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ACE2 Receptor in the skin and Cutaneous Manifestations of SARS-Cov-2: A Review of the Literature

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a newly discovered coronavirus that causes Coronavirus Disease 2019 (COVID-19). The interaction of SARS-CoV-2 transmembrane spike (S) glycoprotein with the human angiotensin-converting enzyme-2 (hACE2) is the primary method of virus entry to the cell. ACE2 is a transmembrane enzyme involved in the renin-angiotensin-aldosterone system. This enzyme plays pivotal roles in blood pressure regulations and also electrolyte homeostasis. The expression of ACE2 in various skin cells has been demonstrated in previous studies. Keratinocytes in the epidermis show an exceptionally high expression of ACE2. In addition to human skin, ACE2 is also found in animals' tissues and were exceptionally high in cats and dogs' skin and eyes. This finding suggests their obscure role in COVID-19 transmission. Cutaneous symptoms of COVID-19 in humans exist as the consequence of ACE2 presence in the skin. The possible mechanisms of COVID-19 clinical manifestations in the skin are upregulated innate immune human response, hypercoagulable state, and non-structural proteins in SARS-CoV-2. These processes are presented as different dermatologic manifestations, which are maculopapular rash, papulovesicular rash, and livedo reticularis. This review aims to link the theoretical framework and published findings to establish the connection between ACE2 expression in skin and cutaneous manifestations of COVID-19.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel virus that causes the coronavirus disease 2019 (COVID-19) outbreak. It was discovered as the seventh coronavirus that infects humans after SARS-CoV, MERS-CoV, HKU1, NL63, OC43, and 229E.[1] A zoonotic origin of SARS-CoV-2 has been proposed to be the source of this new coronavirus.[1] To this date, there have been more than 45 million confirmed cases and over one million deaths worldwide, according to the World Health Organization.

Human-to-human transmission may occur through respiratory droplets, aerosols, or direct contact with contagious secretions such as sputum, serum, blood, and feces of the COVID-19 patients.[2] Droplets are generated when a symptomatic person sneezes, coughs, talks, or exhales. Even though some droplets are too heavy to float in the air, some of them may eventually transform into aerosol particles, thus become airborne.[2] Many physical transformations can happen in the air to these emitted particles and affect their viability. However, in general, it has been established that respiratory particles are the main culprit of COVID-19 spread.[3] Transmission through surface contact on environmental contamination is reported to be unlikely.[4] Although SARS-CoV-2 has been found to exist on several materials such as plastic, stainless steel, and glass up to hours and days.[5]

The interaction of SARS-CoV-2 transmembrane

spike (S) glycoprotein with the human angiotensin-converting enzyme-2 (hACE2) is the primary method of virus entry to the cell. The S protein is comprised of two subunits, S1 and S2. The receptor-binding domain (RBD) located in the S1 subunit serves to facilitate the virus's attachment to the ACE2 receptor, while the S2 subunit functions to fuse the membranes of the virus and human cell.[6] It is known that the ACE2 receptor is widely spread in human tissues. Thus, there exist a plethora of clinical manifestations of COVID-19 as opposed to it being limited only to the respiratory tracts. Recently, researchers have found that the ACE2 receptor is also expressed in skin tissues.[6] Keratinocytes show the highest expression of hACE2 among endothelial cells, fibroblasts, hair follicles, melanocytes, sweat gland cells, and immune cells in the skin. This arises a unique challenge due to the skin's nature as our first-line defense from the environment. As such, many cutaneous clinical manifestations have also been found in COVID-19 patients.

20.4% of patients with COVID-19 had skin findings, and three of these showed urticarial lesions[7]. These lesions were predominantly distributed over the trunk, but the urticarial eruption was not related to the disease severity. Early research observed that the urticarial eruption of patients with COVID-19 occurred in the prodromal stage of the infection[8]. The maculopapular eruption is also a common cutaneous condition in patients with COVID-19. Some of them showed a perifollicular distribution and scaling, while some were similar to pityriasis rosea.[9] A few cases showed infiltrated papular lesions, resembling erythema elevatum diutinum, or erythema multiforme. In addition to the primary cutaneous disease, many viral infections can be manifested with vesiculobullous and papulovesicular eruptions

Patients with severe Covid-19 showed purpuric lesions with pauci-inflammatory thrombogenic vasculopathy and C5b-9 and C4d accumulation in histopathological examination. Progressive ischemia with or without any evidence of systemic disease caused by COVID-19 can be associated with livedo reticularis findings on skin. The lesions might be associated with microthrombosis.[10] Asymmetrical acral erythema and edema with vesicles or pustules, which were described "pseudo-chilblain" were identified in 19% of 375 patients with COVID-19.[9] Purpuric lesions, livedo reticularis, and thrombotic-ischemic lesions reported concerning the disease, hypercoagulation may play an essential role in the high mortality rate of the infection.

