Review Article

Literature review: manifestation of skin lesion on COVID-19

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ABSTRACT

New cases of pneumonia, which spread rapidly and are deadly, have spread throughout the world. This disease is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or corona virus disease 2019 (COVID-19) with a viral etiology in the form of novel coronavirus 2019 (2019-nCoV). This disease has extensive clinical manifestations starting from the lungs, hematology system, heart, nerves, reproduction, and the skin. The thing to be aware of is that the skin manifestations in the form of atypical lesions are often found in COVID-19. Common skin manifestations on COVID-19 are erythema-edema with vesicles or pustules (pseudo-chilblain), vesicular eruption, maculopapular rash, urticaria, and livedo lesion. This literature review discusses comprehensively what kind of skin lesions can be suspected of being part of a COVID-19 infection. This literature review is useful for increasing the awareness of doctors about COVID-19 infection and may help in early diagnose of COVID-19 infection and prevent further transmission.

Keywords: Skin manifestation, COVID-19, SARS-CoV-2

INTRODUCTION

A new and unexplained pneumonia case started in Wuhan city, China in December 2019. Experts and the government are taking immediate steps to determine the etiology to prevent the epidemic. The world health organization (WHO) gave the new virus terminology as novel coronavirus 2019 (2019-nCoV) on January 12, 2020 and gave the disease caused by 2019-nCoV as corona virus disease 2019 (COVID-19) and coronavirus study group (CSG) from the international committee on virus taxonomy called 2019-nCoV a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and became a global epidemic as a marker of a very serious problem on January 20, 2020.1–3 The confirmed case of infection from SARS-COV2 on August 20, 2020 has infected 22,213,869 cases worldwide with a total death of 781,677 people. The country with the highest SARS-CoV infection is the United States with 11,887,224 cases, Europe 3,841,452 cases, Southeast Asia 3,308,987 cases, Eastern Mediterranean with 1,776,889 cases, and Africa with 966,352 cases.4 Indonesia as part of a Southeast Asian country reported 147,211 confirmed cases, 40,119 in treatment, 100,674 recovered and 6,418 deaths (case fatality rate: 4.4%) on 20 August 2020.5,6

The clinical manifestations of COVID-19 infection are very unclear and resemble many other diseases. Reports from around the world have revealed that the spectrum of this disease is not only centered on the lungs but can extend to various organs to multiple organs with clinical symptoms from mild to severe and lead to death. Reports from various studies state that Covid-19 can attack the nervous system, gastrointestinal-hepatobiliary system, urological system, cardiovascular and metabolic systems, hematology system, reproductive system especially in pregnancy, integumentary or mucocutaneous system with
a form of efflorescence that is actually typical for other
diseases, such as varicella.7-28

The most common symptoms form COVID-19 are fever,
myalgia, cough, fatigue, pneumonia, and respiratory
problems. Rare disorders include headache, hemoptysis,
diarrhea and coughing up blood.29-31

**EPIDEMIOLOGY AND ONSET**

In mid-August 2020 cases of COVID-19 were found that
hit all countries, even though several countries had
started declaring countries free of new COVID-19 cases
but in fact, COVID-19 infection had to be watched out
for because the transmission method was easy and had
very clinical symptoms, diverse. One of the clinical
symptoms that appear is skin manifestation. Symptoms or
skin lesions do not always appear in all patients with
confirmed COVID-19. Recalcati described that only
20.45% of COVID-19 patients treated at the Lecco
hospital (Lombardy region, Italy) manifested in the form
of an erythematous rash (n=14), extensive urticaria (n=3)
or varicella-like vesicles (n=1).32 Firmansyah, Elizabeth,
and colleagues’ study that reviewed clinical
manifestations in key populations found that only 42.86%
of patients presented with skin lesions.30

