

## Skin manifestations in coronavirus disease 2019 (COVID-19): A literature review

Odilia Dea Novena<sup>1\*</sup><sup>1</sup>General Practitioner at Bangli General Hospital, Bali, Indonesia\*Corresponding:  
Odilia Dea Novena; General Practitioner at Bangli General Hospital, Bali, Indonesia;  
odiliadeanovena@gmail.comReceived: 2021-07-30  
Accepted: 2021-09-28  
Published: 2021-10-05

### ABSTRACT

To date, skin manifestations in Coronavirus Disease 2019 (COVID-19) patients cannot be certainly described and predicted, as immunologic factors, viral load, hypercoagulable state, and treatment response varied among each case. Skin lesions in COVID-19 are similar to other viral infections, including dengue fever, morbilli, or varicella. The skin has Angiotensin-Converting Enzyme-2 (ACE-2) receptors that bind to spike proteins on SARS-CoV-2. Damaged skin surface can be the port d'entrée for the virus to reach ACE-2 receptors in keratinocytes. Skin manifestations in COVID-19 include maculopapular eruption, pseudo-chilblain, urticarial lesions, vesicular eruption, and vasculopathy-related lesions such as petechiae, purpura, livedo, acrocyanosis, thrombosis/ischemia, and dry gangrene/necrosis. Pseudo-chilblain and urticarial lesions are associated with younger age and milder disease, while vasculopathy-related lesions are often seen in severe infections. Treatment depends on the severity, morphology of the lesion, and the symptoms that the patient complains of. The treatment may consist of systemic/topical corticosteroids, antihistamines, and emollients. More research regarding the correlation between the etiopathogenesis of skin lesions in COVID-19 and the prognosis are needed. By identifying skin manifestations in COVID-19, clinicians can differentiate COVID-19 from other similar-looking lesions; therefore, early diagnosis, transmission prevention, treatments, and complication prevention can be conducted accordingly. This literature review aims to discuss the skin manifestations in COVID-19, understand the underlying etiopathogenesis, and explore the proper treatment for each case.

**Keywords:** COVID-19, dermatology, exanthema, pseudo-chilblain

**Cite this Article:** Novena, O.D. 2021. Skin manifestations in coronavirus disease 2019 (COVID-19): A literature review. *IJBS* 15(2): 113-116. DOI: [10.15562/ijbs.v15i2.339](https://doi.org/10.15562/ijbs.v15i2.339)

### INTRODUCTION

At the end of December 2019, there was a report of the first pneumonia case of unknown cause in Wuhan, China. After examining the respiratory tract isolates, a new coronavirus variant called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was found. The disease caused by this virus is called Coronavirus Disease 2019 (COVID-19), with a fast transmission rate to the point that in March 2020, COVID-19 was declared a pandemic by the World Health Organization (WHO). COVID-19 can be asymptomatic or symptomatic. The symptoms include fever, dry/productive cough, shortness of breath, sore throat, malaise, myalgia/arthralgia, nausea/vomiting, diarrhea, and abdominal pain.<sup>1</sup> Although skin manifestations are rare in COVID-19 patients, skin manifestations ranging from viral exanthema to vasculitis,

with or without other symptoms, have been reported in some cases. To date, skin manifestations in COVID-19 patients cannot be described or predicted with certainty because this is influenced by various factors such as immunological status, viral load, hypercoagulable state, and response to therapy.<sup>2</sup>

Some of the dermatological features found in COVID-19 patients include chilblains (swelling and erythema on the tips of fingers or toes), erythematous/maculopapular/ morbilliform rash, urticarial rash, vesicular rash, acute generalized exanthematous pustulosis (AGEP), erythema multiforme (EM), reticular livedo, vascular lesions/vasculitic purpura, and other polymorphic/atypical reactions. Most skin manifestations occur with or after the appearance of systemic symptoms such as fever and/or respiration.<sup>3-5</sup> The appearance of skin

lesions due to COVID-19 at first glance looks similar to other viral diseases, such as dengue fever, morbilli, and varicella. Therefore, this literature review was done to discuss the skin manifestations of COVID-19, understand the underlying etiopathogenesis, and proper management.

