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REVIEW ARTICLE

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Immunological aspects of COVID-19-related skin manifestations: Revisiting pathogenic mechanism in the light of new evidence

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Abstract

The newly emerged coronavirus disease 2019 (COVID-19), induced by a novel strain of the coronavirus family, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a rapidly spreading global threat. This virus affects a fair number of tissues in the human body by availing itself of potential target receptors like Angiotensin-Converting Enzyme 2 (ACE2). Presenting with diverse clinical manifestations, COVID-19 has raised the urge for extensive research in different medical fields, including dermatology. Developing a comprehensive knowledge of cutaneous manifestations is highly important as it can help us in early diagnosis and better management of the ongoing pandemic. The dermatological presentations of COVID-19 are classified into main categories of vascular and non-vascular (exanthematous) patterns. Though not yet fully confirmed, the pathogenesis of these cutaneous presentations has been suggested to be more related to the overactivation of the immune system. In this review, we discuss in detail the clinical features of the diverse skin lesions in COVID-19 patients and the imperative role of the immune system in their pathogenesis and development. Furthermore, we will discuss the reasons behind the accentuation of skin lesions in COVID-19 compared to the same virus family predecessors.

KEYWORDS
COVID-19, cytokine storm, dermatology, immunology, SARS-CoV-2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), induced by a novel strain of the coronavirus family, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global public health crisis. SARS-CoV-2 engages host cell receptors through angiotensin-converting enzyme 2 (ACE2), the spike receptor that facilitates viral entry to host cells. ACE2 is expressed in a variety of organs, including cutaneous and subcutaneous tissues and therefore contributes to dermatologic findings of the disease. ACE2 expression is considerably higher in keratinocytes than other skin cells such as fibroblasts and melanocytes.[1]

Dermatological manifestations associated with COVID-19 have been considerably reported. Some of these might have a pivotal role in increasing diagnostic accuracy. Cutaneous manifestations of COVID-19 can be classified into either exanthematous or vascular. Viral exanthems result from the immune response to viral nucleotides in the skin, while vasculopathic or micro-thrombotic skin lesions are the consequence of a systemic immunologic response to SARS-CoV-2 infection.[2]

The human immune system plays a double-edged sword-like role in the course of COVID-19 infection. Both cellular and humoral adaptive immune responses are integral in SARS-CoV-2 virus clearance,

though may potentially contribute to the exacerbation of the disease by causing excessive inflammatory responses. This is induced through a sudden increase in the amount of different pro-inflammatory cytokines in circulation and the subsequent influx of various immune cells into the infection site. Subsequently, immunopathological conditions referred to as "cytokine storm" and macrophage activation syndrome (MAS) emerge that could lead to multi-organ failure. Thus, two interesting aspects of SARS-CoV-2 functions in confrontation with our immune system are the way it blocks immune responses (i.e., lymphopenia and decreased T-cell count[3]) and the way it contributes to disease progression by exaggerating immune responses (i.e., cytokine storm).

The mainstays of immunity components in the skin against viral infection are macrophages, lymphocytes, dendritic cells, and mast cells. Studies have discovered deposition of complement components, C5b-9 and C4d, within the cutaneous microvasculature of patients presenting petechiae and purpura, which are colocalized with spike glycoproteins of SARS-CoV-2. Moreover, endothelial damage in the dermo-hypodermal junction as well as upper dermis, possibly due to secondary damage by COVID-19 infection, has been detected.

As the etiological agent of this respiratory tract infection rapidly continues to evolve, and new variants of the virus emerge in different countries, developing a thorough guide for desirable management of the ongoing pandemic entails knowledge of all potential clinical characteristics. In this review, we provide a comprehensive overview of varied cutaneous presentations observed in COVID-19 patients, and the possible role of immune responses of the body in evoking skin reactions. Furthermore, we make a delicate comparison among the spectrum of skin manifestations of similar viral infections and mention the gaps in the current knowledge to aid future studies.

2 | CUTANEOUS MANIFESTATIONS OF COVID-19

As the newly emerging COVID-19 challenges different fields of medicine, dermatology has come under more scrutiny compared with the similar viral pandemics of the past. Gaining a comprehensive understanding of accompanying dermatological features of COVID-19 is expected to be useful in identifying asymptomatic carriers with skin signs and also will help in better understanding whether these signs could be a part of the potential transmission route for COVID-19.[4] Recently, these manifestations have been reported to happen either alone or before other classical symptoms and to be of considerable diagnostic value.[5] Table 1 summarizes some features of the above-mentioned cutaneous manifestations.