Regarding the onset of skin manifestations presented in
the literature in a very varied range. Research by Zhao et
al reviewed skin lesions appearing 9.92 (1-30) days after
the appearance of systemic symptoms such as fever,
cough, diarrhea, weakness, fatigue, lethargy, and
difficulty breathing.29 Research by Firmansyah,
Elizabeth, and colleagues revealed that maculopapular
skin manifestations appeared 10.7 (7-13) days after the
appearance of clinical symptoms of COVID-19.30 Other
studies have also revealed that skin manifestations can
appear more than 30 days after the first onset
of symptoms of COVID-19.35

**PATHOGENESIS**

The new study concluded ACE-2 as a functional host
receptor for infection from SARS-CoV-2. The expression
of the ACE-2 receptor with its binding affinity for the
SARS-CoV 2 virus was 10 to 20 times higher. It is on the
basis of this receptor expression that clinical
manifestations, replication, severity, and transmission of
the SARS-CoV 2 virus are explained at the level of
molecular biology. Research using animal or mouse
studies found that the expression of ACE-2 plays an
important role in the incidence of vascular disorders, lung
pathology, severity of infection, and the occurrence of
respiratory acidosis mechanisms that trigger respiratory
failure.36 Physiologically, the ACE-2 receptor is spread in
various body tissues, one of which is excreted in
keratinocyte tissue and epidermal basal cells.37,38 Recent
research has shown that the expression of ACE-2 extends
to the basal cell layer of hair follicles, sebaceous gland
cells and smooth muscle cells surrounding the sebaceous
glands, and eccrine cells.39 These results were further
confirmed by IHC, which showed ACE2 positive
keratinocytes in the basal stratum, spinosum stratum,
and epidermal granulorum stratum.40 In addition, Li et al.
found that CD8 and T cells had a significant positive
correlation with ACE2 expression in the skin.41 On the
basis of the pathophysiology and pathogenesis of SARS-
Cov 2 virus infection and its relationship with the ACE-2
receptor which is not only spread in the lungs but
throughout the skin layer, it is not surprising if the
manifestation of skin lesions also appears as a result of
the similarity of the ACE-2 receptor on both types of
organs

![Image](https://example.com/image.png)

**CLASSIFICATION**

The various efflorescence of the skin manifestations
caused by COVID-19 make it difficult to classify
COVID-19 because of its manifestations that resemble
other diseases. Joob et al reported a petechial rash in a
COVID-19 patient from Thailand.42 The Italian study
reported on varicella-like lesions, Fernandez (Spain)
reported the appearance of urticaria rash (urticariiform rash) after 6 days of symptom onset.\textsuperscript{37} Zhang (China) reported urticaria lesions.\textsuperscript{38} Estebanez (Spain) reported a pruritic lesion of the heel, Henry (France) reported urticarial lesions and disseminated erythematous plaques eruption.\textsuperscript{39–43} Sachdeva (Italy) reported maculo-papular lesions, morbilliform spots and hemorrhagic macular patches.\textsuperscript{40} Mazzota (Italy) reported round red-purple lesions measuring 5-15 mm with indistinct margins on the soles of the feet.\textsuperscript{40} Alramthan (Qatar) reported bilateral ischemic lesions on the acral with purplish red color on the dorsal part of the fingers.\textsuperscript{41}