### EPIDEMIOLOGY

The number of COVID-19 cases worldwide has reached more than 200 million cases, of which there have been 4.32 million deaths. Currently, in Indonesia, a total of 3.72 million cases of COVID-19 have been reported, with the death toll reaching 111,000 people.<sup>6</sup> The most common initial clinical manifestations in COVID-19 patients are fever, cough, shortness of breath, followed by other systemic/organ symptoms. Skin manifestations of COVID-19 have been reported less frequently. Recalcati et al.

reported that 18 (20.4%) out of 88 patients confirmed positive for COVID-19 had skin manifestations in a hospital in Italy. Eight patients had symptoms at onset, and ten patients developed new symptoms after hospitalization.<sup>7</sup>

In addition, Giavedoni et al. reported that in a hospital in Barcelona, Spain, 58 (2.1%) of the 2,761 patients who were confirmed positive for COVID-19 complained of skin manifestations.<sup>5</sup> In a systematic review conducted by Jamshidi et al., the overall frequency of skin manifestations in COVID-19 was 5.95%, and 48% of patients had mild severity with pseudo-chilblain and urticaria lesions. Among the 32% of moderately severe cases, 37% developed a maculopapular rash, especially in adult women between 40-60 years old. In 20% of patients with severe symptoms, vascular lesions were observed. As many as 72% of patients with pseudo-chilblains recovered without treatment. The mortality rate for patients with vascular lesions was 18.2%, while the mortality rate for patients with urticarial lesions was 2.2%.<sup>8</sup> To date, data on the incidence of skin manifestations in COVID-19 patients in Indonesia are still scarce. However, several case reports from various hospitals have described the presence of varied skin lesions.<sup>9,10</sup>

## ETIOPATHOGENESIS

SARS-CoV-2 is a  $\beta$ -coronavirus (enveloped virus, single-stranded, positive RNA), with an average diameter of 60-140 nm, oval/round in shape with spikes on the surface. Like the gp120 protein in Human Immunodeficiency Virus (HIV), the SARS-CoV-2 spike protein recognizes cell surface receptors, allowing the virus to enter host cells. The difference lies in the specific receptors, and targeted cells, namely SARS-CoV-2 binds to the Angiotensin-Converting Enzyme 2 (ACE-2) receptor and enters mucosal epithelial cells. In contrast, HIV binds to CD4 receptors and enters CD4+ T cells. Researchers have estimated that SARS-CoV-2 takes 96 hours to enter the human respiratory epithelial cells via respiratory droplets, and close contact dramatically influences the likelihood of transmission. At the same time, the average time from viral infection to the onset of symptoms

is approximately 12.5 days. ACE-2 is part of the angiotensin-converting enzyme (ACE), which plays a physiological role in cell proliferation and hypertrophy, inflammatory response, blood pressure regulation, and fluid balance. ACE-2 is highly expressed in the lungs and small intestine and on endothelial cells and smooth muscle cells in almost all other organs. Therefore, when it reaches the circulatory system, SARS-CoV-2 is likely to spread through the bloodstream and might alter the gastrointestinal, urogenital, central nervous, and circulatory systems.<sup>11</sup>

According to studies conducted by Xue et al. and Bourgonje et al., it was found that ACE-2 was also expressed in skin tissue and was significantly higher in keratinocytes than in fibroblasts and melanocytes. ACE-2 receptors are located in the stratum basale of the epidermis and the eccrine glands in the skin. The damaged skin surface can be a port d'entrée for the virus to reach the ACE-2 receptor on keratinocytes.<sup>12,13</sup> Some theories suggest that the erythematous and vesicular rash and urticaria result from immunological activation against SARS-CoV-2, as with other viral exanthemas. On the other hand, reactivation or coinfection with the herpes virus and drug hypersensitivity may also be the underlying cause of skin manifestations in COVID-19. Concerning lesions of vascular origin, ischemic/necrosis lesions may result from hypercoagulable conditions in severe infections.

