



CUTANEOUS MANIFESTATIONS AND TREATMENT APPROACH OF VIRAL INFECTION DURING THE PANDEMIC

Inda Astri Aryani

Departement of Dermatology and Venereology, Dr. Mohammad Hoesin General Hospital
Faculty of Medicine, Universitas Sriwijaya, Palembang
Email: indaastri70@gmail.com

ABSTRAK

Coronavirus disease-19 (COVID-19) merupakan infeksi pandemic disebabkan *severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)* yang tidak hanya bermanifestasi pada pulmonal namun juga ekstrapulmonal. *COVID-19-associated cutaneous manifestations* diklasifikasikan menjadi lima kelompok besar, dapat menjadi salah satu petunjuk diagnosis dan keparahan infeksi virus. Pendekatan terapi diberikan berdasarkan temuan klinis dan keparahan penyakit. Di era pandemik ini juga pada September 2022, *Center for Disease Control and Prevention (CDC)* menyatakan terjadi *outbreak monkeypox* di seluruh dunia. Kasus pertama terkonfirmasi laboratorik *monkeypox* di Indonesia dilaporkan pada Agustus 2022. Mengenali manifestasi kulit infeksi *monkeypox virus* dapat membantu deteksi dini penyakit, terapi dan pencegahan untuk pencegahan penyebaran lebih lanjut.

Kata Kunci: infeksi virus, COVID-19, *monkeypox virus*, manifestasi kulit, terapi

ABSTRACT

Coronavirus disease-19 (COVID-19) in an ongoing pandemic viral infection caused by the “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) that not only effect pulmonary but also extrapulmonary. COVID-19-associated cutaneous manifestations are classified in five main pattern that can be clues to diagnostic and severity of virall illnesses. Treatment approach are made based on clinical manifestation and severity of diseases. In pandemic era also Center for Disease Control and Prevention (CDC) state an outbreaks of monkeypox worldwide by September 2022. First laboratory confirmed of monkeypox virus infection case in Indonesia was reported in August 2022. Recognizing sign of cutaneous manifestation of monkeypox virus infection lead to early detection, treatment and prevention of the disease.

Keywords: viral infection, COVID-19, monkeypox virus, cutaneous manifestation, treatment

INTRODUCTION

COVID-19 still continues to spread globally. The most common clinical features of COVID-19 at the onset of illness are fever, cough and fatigue.¹ Along with the respiration symptom, number of reports worldwide concern the cutaneous manifestations of COVID-19.²

Although COVID-19-associated cutaneous manifestations have been increasingly reported, their pathomechanisms are largely unknown. The role, direct or indirect, of SARS-CoV-2 in their pathogenesis is still debated.² Numerous cutaneous morphologies of COVID-19-associated manifestations has been recorded. Cutaneous findings on COVID-19 infections can be clues to diagnosis and predictive factor of infection severity.³ Treatment regimen for cutaneous manifestation of COVID-19 that can be used includes anticoagulants, corticosteroids, and antihistamine. These optional treatments are administered with cautious depends on the clinical and severity of manifestation.⁴

During this ongoing COVID-19 pandemic, in June 2022, World Health Organization (WHO) declare monkeypox an “evolving threat of moderate public health concern” because more than 3000 monkeypox virus infections have been reported in more than 50 countries worldwide.^{5,6} This



disease transmission occurs through large respiratory droplets, close or direct contact with skin lesions, and possibly through contaminated fomites.^{6,7}

Monkeypox manifested with a variety of dermatologic and systemic clinical findings that recently found manifested typically and atypically. Monkeypox is generally self-limited, with case fatality rates of 1 to 10%. Complications include pneumonitis, encephalitis, keratitis, and secondary bacterial infections. Young children and immunocompromised persons, including persons living with human immunodeficiency virus (HIV) infection, have been reported to be at increased risk for severe outcomes.⁵

COVID-19 and monkeypox viral infection, both emerging diseases that still ongoing to be a great burden over the already drained healthcare system worldwide. Identification cutaneous manifestation of these viral infection might help physicians to earlier diagnosis, management and preventing further outbreaks.