2.1 | Lesions with exanthema pattern

Acute urticaria has been documented in COVID-19 patients both with and without angioedema. Studies suggest that urticarial rash combined with pyrexia is suggestive of more severe COVID-19 infection.[6]

In general, urticaria results from increased vascular dilation and permeability (Figure 1). The pathophysiological process responsible for inducing urticarial lesions in COVID-19 has not been evaluated specifically. However, the degranulation of lung residing mast cells has been implicated in the pathogenesis of COVID-19-related respiratory diseases, and thus it could be speculated that a similar condition may also happen regarding the mast cells within the dermal layer of the skin. The classical complement pathway is activated through IgG auto-antibodies bound to IgE or IgE receptor on mast cells and produces C5a, leading to mast cell activation and secretion of mediators that give rise to urticarial lesions.[22] Since the onset of urticarial lesions is earlier than the time predicted for the formations of antibodies after SARS-CoV-2 infection, it seems that the classical pathways cannot fully explain the occurrence of such lesions.[23] Studies on other viral-associated urticaria have suggested that the innate immunity receptors may be responsible for mast cell activation in early lesions.[24] Additionally, drug-induced urticarial reactions resulting from type I drug hypersensitivity reactions, direct mast cell activation, immune complex formation, and complement activation during serum sickness should always be considered in the setting of COVID-19.[25]

Vesicular rashes have been documented numerously in patients afflicted with COVID-19. Although none of the COVID-19 skin presentations is proven to be specific for COVID-19, a study has hypothesized that varicella-like exanthems could be specific COVID-19-associated skin manifestations.[26] They are associated with the intermediate severity of the disease, and show either diffuse polymorphic or localized monomorphic patterns.[8]

The vesicles are suggested to result from either direct cytopathic effects of SARS-CoV-2 or the over-reactivity of the immune system.[27] The keratinocytes express the ACE2 receptor required for viral entry to the cells. This fact makes them potential target cells for the virus in the state of viremia and also suggests that in case of skin barrier dysfunction, SARS-CoV-2 can be transmitted via the percutaneous route.[1] Thus hypothetically, SARS-CoV-2 could infect keratinocytes and induce cytopathic effects. However, this does not seem to be the case for COVID-19 since the occurrence of vesicular lesions is relatively rare. Unlike typical vesicle forming viral infections such as herpes and varicella-zoster, which have complex machinery that allows them to replicate in the keratinocytes and produce glycoproteins that promote cell-to-cell fusion, the SARS-CoV-2 has only occasionally been isolated from skin lesions.[28,29] Accordingly, it could be speculated that the immunological mechanisms might be responsible for these lesions. Expression of certain virus RNA fragments by keratinocytes, cross-reaction between viral antigens and skin-specific antigens, and epitope spreading are some of the proposed mechanisms.[30]

Erythema multiforme (EM), associated with viral infections, has been observed in COVID-19 patients. It is reported to mostly occur in children; thus, it is associated with a milder COVID-19 course.

One theory proposed that EM results from an immune attack on keratinocytes by CD4+ T cells. Fragments of viral nucleic acids are up-taken by scavenger cells such as precursors of Langerhans cells.