In contrast, chilblains are associated with interferon-I, which is mainly produced to stop viral replication. AGEP is triggered by drugs, while erythema multiforme can be caused by a delayed immune response to viruses or a hypersensitivity reaction to medications started by an inflammatory process to fight viral infections.<sup>4</sup> Based on available data, chilblain is correlated with younger age and milder disease, whereas ischemic manifestations are more common in elderly patients with severe infections.<sup>4,5</sup>

## CLINICAL MANIFESTATIONS OF THE SKIN RELATED TO COVID-19

In a study, Casas et al. reported that the COVID-19-related skin manifestations observed in 375 samples consisted

of maculopapular eruptions (47%), erythematous areas on the acral with vesicles or pustules (pseudo-chilblain) (19%), urticarial lesions (19%), other vesicular eruptions (9%), and livedo/necrosis (6%). Vesicular eruptions appear early in disease onset (15% occurs before other symptoms develop), whereas the pseudo-chilblain pattern often appears later (59% occurs after other symptoms develop).<sup>2</sup>

A maculopapular rash is the most common skin manifestation of COVID-19, similar to other viral exanthemas, and is sometimes referred to as a morbilliform rash. This type of manifestation is more common in women and is sometimes accompanied by pruritus. Localization of the maculopapular rash most often occurs on the trunk (chest/abdomen/back) and arms with a diffuse distribution pattern.<sup>2,14-17</sup> In a case report by Joob et al. in Thailand, a patient came with a rash and petechiae. The patient also had dengue-fever-like thrombocytopenia without respiratory symptoms. Therefore, the patient was diagnosed with dengue fever at first. After several days of treatment, respiratory complaints began to appear, and the patient was confirmed positive for COVID-19.<sup>18</sup>

In addition, Putra et al. also reported a case of COVID-19 in Indonesia with a maculopapular rash on the upper and lower extremities that did not spread to the trunk, accompanied by needle-like pain. These complaints appeared on the fourth day after the fever disappeared.<sup>9</sup> Some COVID-19 medications/drugs have the potential to cause effects similar to maculopapular/morbilliform rashes. These include ribavirin, colchicine, intravenous immunoglobulin (IVIg), lopinavir, ritonavir, and antiretroviral drugs. However, in a case reported by Putra et al. and in some other cases, the patient had no previous medication history. Therefore, this rash was not only related to medication. Furthermore, a study by Singh et al. demonstrated a hypothesis that a cytokine storm induced by a hyperactive immune system could trigger the rash after observing a maculopapular eruption of later onset. Another theory mentions Langerhans cell aggregation, high lymphocyte count

without eosinophils, edema of the stratum papillary dermis, spongiosis of the epidermis, and lymphohistiocytic infiltrate.<sup>8,9,14</sup>

As previously explained, chilblain is a term for swelling accompanied by pain sensation and erythema on the tips of fingers/toes, which is usually caused by exposure to freezing air or long-term exposure to cold air. However, the chilblain-like manifestations of COVID-19 are not caused by cold air, and the underlying pathophysiology is also different, hence the name pseudo-chilblain. In COVID-19 patients, chilblains appear late in the course of the disease or in the convalescent period (2-3 weeks after other symptoms have disappeared).<sup>2,16,19</sup> Pseudo-chilblains usually occur in young patients or children, who rarely have systemic symptoms or pulmonary infiltrates on radiology examination. The admission rates to hospital and intensive care units are also lower.<sup>5</sup> Histological features of this condition include epidermal vacuolization, lymphocytic infiltration in the superficial and deep dermis with a perivascular or periadnexal pattern, and dermal edema.<sup>15</sup>

Urticaria lesions are also quite common COVID-19 cases and generally occur along with other symptoms such as fever. Urticaria lesions are commonly found on the face and trunk, especially in women and adults, and are usually accompanied by itching.<sup>4</sup> Gunawan et al. have reported a case in Indonesia, namely a 51-year-old COVID-19 patient with complaints of cough, fever, shortness of breath, and diarrhea. After three days of hospitalization, facial urticaria appeared. The complaints improved with the administration of antihistamines.<sup>10</sup> A biopsy of a COVID-19 positive patient with an urticarial rash usually shows perivascular lymphocytic infiltration with eosinophils and upper dermal edema.<sup>15</sup>

Moreover, Wang et al. revealed several studies that reported vesicular manifestations in COVID-19 patients. Some of the lesions were described as similar to chickenpox/varicella, herpes zoster, herpetiform lesions, oral vesicles, and vesicular eruptions. One report noted that the lesions were small and monomorphic, unlike true varicella.