COVID-19- Associated Cutaneous Manifestation

Mechanism of cutaneous manifestations that has been proposed maybe due to two mechanisms: (i) the interaction of the virus with the skin, through the ACE2 receptor of the basal layer of the epidermis located in the membrane of the host cell; (ii) hyperactive immune responses, by complement activation or by microvascular injury.^{8,9,10}

A literature review from 51 articles from November 2019-September 2020 with a total 1211 patient COVID-19, cutaneous manifestation can be classified into 5 major classes base on severity illnesses: (1) vaso-occlusive lesions, (2) vesicular lesions, (3) erythematous rash, (4) urticarial lesions, and (5) pseudo-chilblains.¹¹ Morphologic presentation, onset rates, survival rates and other associated symptom are described in Tabel 1.^{3,11}

Tabel 1. Major categories of cutaneous eruption in COVID-19.^{3,11}

Category	Presentation	Onset rates	Survival rates	Additional notes
Morbilloform Pink-erythematous	blanching macules and papules, commonly on trunk and lasting < 1 week	Usually within 2 weeks of COVID-19 symptom onset	High ^a	Most common cutaneous finding in confirmed COVID-19 cases
Urticarial	Transient, pruritic edematous papules and plaques lasting about 1 week	Can be before COVID-19 symptoms	High ^a	Reported association with gastrointestinal symptoms
Vesicular	Minimally pruritic vesicular eruption that can be localized or diffuse	Can be before COVID-19 symptoms	High ^a	Reported association with neurologic symptoms
Pseudo chilblains	Younger, healthy patients with tender red-purple papules affecting toes more than fingers	Usually within 2–4 weeks after COVID-19 symptom onset Recently reported in “long-haulers”	High ^a	Association with SARS- CoV-2 infection is debated
Vaso-occlusive	Hospitalized patients with retiform purpura, livedo racemosa, acral necrosis, or sacral ulcers	Usually within 2 weeks of COVID-19 symptom onset	Lower ^b	Linked to systemic vascular thrombosis

^a More than 95%

^b About 80%.

Cutaneous Manifestation

Vaso-occlusive lesions

Vaso-occlusive skin lesions of COVID-19 included fixed livedo racemosa (netlike violaceous skin lesions composed of irregularly broken macules with an annular pattern), retiform purpura (stellate purpuric skin lesions), and acral ischemia (ischemic lesions on the digits or toes) (Figure 1). Vaso-occlusive lesions were the least common but were associated with the lowest survival rate of 78.9%.¹¹

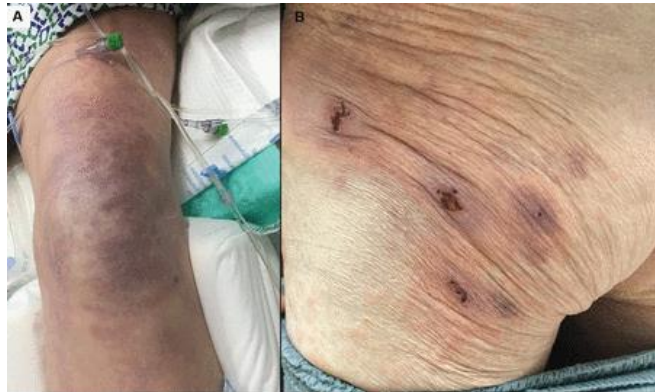


Figure 1. Vaso-occlusive lesions in COVID-19.¹⁰ⁱⁱ

Acral arrangement of violaceous lesions in fingers and toes association with SARS-CoV-2 infection that do not pale is indicative of acral ischemia, referred to as “COVID fingers”. These lesions are frequent seen in elderly patients and in those with severe SARS-CoV-2 disease. Reported prevalence of acral ischemia is 6%. These lesions are considered secondary to a context of vascular micro-occlusion and acral ischemia due to a general deterioration of the patient and/or coagulation disorders attributed to COVID-19”.¹² Therefore, the use of anticoagulant therapy is needed in this cutaneous manifestation.¹³

Vesicular lesions

Vesicular lesions tended to affect the trunk and whose configuration varied. Vesicular eruptions were also commonly noted before other COVID-19 symptoms.⁶ This form of skin clinical manifestation of COVID-19 initially described as “varicella-like”.¹⁴

The localized pattern is characterized by monomorphic vesicles in the same stage of evolution that are confined to the trunk.³ Herpetiform, varicella-zoster-like, and monomorphic vesicle formation had been described previously in the literature on COVID-19. Vesicular lesions were reported as usually occurring at the onset of COVID-19 symptoms. Among patients with COVID-19 and vesicular lesions, the survival rate was 96.1% (Figure 2).^{3,11}

No standardized treatments for COVID-19-related papulovesicular exanthem are available, also given that it is self-healing within a short time frame. These lesions resolve within a few days, a period of about one week, and without scarring. A “wait-and-see” strategy may be recommended.^{2,12}

Erythematous rash

This group containing macules and papules, predominantly involving the trunk. More than half of the affected patients were female, and itchiness was the major symptom. Among patients with COVID-19 and rash containing macules and papules, the survival rate was 98.2% (Figure 3).^{3,11}