TABLE 1 Classification of COVID-19 cutaneous manifestations' features

Skin lesion	Frequency	Age group	Onset	Duration	Important DDX	Histopathologic findings	Management	References
Urticarial lesions	7%–40%	Adults (middle-aged)	Early phase of the infection	6.8 days	Acute idiopathic urticaria; Urticarial drug-induced rash	Perivascular infiltrate of lymphocytes; a few eosinophils and upper dermal edema	Antihistamines and steroids; ketotifen; omalizumab; cyclosporine A; montelukast; epinephrine	6,7
Vesicular lesions	1.1%–15%	Adults (middle-aged)	Before other symptoms	10 days	Chickenpox rash; AGEP	Intraepidermal vesicles associated with mild acantholysis and ballooned keratinocytes; basket-weave hyperkeratosis; slightly atrophic epidermis	Usually self-limiting; no confirmed treatment is available	7,8
Erythema multiforme	9.7%	Adults and children	After other symptoms	9.7 days	Herpes simplex -associated erythema multiforme	Epidermal spongiosis; dilated vessels in dermis filled with neutrophils; extravasation of red blood cells; lymphocytic perivascular and interstitial infiltrate	Steroids or antihistamines	7
Maculopapular lesions	16%–47%	Adults and children	Concomitantly with other symptoms	3–10 days	Drug-induced reactions; measles; pityriasis rosea	Mild spongiosis; basal cell vacuolation; mild perivascular lymphocytic infiltrate	Mostly self-limiting; corticosteroids and liberal moisturization	7,9,10
Pityriasis rosea	NR	Adults	3 days after the onset of COVID-19 pneumonia	NR	–	Mild diffuse epidermal spongiosis; spongiotic vesicles containing lymphocytes and Langerhans cells; slightly edematous papillary dermis; lymphohistiocytic infiltrate in the upper dermis	Mainly self-limiting; acyclovir; corticosteroids; Emollients; antihistamines; UV light	11
Chilblains	19%–40%	Adults	Later in the disease course	13 days	Chilblain lupus	Superficial and deep angiocentric and eccrinotropic lymphocytic infiltrate; papillary dermal edema; vacuolar degeneration of the basal layer and lymphocytic exocytosis to the epidermis and acrosyringia	Self-limiting; heating; NSAIDS; mid-to-high-potency topical steroids; vasodilators; recombinant ACE2; nitrovasodilators; RAAS inhibitors; Janus kinase inhibitors such as tofacitinib	12,13

(Continues)

TABLE 1 (Continued)

Skin lesion	Frequency	Age group	Onset	Duration	Important DDX	Histopathologic findings	Management	References
Livedo reticularis	2.3%–6%	Adults (the elderly)	Concomitantly with other symptoms	9.4 days	–	Perivascular lymphocytic inflammation; increased superficial dermal mucin; necrotic keratinocytes	Complement inhibitors (narsoplimab, eculizumab, AMY-101)	14
Retiforme purpura	NR	Adults	NR	NR	–	Pauci-inflammatory vascular thrombosis with extensive complement deposits; detection of SARS-CoV-2 protein localized to endothelial cells		15,16
CSSV	NR	Adults	NR	NR	Medication-induced or hypersensitivity vasculitis	Leukocytoclastic vasculitis with extravasation of red blood cells; basal epidermal necrosis; perivascular neutrophilic infiltration and fibrin deposition; Small vessel damage with fibrinoid necrosis of vessel wall; leukocytoclasia; extravasated erythrocytes; granular deposition of C3; Spongiosis, focal vacuolar degeneration of base keratinocytes and focal lymphocytic exocytosis; slight inflammatory lymphomorphonuclear infiltrate of the superficial dermis	Corticosteroids; colchicine; dapsone; olanzapine; quetiapine	17
Sacral ulcers	NR	Adults (middle-aged)	NR	NR	–	Fibrin thrombi in numerous blood vessels, consistent with a thrombotic vasculopathy	Wound care	18
Petechiae/ purpura	3%–11.8%	Adults (middle-aged)	After other symptoms	5 days	Enterovirus, parvovirus B19, and dengue virus-associated petechiae; drug-induced rashes by potential COVID-19 drugs, intravenous immunoglobulin (IVIG) treatments, and camostat mesylate	Significant interstitial and perivascular neutrophilia along with prominent leukocytoclastic; perivascular lymphocytic infiltrate with abundant red cell extravasation and focal papillary edema; focal parakeratosis and dyskeratotic cells in the epidermis	Corticosteroids	16,19

TABLE 1 (Continued)

Skin lesion	Frequency	Age group	Onset	Duration	Important DDX	Histopathologic findings	Management	References
SDRIFE	NR	Adults (the elderly)	Approximately 4 days after the onset of COVID-19 infection	NR	-	Subcorneal pustules and superficial infiltrates of lymphocytes and eosinophils	-	20
AGEP	Rare	Adults (the elderly)	After receiving treatment	NR	-	Subcorneal pustule with mild focal acanthosis and spongiosis; neutrophilic exocytosis; sparse Keratinocyte necrosis; a perivascular lymphocytic infiltrate with rare neutrophils and eosinophils	-	21

Abbreviations: ACE2, angiotensin-converting Enzyme 2; AGEP, acute generalized exanthematous pustulosis; CSSV, cutaneous small-vessel vasculitis; DDX, differential diagnosis; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; RAAS, Renin-angiotensin-aldosterone system; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; UV, Ultraviolet.