Vesicular lesions are more often located on the trunk, less frequently on the extremities, and occasionally on the oral mucosa. Vesicular lesions are more common in adults.<sup>15</sup> In vesicular lesions, histologically, it was observed that there was no inflammatory infiltrate. The epidermis appeared atrophic, hyperkeratosis with a basket weave pattern, stratum basale vacuolization, multinucleated keratinocytes, and dyskeratotic cells.<sup>8,15</sup>

Several studies have also reported vasculopathy-associated lesions such as petechiae, purpura, livedo, acrocyanosis, thrombosis/ischemia, and dry gangrene/necrosis. Livedo often occurs on the trunk, arms, and legs; acrocyanosis occurs on the toes; ischemia/necrosis occurs on the tips of the fingers or toes; Purpura is often found on the rectum and trunk. COVID-19 patients who present with vascular lesions are generally associated with respiratory failure and require mechanical ventilation due to hypoxia. These patients have a high intensive care unit admission rate. Skin biopsy in these patients revealed vascular thrombosis in the deep dermis, and immunohistochemical examination revealed deposits of complements (C5b-9, C3d, C4d) and IgM in the dermis and blood vessels.<sup>8,15</sup>

In some cases, EM and AGEP-like target lesions were found, both located on the trunk. EM lesions are thought to result from an immune response to SARS-CoV-2, which is rare. On skin biopsy examination, telangiectasia of the dermal blood vessels was found with neutrophil infiltration, perivascular lymphocytic infiltration, and erythrocyte extravasation. AGEP has been reported to occur in patients who are sensitive to hydroxychloroquine and is not a direct result of the response to SARS-CoV-2.<sup>4,15</sup>

## TREATMENT

Most skin lesions require systemic corticosteroids (47%) or undergo spontaneous remission (23.5%). Systemic corticosteroids are commonly used for vascular lesions (71%). Antihistamines are frequently used, especially for urticarial lesions (57%).<sup>8</sup>

To date, there is no specific therapy for pseudo-chilblain lesions yet. Some

studies suggest using steroids to treat pruritus or its progression to hardened plaque lesions, while other studies indicate emollients. Usually, pseudo-chilblains resolve spontaneously within a few days to 2-4 weeks. Antiseptic mouthwash, hyaluronic acid, and valacyclovir are also recommended for oral vesicular lesions.<sup>15</sup>

## CONCLUSION

COVID-19 can affect various organs, including the skin. The skin has an ACE-2 receptor that can bind to the spike protein in the SARS-CoV-2 virus. The damaged skin surface can be a port d'entrée for the virus to reach the ACE-2 receptor on keratinocytes. Skin manifestations found in COVID-19 include maculopapular eruptions, pseudo-chilblains, urticarial lesions, vesicular eruptions, and vasculopathy-related lesions such as petechiae, purpura, livedo, acrocyanosis, thrombosis/ischemia, and dry gangrene/necrosis. Pseudo-chilblain and urticaria are correlated with younger age and milder disease, whereas vasculopathy lesions were more common in severe cases. Treatment depends on the severity, morphology of the lesion, and the symptoms that the patient complained about. Several therapies that can be used include corticosteroids (both systemic and topical), antihistamines, and emollients. Antiseptic mouthwash can also be used on oral vesicular lesions. More researches regarding the correlation between the etiopathogenesis of skin lesions in COVID-19 and the prognosis are needed. By identifying skin manifestations in COVID-19, clinicians can differentiate COVID-19 from other similar-looking lesions. Therefore, early diagnosis, transmission prevention, treatments, and complication prevention can be conducted accordingly.