| Author                      | Country            | Efflorescence                                                                 | Author's Comments Regarding Clinical Associations                                                                 |
|-----------------------------|--------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Alramthan 2020\textsuperscript{41} | Qatar              | Reported 2 cases of 2 ischemic lesions and papules on the acral area with red-purplish color. | Ischemic lesions have the most common distribution appearing in the distal limbs, especially the lower limbs. |
| Firmansyah, et al\textsuperscript{40} | Indonesia          | Reported 3 cases with the maculopapular lesions with and without the itching which generally focused on lower limb area. | It is a key population group, namely health workers with an age range of 22-25 years.                          |
| Estébanez 2020\textsuperscript{39} | Spain              | Reported 1 case of urticaria with itching (Confluent-erythematous-yellowish papules). | The patient is 28 years old (Female). The skin lesions appeared on the thirteenth day with persistent lesions and continued to evolve into thickened erythematous plaques and severe itching. |
| Fernandez 2020\textsuperscript{47} | Madrid, Spain      | Reported 1 case of urticaria.                                                                                                    | The patient was 32 years old (female) who appeared on the sixth day of symptoms. Treatment therapy using hydroxychloroquine and azithromycin. |
| Gianotti, 2020\textsuperscript{42} | Milan, Italy       | 5 cases with varying efflorescence in the form of exanthema on the trunk and legs, papular erythematous exanthema on the trunk, and undefined maculopapular eruption in 3 cases on the trunk, and maculo-papular purpura. | Male sex with papular erythematous exanthema.                                                                 |
| Henry 2020\textsuperscript{43}   | Orléans, France    | Reported 1 case with disseminated erythematous plaques eruption and urticaria lesions on face, hands and feet. | Generally, these lesions focus on the limb area, with pruritic lesions (similar to neurodermatitis). |
| Hunt 2020\textsuperscript{44}    | New York, USA      | Reported 1 case with varying efflorescence starting from indefinitely demarcated, morbilliform, maculopapular lesions, and patches without itching spread over the trunk and extremities and even the face area. | Variety of efflorescence over large areas may be due to prolonged fever.                                          |
| Jimenez 2020\textsuperscript{45}  | Madrid, Spain      | Reported a case of purpuric-erythematous measuring millimeters in the peri-axillary flexural region.                            | The possibility of these lesions arising from old age (84 years) with treatment therapy in the form of hydroxychloroquine and lopinavir/ritonavir. |
| Joob 2020\textsuperscript{56}    | Thailand           | Reported skin patches with petechia.                                                                                             | No further data regarding follow-up symptoms.                                                                   |
| Kolivras 2020\textsuperscript{57} | Brussels, Belgium  | Reported 1 case with plaque lesion with infiltration and redness on the dorsal and lateral part of the foot.                 | Symptoms appear after 3 days of respiratory manifestations. This lesion is the only lesion with subjective pain. |
| Mahé 2020\textsuperscript{47}    | Colmar, France     | Reported 1 case of erythematous spots in the antecubital fossa area that spread to the trunk and armpit folds                 | The patient was 64 years old (female) who appeared 4 days after fever and disappeared on the ninth day.         |
| Manalo 2020\textsuperscript{48}   | Atlanta, Georgia   | Reported 2 cases of unilateral livedoid patch resembling livedo reticularis without itching in the anterior thigh area and 1 case of asymptomatic patches such as livedo reticularis. | There was no association between age and gender because the respondents aged 67 (male) and 47 (female) generally appeared 7-10 days after the onset of symptoms. |

Table 1: Comparison of skin lesions from different case reports.
| Author          | Country       | Efflorescence                                                                 | Author's Comments Regarding Clinical Associations |
|-----------------|---------------|-------------------------------------------------------------------------------|---------------------------------------------------|
| Marzano 2020    | Italy         | Reported 22 cases with Varicella-like papulovesicular exanthem skin lesions on the limbs and trunk. | The age distribution is quite wide with a mean age of 60 years with 73% of respondents being male. Symptoms appear on days 2-12 and disappear after 4-15 days of treatment. |
| Mazzotta 2020   | Italy         | Reported 1 case of red-purplish patches with a circular shape measuring 9-15 mm and indistinct borders, focusing on the extremities. | This case occurs in children. Such lesions are generally in the lower leg area with additional manifestations of irritating itching |
| Najarian 2020   | New Jersey, USA | Reported 1 case of morbilliform skin lesions in all four extremities and the entire trunk. | These numerous and extensive lesions appeared 1 day after the onset of respiratory symptoms. Case treated with azithromycin and benzonatate. |
| Recalcati, 2020 | Recalcati     | Reported 18 cases with 14 cases of erythematous patches, 3 cases of urticaria that spread over the trunk, and 1 case of chickenpox-like vesicles. | There was no association between the type of skin lesion and the severity of the disease, generally symptoms appeared on days 8-10 of illness or after hospital admission. |
| Sachdeva et al  | Milan, Italy  | Reported 3 cases with maculopapular skin lesions with 1 case of Maculopapular itchy rash resembling Grover disease, 1 case of Diffuse maculopapular exanthem (morbilliform), macular hemorrhagic rash, and 1 case of Papular-vesicular, pruritic eruption. | Generally, patients are elderly group> 70 years. |
| Zhang 2020      | Wuhan, China  | Reported 7 cases that were quite unique in the form of ischemia in the acral area with accompanying symptoms such as cyanosis of the toes, bullae, and dry gangrene. | All of these cases focused on the leg area with symptom onset on day 19 (11-23) day. The possibility of such efflorescence arises due to COVID-19 therapy using low molecular weight heparin Treatment |