These cells eventually settle in the skin and, through unknown mechanisms, transfer these genetic materials to keratinocytes. These viral nucleic acids are translated to antigenic proteins and are expressed by MHC molecules on the surface of keratinocytes. CD4+ T-cells identify these foreign antigens and induce an IFN-γ mediated immune attack that results in the recruitment of natural killer (NK) cells, leukocytes, monocytes, and T cells, and Fas-induced keratinocyte apoptosis.[31] The isolation of nucleic acid particles of herpes simplex and orf from EM lesions supports this theory.[32,33] Alternative explanations include direct toxin effect, involvement of antigen–antibody (Ag-Ab) complexes, formation of neo-antigens, and promotion of antigen mimicry.[34] The Ag-Ab complexes travel through the vessels, precipitate within the distal skin capillaries and provoke a type III hypersensitivity reaction.[29]

Based on the time course of the appearance of the lesions and seroconversion, we assume that the pathogenesis of COVID-19 related EM lesions might be similar to herpes and orf related EM rather than the type III hypersensitivity reactions.[29] However, further studies utilizing polymerase chain reaction (PCR) testing of skin samples for SARS-CoV-2 are required for revealing the true nature of this reaction.[29]

Maculopapular or morbilliform lesions are the most common cutaneous manifestation observed in COVID-19 patients and associated with a more severe course of coronavirus infection.[7,9] However, since these lesions occur in the setting of severe infection where patients are also receiving multiple drugs, there is a bit of hesitancy in solely attributing the manifestations to the virus.[7] Thus, the morbilliform eruption is the least diagnostic manifestation of COVID-19.

Maculopapular exanthems are usually caused by drug hypersensitivity and T-cell-mediated delayed hypersensitivity. However, they can happen as a result of the interplay between drug-induced and virus-induced immune stimulation.[35] In viral infections other than COVID-19, the emergence of morbilliform eruptions is attributed to the activity of CD4+ and CD8+ T cells and cytokines against the virally infected keratinocytes, endothelial cells, and fibroblasts. In drug-induced maculopapular rashes, the main mechanism is the type IV hypersensitivity reaction that involves T cells.[25] Whether the pathogenesis of COVID-19 associated morbilliform eruption is similar to other viral exanthemas or not still remains elusive.

Pityriasis rosea is another cutaneous lesion associated with COVID-19. There is evidence that suggests a predominantly T-cell-mediated immune response against reactivated viruses such as human herpes virus-6 (HHV6) and HHV7 may be involved.[36] It has been suggested that a robust immunologic-inflammatory response to SARS-CoV-2 could result in endogenous viral reactivation, giving rise to pityriasis rosea lesions.[37] Reports have documented the reactivation of HHV6 and HHV7 after SARS-CoV-2 infection.[38] A large case series demonstrated that patients with COVID-19 and skin diseases (irrespective of the type of skin involvement) were significantly more likely to have positive HHV6 IgM antibodies than normal controls. However, there was no significant difference between COVID-19 patients with skin involvement and those without cutaneous manifestation in seropositivity.[39]