This review tries to elucidate the connection between ACE2 receptor present in the skin, cutaneous clinical manifestations of COVID-19, and possible future indications.

2. Search Strategy

References of this review were identified through a search on PubMed, EMBASE, and Google Scholar by using relevant terms related to COVID-19, SARS-CoV-2, ACE2, and skin manifestations caused by COVID-19. Reference lists of the articles identified by this search strategy were also searched. Only articles published in English were included in this review. Fourteen articles were deemed relevant to the purpose of this review.

ACE2 Expression in The Skin

Before we try to discuss the possible clinical implications of COVID-19 in human skin, the function of ACE2 and its presence in skin cells must be established. ACE2 is a transmembrane enzyme involved in the renin-angiotensin-aldosterone system.[11] It has pivotal roles in blood pressure regulations and also electrolyte homeostasis. Angiotensin II, a peptide hormone, is cleaved by ACE2 and transforms into Angiotensin 1-7, which will cause vasodilation and have anti-inflammatory effects. SARS-CoV is a coronavirus that caused the 2003 SARS outbreak. Identical with SARS-CoV-2, it also utilizes ACE2 as a door to enter the human cells. However, SARS-CoV-2 is the more infectious one due to its 10 – 20-fold higher binding affinity to ACE2. Therefore, the existence of ACE2 in skin cells would signify a considerable relevance to the epidemics of COVID-19.

Hamming *et al.* first published and showed the presence of ACE2 in the skin, particularly in the basal cell layer of the epidermis extending to the basal cell layer of hair follicles.[12] This study utilized immunohistochemistry staining using polyclonal rabbit anti-ACE2 antiserum (Millenium Pharmaceuticals, Inc, Cambridge, MA, USA). In sebaceous glands, cytoplasmic staining of ACE2 was weakly observed. Besides the sebaceous glands, the surrounding smooth muscle cells also expressed ACE2. The eccrine glands, especially on the palm, shown a strong granular staining pattern for ACE2. This study kicked the first attempt to establish ACE2 existence in the skin. Many others eventually followed due to the COVID-19 outbreak.

Several months into the pandemic, researchers from Shandong, China, analyzed public databases for ACE2 messenger RNA (mRNA) in public databases Gene Expression Profiling Interactive Analysis 2 (GEPIA2) and All RNA-seq and ChIP-seq Sample and Signature Search (ARCHS4).[13] The analysis was then followed by RNA sequencing in tissue samples, which were also validated by quantitative real-time RT-PCR. It was found that ACE2 is expressed in multiple cells of the skin: keratinocytes, endothelial cells, fibroblasts, hair follicles, immune cells, lymphatic endothelial cells, melanocytes, and sweat gland cells. Small conditional RNA sequence (scRNA-seq) analysis found that 0.19% of skin cells are positive for ACE2, with keratinocytes being the most abundant place. Further immunohistochemistry using rabbit anti-human ACE2 polyclonal antibody (Proteintech, Rosemont, IL) found ACE-2 positive keratinocytes in stratum basale stratum spinosum and stratum granulosum of the epidermis, mainly in keratinocytes and basal cells that are currently differentiating.

It has been confirmed that ACE2 is not exclusive to humans. Analysis of the ACE2 phylogenic tree shows that many animals conserve the gene at both DNA and peptide levels.[14] This becomes important due to the risks of SARS-CoV-2 spread by these animals that live close to humans. In fact, several mammals share the same amino-acids of virus-binding hotspots to the human ACE2 (hACE2). Pets possess a greater risk of transmitting the virus to humans due to their place in our society. As it happens, ACE2 expression was found notably high in the skin and eyes of cats and dogs, suggesting their obscured roles in the COVID-19 pandemic. The reference genomes and Ref-sequence gene annotations of the animals were obtained from the National Center for Biotechnology Information (NCBI). The human genomic data was acquired from the Genotype-Tissue Expression Project (GTEx) and the Encyclopedia of DNA Elements (ENCODE).