There is a study that categorizes these skin manifestations very well, namely the study of Casas and colleagues who classified these skin manifestations into 5 main classifications based on three hundred seventy-five cases of patients infected with COVID-19 in Spain. The classification includes: 

- Erythema-edema with vesicles or pustules (pseudo-chilblain) in the leg area is found in 19% of cases in Spain. Some additional manifestations of this classification are the possible presence of cold acral, and there is purpura which focuses on the area of the extremities (hands and feet) which are generally asymmetric.

- Vesicular eruptions that generally appear in the trunk area are monomorphic to poliform and contain hemorrhagic content in these vesicles which, if not managed properly, will become larger and spread rapidly to other areas of the body.

Figure 2: Efflorescence erythema-edema with vesicles and pustules (pseudo-chilblain) in the acral area. 

Figure 3: Distribution of monomorph vesicles in the trunk area of a person with COVID-19 is confirmed.
Urticaria lesions mostly spread over trunk to extremities. It was found in 19% of cases of skin manifestations.

Figure 4: Urticaria lesions in lower extremity of COVID-19 confirmed.52

Maculopapular rash of various sizes and numbers (Figure 5 A). Several case reports reveal a similar distribution picture of pityriasis rosea. A review of other cases also revealed infiltrated papules in the extremities (dorsum of the hands), pseudo vesicles (Figure 5 B) and erythema multiform is (Figure 5 C).

Figure 5: Erythema multiforme in the acral area of a confirmed COVID-19 patient.52

Figure 6: Livedo or necrosis arising as a manifestation of occlusive vascular.52

Livedo or necrosis that arises as a manifestation of vascular occlusive and is spread over the trunk and acral areas. This type of lesion was reported to occur in 6% of cases of patients with confirmed COVID-19 manifestations (Figure 6).

PREDISPOSITION FACTORS WITH SKIN MANIFESTATIONS ON COVID-19 INFECTION

There are still few studies that describe predisposing factors for the appearance of skin manifestations in COVID-19. Several studies have attempted to reveal the factors predisposing to the appearance of skin lesions in COVID-19, although they have not yet reached an advanced stage of research but can be considered as a factor predicting the appearance of skin lesions in COVID-19.

Age and gender

The distribution of data on age and sex in people with COVID-19 with skin manifestations is very broad. The distribution of age data in Zhao and colleagues’ study revealed a very large age range starting from 5 years old to 91 years old with a mean age of 49.03 years. Research in China is also in line with Zhao's research, with the average age of people with COVID-19 and skin manifestations of 45.55 years. The distribution of sex also cannot be used as a benchmark for the appearance of skin manifestations, but from some epidemiological data it is found that men are more likely to develop skin manifestations when compared to women (53 to 65%).54

An interesting thing about the relationship between age and skin manifestations was shown by the research of Nieto and colleagues which revealed a tendency for younger ages (children) with a mean age of 12 years (1-29 years) to have a tendency for skin lesions in the form of erythema multiforme while at age the older adults with a mean age of 23.4 (2-56) years were dominated by erythema-edema efflorescence with vesicles and pustules (pseudo-chilblain). The age difference between these two groups was statistically significant (p<0.05).52