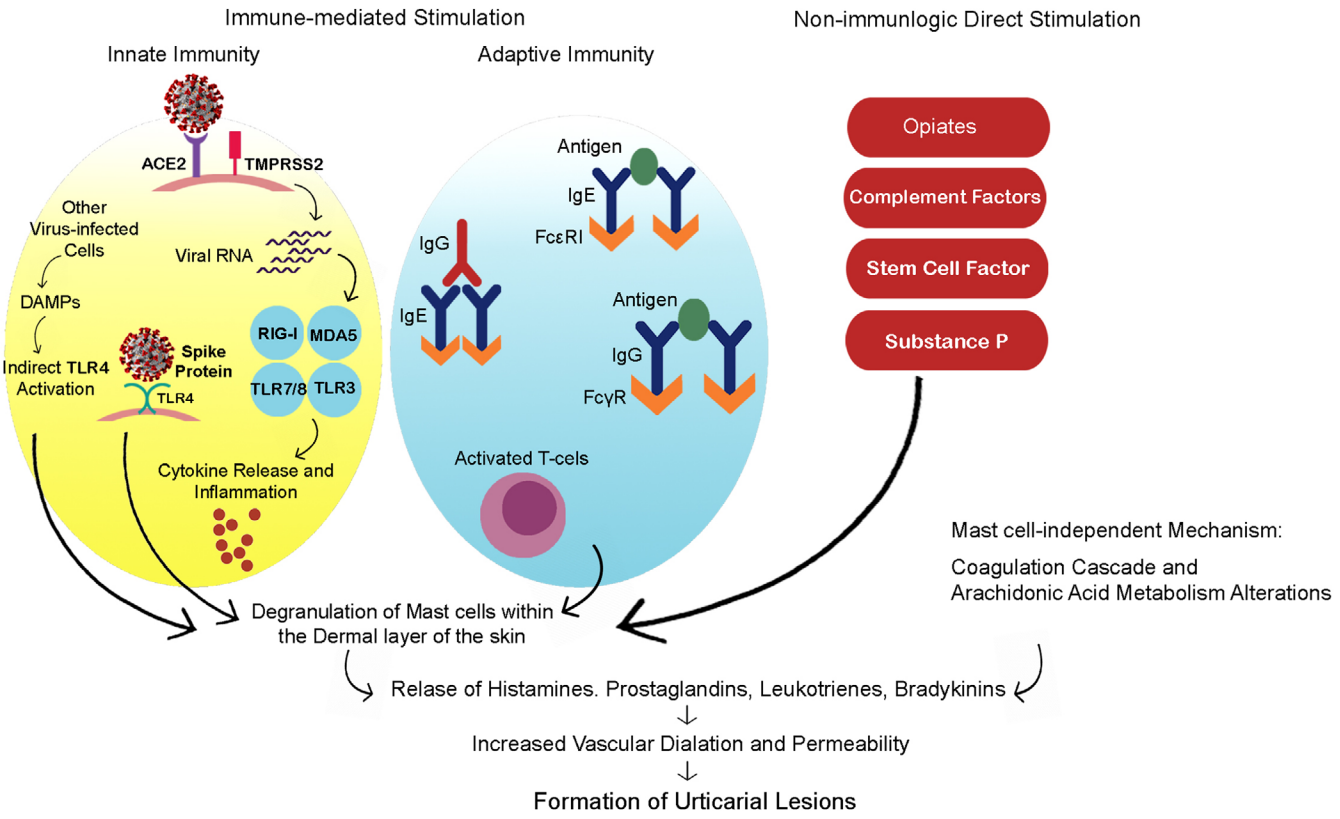

FIGURE 1 The proposed pathogenic mechanism of urticaria formation due to COVID-19 infection

2.2 | Lesions with vascular pattern

The ACE2 receptor is expressed in endothelial cells. Thus, a direct action of the virus on endothelial cells is plausible, and few cases have been able to detect SARS-CoV-2 viral particles in the endothelial tissue.[40] The SARS-CoV-2 infection could indirectly cause microvascular injury by triggering immune reactions that lead to uncontrolled complement activation. Also, COVID-19-associated imbalance in the coagulation pathway and disseminated intravascular coagulation (DIC) can contribute to the appearance of vascular lesions.

Chilblains, in COVID-19 patients, are presented as erythematous to violaceous papules or plaques.

One theory blames COVID-19-induced dysregulation of the renin-angiotensin-aldosterone system (RAAS) for the dysfunctional vascular response to the cold environment and the occurrence of chilblain lesions. Within the endothelial cells, this process could promote vasoconstriction and perniosis.

Another possible explanation for COVID-19-induced perniosis involves the overactive innate immune response and type I IFN production resembling familial chilblain lupus. This syndrome results from mutations in the *TREX1* gene. High levels of IFN result in the breach of self-tolerance and autoimmunity, which could target endothelial cells and induce vasculitis-like inflammation.[12]

It has been suggested that in the setting of SARS-CoV-2 infection, intracellular viral replication could trigger IFN production either through engaging with intracellular pattern recognition receptors or overwhelming the TREX1 enzyme, which leads to the activation of intracellular sensing elements.[41] It has been demonstrated that individuals suffering from chilblain lesions had increased levels of IFN-α after in vitro stimulation compared to age-matched SARS-CoV-2+ patients with mild-to-severe disease.[41] The higher levels of IFN-α also explain the lower rates of seropositivity and PCR positivity in these patients since they can eliminate the infection in its early stages before getting the adaptive immunity involved.[41]

