree of clinical suspicion about possible SARS-CoV-2 infection in patients attending with an acute dermatosis, such as erythematous rash accompanied by fever, to prevent inadvertent contagion to dermatologists, especially if patients do not present respiratory symptoms initially.

Furthermore, great attention should be paid to the possible association between the pharmacological agents used to treat the infection and the development of new cutaneous lesions. For instance, hydroxychloroquine has been associated with rash, hyperpigmentation of the skin, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, among other dermatological side effects [87]. Similarly, reports of cutaneous side effects of tocilizumab, a humanized monoclonal antibody against the interleukin-6 (IL-6) used in the management of severely ill COVID-19 patients [1], has been described in the past [56, 79]. Indeed, tocilizumab administration was recently associated to the acute onset of pruritic generalized rash and eosinophilia in a patient with confirmed SARS-CoV-2 infection [86].

The implications of the pandemic caused by SARS-CoV-2 may obligate to some changes in the normal care to patients with dermatological disorders at medical centers that were re-allocated to receive patients with COVID-19 [33]. Of special importance is the possible impact of this pandemic in the management of patients with chronic inflammatory conditions of the skin due to the interruption of activities at many dermatology clinics. This type of patients might also be at higher risk for SARS-CoV-2 infection, as demonstrated before in the case of patients with psoriasis, which is a condition independently associated with an increased risk of serious infections [80]. A special attention should be paid to patients under biological therapies for inflammatory cutaneous disorders [85, 116], such as those receiving anti-tumor necrosis factor therapy. Although tumor necrosis factor seems to play a pathogenic role in severe cases of COVID-19 [30], this cytokine might also mediate a protective function in other patients with less severe forms of the disease. Thus, pharmacological blocking of tumor-necrosis factor in patients with psoriasis might cause an increased risk for SARS-CoV-2 infection.

This dual role of inflammatory mediators in the pathogenesis of COVID-19 might have important implications for the use of biologics targeting different cytokines in patients with psoriasis and other inflammatory, autoimmune, and allergic skin disorders. In this regard, although the protective or pathogenic role of the IL-23/IL-17 axis in immune responses against SARS-CoV-2 is unknown, three reports of psoriatic patients receiving anti-IL-23 and anti-IL-17 antibodies showed no increased risk of severe disease after testing positive for COVID-19 [8, 10, 75], and even one case showed improvement of the respiratory symptoms after the administration of Guselkumab [10]. Meanwhile, blocking type 2 cytokine axes seems not to increase the risk of SARS-CoV-2 infection, as demonstrated by several reports about the safety of dupilumab, a human monoclonal antibody against the alpha subunit of IL-4 receptor, in patients with atopic dermatitis [14, 15, 31].

Finally, the impact of SARS-CoV-2 infection in the immunosuppressive therapy of patients with other autoimmune skin disorders is unknown. Nonetheless, some authors and dermatology associations have not recommended to discontinue immunosuppressant drugs, as it is possible that the reactivation of the underlying pathology could imply additional risk to SARS-CoV-2 infection [23, 55].

Conclusions

The clinical phenotype of COVID-19 encompasses a spectrum of cutaneous manifestations of varying severity. The present review constitutes a useful informative tool to improve our understanding of the pathophysiological mechanisms of SARS-CoV-2 infection, as well as about the possible implications of the current pandemic in the field of dermatology.

Author contributions MG-S, and JC-B conceived the idea of the manuscript, participated in the analysis of scientific literature, and contributed to the writing process of the paper. JC-P searched and analyzed scientific literature and drafted the manuscript. All the authors read and approved the final version of the paper.

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Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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