Figure 7: Efflorescence erythema-edema with vesicles and pustules in the acral region.53
Comorbidity and history of previous disease

A literature that discusses the relationship between comorbidity and previous disease history is presented by Galvan and colleagues who in their paper found no difference between smoking, hypertension and diabetes on the appearance of skin manifestations in COVID-19 sufferers. The search from various sources revealed 44 of the 375 patients smoked. 10 out of 18 patients had hypertension, and 6 of 18 patients had a history of diabetes mellitus. This variable was chosen because the hypothesis in the form of skin manifestations emerged as a result of low body immunity.

Immunity reaction and laboratory parameters

Deductively, lower immunity will cause more severe clinical manifestations than population groups with a better immune system. Research from Zhao and colleagues revealed that the group with skin manifestations of COVID-19 infection found lymphocytopenia in 76.92% of cases, an increase in CRP in 33.33% of cases, an increase in LDH in 46.17% of cases. On the other hand, Zhang et al also revealed thrombocytopenia as an important factor in the occurrence of petechias in confirmed cases of COVID-19 infection.

Research from Firmansyah and colleagues also revealed a possible correlation between laboratory profiles and the incidence of COVID-19 skin manifestations in key population groups, namely health workers of the same age, found the fact that levels of hemoglobin, hematocrit, platelets, erythrocytes, leukocytes, and neutrophil-lymphocyte Ratio (NLR) was lower in COVID-19 cases with skin manifestations.

Infection severity

The severity of infection as a predictor of the incidence of skin manifestations of COVID-19 was described by Zhang et al who reported 7 cases of COVID -19 infection with critical clinical symptoms and physical parameters that found limb ischemia with various symptoms followed by other manifestations of cyanosis, purpura, and dry gangrene. This may be caused by multiple organ damage due to immune system reactions and vascular disorders.

Contradictory to the literacy of Galvan et al revealed that the increasing severity of pneumonia will increase the likelihood of skin manifestations ranging from vascular lesions, urticaria lesions, maculopapular lesions, pseudo-chilblain lesions, to necrotic lesions.

PROGNOSIS AND MANAGEMENT

Until mid-August 2020 (August 16th 2020), confirmed cases had reached 21,462,593 incidents with a cure rate
of 13,448,779 events and a case fatality rate of 3.59%. Indonesia has recorded a number of confirmed cases of 137,468 cases with a case fatality rate of 4.4%. The overall prognosis of the incidence of COVID-19 is dubious and bomam. Some cases of death occur because of comorbid factors, with causes of death in the form of respiratory failure, hypoxemia, and respiratory acidosis. Management of the manifestations of skin lesions in COVID-19 is still supportive, such as treatment with antihistamine drugs, topical steroids and other symptomatic drugs. Special management of COVID-19 infection includes administration of hydroxychloroquine, vitamin C, azithromycin, levofoxacin, and others.53

CONCLUSION

COVID-19 infection has various target organs, one of which is the skin. The skin manifestations of COVID-19 infection can resemble other diseases, are not specific and do not necessarily appear in all patients, but can help make the diagnosis. Some of the clinical features that have been reported are erythema-edema with vesicles or pustules (pseudo-chilblain), vesicular eruption, maculopapular rash, urticaria, and livedo lesion. Cutaneous manifestations usually appear at the end of the acute phase, following the respiratory symptoms. Age, sex, and lower immunity are thought to be predisposing factors for skin manifestations. Management of skin manifestations to date has been in the form of conservative medical therapy.

Recommendations

Clinicians should consider cutaneous manifestations as a characteristic feature of COVID-19 infection so that the diagnosis can be made earlier and exclude the differential diagnosis. The most important thing to do in clinical practice is to always keep the hygiene and protect yourself with personal protective equipment. A decrease in awareness of various diseases is a very fatal thing.

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