Livedo reticularis (LR), livedo racemosa (LRC), and retiform purpura (RP) are less common cutaneous manifestations of COVID-19, yet they are associated with a high-grade severity of the disease.[10]

Livedo reticularis, livedo racemosa, and retiform purpura can result from multiple and sometimes overlapping etiologies, including vessel wall abnormalities (vasculitis, vasculopathy, calciphylaxis, and Sneddon syndrome) and intraluminal occlusion (due to abnormal blood components, cryoproteins, hypercoagulability, and emboli). The exact molecular mechanisms for COVID-19-induced LR, LRC, and RP are not fully understood. Based on studies on levels of D-dimer and fibrin degradation products as well as prothrombin time (PT), it is hypothesized that the hypercoagulability state plays an integral role.[42] Moreover, vascular inflammation caused by SARS-CoV-2 infection of endothelial cells could be another possible etiology. There is also evidence of complement activation in these patients.[15] Perhaps, the combination of these mechanisms is involved in the pathogenesis of these lesions in COVID-19.

Acral ischemia and necrosis, presenting with cyanosis of fingers and toes, cutaneous bullae, dry gangrene, and necrotic ulcer are the extreme examples of vascular compromise due to COVID-19-associated hemostatic abnormality (CAHA) with concomitant DIC, which is usually observed in critically ill patients with high mortality rates.[6,43]

Sacral ulcerations that are distinct from sacral decubitus ulcers have been reported in critically ill COVID-19 patients. Development of purpura, violaceous induration, livedoid plaques, and eschars sets them apart from decubitus ulcers. The pathogenesis of sacral ulcers is hypothesized to be a combination of systemic coagulopathy, cutaneous ischemia, and pressure-induced deep tissue injury.[18]

Cutaneous small-vessel vasculitis (CSVV) usually presents as purpuric lesions or erythematous urticaria-like papules with central purpura or hyperpigm entation without extracutaneous organ involvement.[18] These lesions are predominantly induced by immune complex deposition in the small vessels, bringing about complement-mediated inflammation and tissue destruction.[18] Also, Cutaneous leukocytoclastic vasculitis (cLcV) has been recently reported.[44]

2.3 | Other lesions

Petechiae with a less than 2 mm, and purpura with a greater than 2 mm diameter have been reported in association with severe COVID-19. Petechiae and purpura can evolve from maculopapular exanthema. They may also be a feature of purpuric vasculitis (CSVV). Thus varying pathophysiological mechanisms can be involved, including pauci-inflammatory thrombogenic vasculopathy due to extensive deposition of complement components C5b-9 and C4d within the cutaneous microvasculature and thrombocytopenia.[16] SARS-CoV-2 may lead to thrombocytopenia by several mechanisms, including bone marrow suppression, consumptive coagulopathy, immune-mediated platelet destruction, or cytokine release syndrome.[45]

Symmetrical drug-related Intertriginous and flexural exanthema (SDRIFE) represents an ill-defined erythematous rash in COVID-19 patients.[20] SDRIFE is considered to be a cutaneous reaction to systemic drug administration rather than infection with SARS-CoV-2.

Acute-generalized exanthematous pustulosis (AGEP) is a diffuse, pruritic pustular eruption on extremities and the trunk. It may occur as a severe, cutaneous adverse reaction to hydroxychloroquine.[21]

Mottling of the skin, unspecified erythematous rash, and telogen effluvium are other noticed cutaneous presentations in patients who tested positive for SARS-CoV-2.[6]

Although children had not been affected to a great extent during the first months of the pandemic, later on, multiple reports described an inflammatory syndrome in children with Kawasaki disease-like features named multisystem inflammatory syndrome in children (MIS-C).[46] Manifestations of MIS-C in the skin present as erythematous polymorphic rashes with additional purpuric manifestations. Skin manifestations associated with multisystem inflammatory syndrome in children (MIS-C) portend more enigmatic aspects of the disease.