Although ACE2 expression seems universal, the difference between sexes has been studied before. Asian females were found to have a significantly higher level of ACE2 expression in specific organs than males.[15] Human expression of ACE2 also declines with age. However, the correlation between ACE2 expression and COVID-19 fatality was a negative correlation at both population and molecular levels. With these findings, it is crucial to understand the mechanisms in which COVID-19 could affect skin cells and tissues.

Mechanisms of Cutaneous Disease as Clinical Manifestations of COVID-19

The mechanisms of COVID-19 cutaneous disturbances are not yet well known, but some common theories are prevalent. Possible correlation between COVID-19 infection and skin manifestations mechanism are upregulated innate immune human response; hypercoagulable state; non-structural proteins in SARS-CoV-2; ACE2 expressing target cells; and fatal outcome in severe cases of macrophage activation syndrome-like (MAS).[16]

1. In patients with severe COVID-19 infection, their overactive immune responses may induce immunopathological conditions, named “cytokine storm”, and in some individuals leads to macrophage activation syndrome (MAS)-like. Often causing a fatal outcome.[17] 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 urticarial erythema

lesions, vesicles, and others. An earlier study found complement deposition (C5b-9 and C4d) using immunohistochemistry in dermal capillaries of patients with retiform purpura.[18] 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.

2. NSP3, as one of the non-structural proteins in SARS-Cov-2, has a property to block the host's innate immune response and promote cytokine expression. Other non-structural proteins, NSP5, can inhibit interferon (IFN) signaling, and NSP16 avoids MADS (melanoma differentiation-associated gene 5) recognition and depressing innate immunity.[19]
3. Aerosolized uptake of SARS-Cov-2 effects 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.[20]
4. 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 autoinflammatory diseases.[21,22] Earlier studies have shown that direct T cell viral infection by detecting SARS-like viral particles and SARS-CoV RNA in T lymphocytes peripheral blood sample, spleen, lymph nodes, and lymphoid tissue. 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.
5. 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. The ACE2 receptor is also widely expressed on endothelial cells in multiple organs, suggesting that endothelitiis could occur in several sites due to viral involvement and host inflammatory response. COVID-19-endothelitiis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19.[23]

Mechanisms of cutaneous disease caused by COVID-19 showed different types of dermatologic manifestations. Dermatologic manifestations are vital in the diagnosis of various infectious diseases. As COVID-19 tends to produce asymptomatic cases for up to 14 days after infection, the cutaneous manifestations may serve as an indicator of infection, aiding in timely diagnosis. The most common clinical manifestations of cutaneous manifestations and its effects on skin will be reviewed here.

Maculopapular exanthem or a generalized macular lesion (morbilliform) appeared to be the most common cutaneous manifestation in COVID-19 in 36.1% (26/72) patients. A papulovesicular rash (vesicles) was seen in 34.7% (25/72) of patients. Urticaria occurred in 9.7% (7/72) of reported patients, and the presence of painful acral red-purple papules with or without vesicles was seen in 15.3% (11/72) of patients overall. Lastly, 2.8% (2/72) presented with livedo reticularis lesions, and one patient (1.4%) presented with petechiae. Of the 72 cases, lesion location was reported in 67 patients, with most lesions being found on the trunk, hands, and feet. Overall, 69.4% (50/72) of patients experienced lesions on the trunk. Additionally, 19.4% (14/ 72) of patients experienced cutaneous manifestations in the hands and feet.

The maculopapular eruption is a well-known manifestation linked to viral infection. Recalcati *et al.* recently described different skin manifestations in COVID-19 inpatients.[7] They concluded that skin rashes are similar to cutaneous involvement occurring during common viral infections. Asymptomatic maculopapular rash and morbilliform eruptions, not extending to palms and soles are usually noted 3 to 6 days after a fever. The skin rash can heal completely or become generalize and involve the dorsum of hands

and feet, without extending to the palmoplantar regions, and lasting several days.[25]

Recalcati *et al.*, who conducted the first study regarding the cutaneous findings of COVID-19, reported varicella-like lesions in one of 18 patients.[7] He found that varicella like eruption in 12 out of 22 patients with COVID-19, and they concluded that this type of eruption might be a specific manifestation of COVID-19. Another study reported that the vesicular eruptions identified were unlike polymorphic vesicles of chickenpox.