## ACKNOWLEDGMENTS

The author is thankful to everyone for the support and for making this literature review possible to publish.

## CONFLICT OF INTEREST

The author declares that there were no conflicts of interest in this study.

## FUNDING

The author is responsible for the study funding without grants, scholarships, or any other funding resources.

## AUTHOR CONTRIBUTION

The author is fully contributed to the study.

## REFERENCES

- World Health Organization. WHO coronavirus disease (COVID-19) dashboard [Internet]. 2021 [cited 2021 Aug 12]; Available from: <https://covid19.who.int/>.
- Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020;183(1):71–7.
- Genovese G, Moltrasio C, Berti E, Marzano AV. Skin manifestations associated with COVID-19: Current knowledge and future perspectives. *Dermatology*. 2021;237(1):1–12.
- Farinazzo E, Dianzani C, Zalaudek I, Conforti C, Grabbe S, Goldust M. Synthesis of the data on COVID-19 skin manifestations: Underlying mechanisms and potential outcomes. *Clin Cosmet Investig Dermatol*. 2021;14:991–7.
- Giavedoni P, Podlipnik S, Pericàs JM, Fuertes de Vega I, García-Herrera A, Alós L, et al. Skin manifestations in COVID-19: Prevalence and relationship with disease severity. *J Clin Med*. 2020;9(10):3261.
- Gugus Tugas Percepatan Penanganan COVID-19. Data sebaran COVID-19 [Internet]. 2021 [cited 2021 Aug 12]. Available from: <https://covid19.go.id/>.
- Recalcati S. Cutaneous manifestations in COVID-19: A first perspective. *J Eur Acad Dermatol Venereol*. 2020;34(5).
- Jamshidi P, Hajikhani B, Mirsaedi M, Vahidnezhad H, Dadashi M, Nasiri MJ. Skin Manifestations in COVID-19 Patients: Are They Indicators for Disease Severity? A Systematic Review. *Front Med*. 2021;8:634208.
- Putra BE, Adiarto S, Dewayanti SR, Juzar DA. Viral exanthem with “Spins and needles sensation” on extremities of a COVID-19 patient: A self-reported case from an Indonesian medical frontliner. *Int J Infect Dis*. 2020;96:355–8.
- Gunawan C, Angela A, Widsyanto A. Urticarial eruption in coronavirus disease 2019 infection: a case report in Tangerang, Indonesia. *J Eur Acad Dermatol Venereol*. 2020;34(8):e372–e373.
- Zhang Y, Geng X, Tan Y, Li Q, Xu C, Xu J, et al. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. *Biomed Pharmacother*. 2020;127:110195.
- Xue X, Mi Z, Wang Z, Pang Z, Liu H, Zhang F. High expression of ACE-2 on keratinocytes reveals skin as a potential target for SARS-CoV-2. *J Invest Dermatol*. 2021;141(1):206–209.
- Bourgonje AR, Abdulle AE, Timens W, Hillebrands J, Navis GJ, Gordijn SJ, et al. Angiotensin-converting enzyme 2 (ACE-2), SARS-CoV-2, and the pathophysiology of coronavirus disease 2019 (COVID-19). *J Pathol*. 2020;251(3):228–48.
- Singh H, Kaur H, Singh K, Sen CK. Cutaneous manifestations of COVID-19: A systematic review. *Adv Wound Care*. 2021;10(2):51–80.
- Wang CJ, Worswick S. Cutaneous manifestations of COVID-19. *Dermatol Online J*. 2021;27(1):13030.
- Rahimi H, Tehranchinia Z. A Comprehensive review of cutaneous manifestations associated with COVID-19. *BioMed Res Int*. 2020. 2020; 1236520.
- Sachdeva M, Gianotti R, Shah M, Bradanini L, Tosi D, Veraldi S, et al. Cutaneous manifestations of COVID-19: Report of three cases and a review of the literature. *J Dermatol Sci*. 2020;98(2):75–81.
- Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. *J Am Acad Dermatol*. 2020;82(5):e177.
- Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: A worldwide review. *J Am Acad Dermatol*. 2021;2:119–33.



This work is licensed under a Creative Commons Attribution