3 | CUTANEOUS MANIFESTATIONS IN SIMILAR VIRAL INFECTIONS

Three global coronavirus outbreaks have emerged in the last decades: Severe acute respiratory syndrome (SARS) in 2002; Middle East respiratory syndrome (MERS) in 2012; and COVID-19 in 2019. Similar to COVID-19, in SARS and MERS infections, we can expect an upregulated immune response induced by the monocytic-macrophage system, and thus dermatological manifestations are also expected. However, very little is known about their cutaneous manifestations. Both SARS and MERS infections caused severe multi-organ disease, and compared to COVID-19, they demonstrated higher mortality rates in infected people. However, having a higher speed of transition, SARS-CoV-2 has more overall mortality. Thus, it raised considerably more global concern and a more efficient response, resulting in more research into different aspects of the disease, including cutaneous manifestations. Another proposed explanation for the ample evidence in the literature of cutaneous manifestations of COVID-19 compared to its predecessors is the large-scale use of different medications, causing dermatological complications that could be mistaken for direct skin manifestations of COVID-19.[4]

In addition to the epidemiological aspect, ACE2, which is expressed in the apical surface of the epithelial cells, is another component that makes skin diseases more distinguishable in COVID-19 compared with SARS and MERS infections. The virus engagement with ACE2 facilitates its entry to the cell via Transmembrane protease serine 2 (TMPRSS2) and the consequent release of pro-inflammatory cytokines.[25] Thus, the high ACE2 expression in the cutaneous tissue makes the skin more vulnerable to viral invasion. Likewise, the S protein of the MERS virus interacts with TMPRSS2, but its main receptor is dipeptidyl peptidase 4 (DPP4), which is also expressed on keratinocytes, melanocytes, mast cells, and fibroblast.[47] DPP4 is involved in the pathogenesis of bullous pemphigoid, cutaneous lymphoma, and melanoma.[47] In fact, few studies have discussed potential dermatological manifestations associated with MERS, such as petechia.[48] SARS-CoV employs the same receptor (ACE2) and cofactor (TMPRSS2) as the SARS-CoV-2 virus with two additional co-receptors, DC-SIGN (CD209) and L-SIGN (CD209L). Hypothetically, SARS-CoV could also infect keratinocytes and endothelial cells. However, there are no reports on dermatological findings in the SARS.[49]

Despite the insufficiency of reports in the context of cutaneous manifestations in other infections of the coronavirus family, a variety of different viruses, in particular respiratory viruses, have been associated with cutaneous manifestations.[30] These infections include influenza type A and B, some adenovirus serotypes, human bocavirus, nonpolio enteroviruses such as echovirus and coxsackievirus, human metapneumovirus, rhinoviruses, respiratory syncytial virus (RSV), and parainfluenza viruses.

4 | CONCLUSION

In conclusion, taking control of COVID-19 requires a multidimensional outlook and heightened awareness of all possible aspects of the

disease, including the dermatological aspect. Having the property to aid us in the early diagnosis of asymptomatic carriers and gaining a better prognosis, skin pathologies and their associated lesions are gaining increasing attention.

Unfortunately, there is not yet an ultimate treatment for alleviating cutaneous lesions of COVID-19. Besides, lots of gaps in the literature and questions with regard to skin manifestations of this mysterious infection remain unexplored whose responses will hopefully aid in combating COVID-19, not to mention possible similar situations in the future.

SARS-CoV-2 induces urticarial lesions either through degranulation of mast cell within the dermal layer of skin or through mast cell-independent pathways. The degranulation process involves three pathways: (1) innate immunity via pattern recognition receptors (PRR) s activation, cytokine release, and TLR signaling; (2) adaptive immunity mechanisms such as crosslinking of the Fc epsilon receptors (FCεRI) by antigen/immunoglobulin E (IgE) complexes, IgG directed against IgE, IgG/antigen immune complexes bound to FCγRs on mast cells, and activated T cells (However, this is less likely to be the underlying pathway in COVID-19 urticarial lesions because urticaria happens earlier than the formation of antibodies against SARS-CoV-2.); and (3) non-immunologic stimulation.

AUTHOR CONTRIBUTIONS

Sara Mahdiabadi developed the concept and design, performed the literature search, collected the data, drafted and wrote the article, critically revised the manuscript for important intellectual content, and approved the final version. Fateme Rajabi helped draft the article, critically revised the manuscript for important intellectual content, provided feedback, and approved the final version. Soheil Tavakolpour critically revised the manuscript for important intellectual content, provided feedback, and approved the final version. Nima Rezaei supervised the project, developed the concept and design, critically revised the manuscript for important intellectual content, provided feedback, and approved the final version.

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CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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