Livedo reticularis describes a regular, lace-like network of non-fixed, dusky patches forming complete rings surrounding a pale center. This lesion is caused by constriction of central arterioles and subsequent peripheral venodilatation. COVID-19 can cause a procoagulant state, with small blood vessel occlusion.[24] However, the absence of purpura and skin necrosis together with normal coagulation parameters makes thrombi unlikely as a cause of the livedo reticularis. This phenomenon showed the presence of low-grade vascular inflammation and vasodilatation caused by direct SARS-CoV-2-infection of endothelial cells or vessel-associated smooth muscle cells. Both cell types express angiotensin-converting enzyme 2-receptor on their surface, the target of SARS-CoV-2-spike protein.[24]

Most Common Clinical Presentations of Cutaneous Manifestations in COVID-19

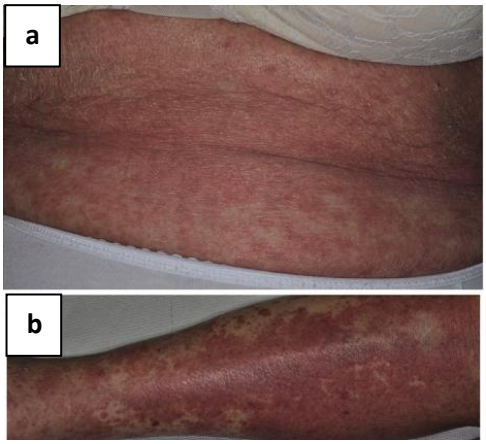

Fig. 1. (a) Maculopapular exanthem on the trunk. (b) Maculopapular exanthem on the legs.[24]

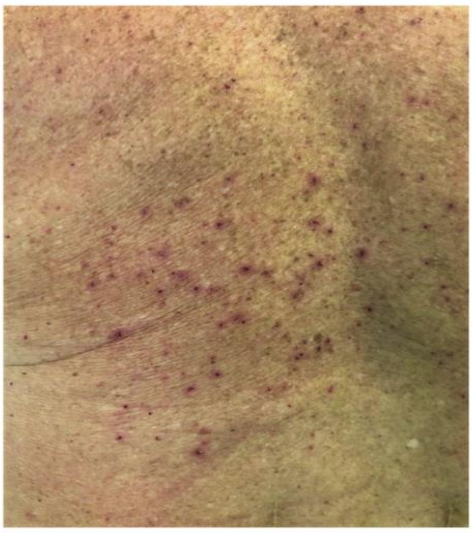

Fig. 2. Maculo-papular itchy rash appeared on the trunk.[24]

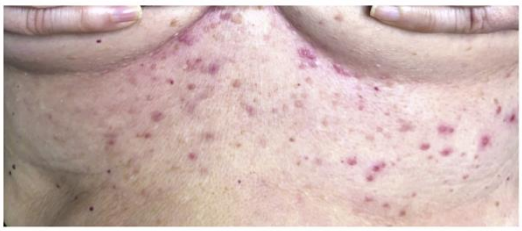

Fig. 3. Papulovesicular rash (vesicles) on the mid trunk.[24]

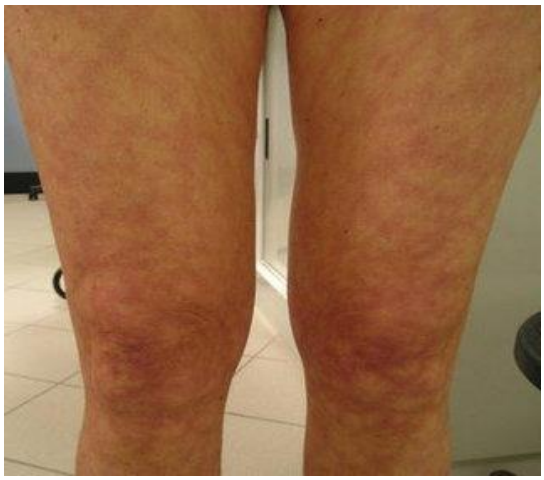

Fig. 4. Livedo reticularis lesions on the thigh.[24]

3. Conclusions

ACE2 is the receptor utilized by SARS-CoV-2 to enter and infect human cells. The presence of ACE2 in the skin possesses a potentially more straightforward virus transmission method and likely risks to a wide range of skin diseases in COVID-19 patients. Several known mechanisms may explain the cutaneous manifestations caused by the virus. However, further research is still required, especially regarding the correlation between COVID-19 patients who demonstrate cutaneous symptoms and their prognosis. Individual factors that may predict the eruption of cutaneous symptoms in COVID-19 are also needed to create a better management plan for each patient.

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