The management of confluent erythematous/maculopapular/morbilliform rash varies according to the severity of the clinical picture. Topical corticosteroids can be sufficient in most cases, systemic corticosteroids deserving to be administered just in more severe and widespread presentations.¹⁵



Figure 2. Vesicular eruption in COVID-19.³

Urticarial Lesion

Urticarial lesions were transient edematous papules and plaques that disappeared within 24 h (Figure 4). Urticarial can also be the first sign of Covid-19.³ In a systematic review of 895 patients with COVID-19, 12% had urticarial lesions, and in 16% of these 105 the urticaria began before the onset of the other COVID-19 symptoms, suggesting that it can be a clue to diagnosis in appropriate clinical settings and can help guide early testing.¹⁶ Urticarial lesions were associated with a survival rate of 97.5%.¹¹



Figure 3. Morbilliform rash in COVID-19.³

Shanshal suggested low-dose systemic corticosteroids as a therapeutic option for COVID-19-associated urticarial rash.¹⁷ Consideration of administering low-dose systemic corticosteroids, combined with nonsedating antihistamines can help in managing the hyperactivity of the immune system in COVID-19, not only to control urticaria, but also to improve possibly the survival rate in COVID-19.²



Figure 4. Urticarial lesions preceding COVID-19 diagnosis.³

Pseudo-chilblains Lesions

Pseudo-chilblains presented as erythematous or violaceous papules on acral surfaces. Vesicles and pustules with purpuric areas have also been described. Pseudo-chilblains were more common in young adults compared with elderly patients (Figure 5).^{3,11} These lesions are most commonly seen in hospitalized patients with moderate to severe COVID-19 and are associated with higher risks of severe pneumonia and intensive care unit admission and relatively low survival rates (78.9% to 81.8%).¹⁸

In the absence of significant therapeutic options for chilblain-like acral lesions associated with COVID-19 and given their tendency to spontaneously heal, a “wait-and-see” strategy may be suggested.²



Figure 5. Pseudo-chilblains.³

CONCLUSIONS

Although COVID-19-associated cutaneous manifestations have been increasingly reported, their pathophysiological mechanisms need to be extensively explored. The skin manifestation of COVID-19 may be distinguished in five main clinical categories. With different clinical presentation, these cutaneous manifestation can predict onset of disease, severity and survival rates thus giving better consideration for adequate treatment.

MONKEYPOX VIRUS INFECTION

Monkeypox virus, a zoonotic orthopox DNA virus first described in humans in 1970 in the Democratic Republic of Congo. Monkeypox infection in humans was seldom reported outside African regions where it is endemic.^{5,6}

Transmission

Monkeypox is transmitted mainly by direct animal contact via bodily fluids, blood, aerosol, or infected lesions (Figure 6).⁷ The current global outbreak of monkeypox virus infection in humans suggests changes in biologic aspects of the virus, changes in human behavior, or both. There is no clear evidence of sexual transmission through seminal or vaginal fluids but the current spread has disproportionately affected men who are gay or bisexual and other men who have sex with men, which suggests amplification of transmission through sexual networks.^{6,7} The suspected means of monkeypox virus transmission as reported by the clinician over 16 countries was sexual close contact in 95% of the persons.⁵

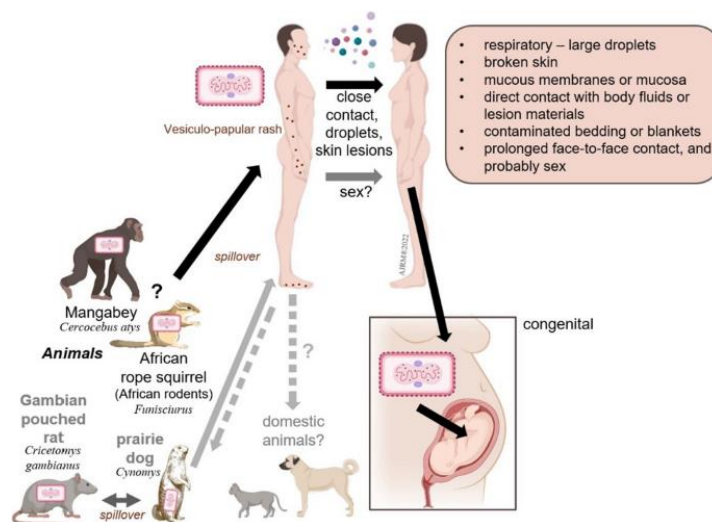


Figure 6. Transmission of monkeypox infection.⁷

Clinical Manifestation

Monkeypox has a 7–21 day-incubation period before the beginning of manifestations. The classic signs and symptoms of monkeypox closely resemble those of smallpox. (Figure 7). Fever, headache, cough, and lymphadenopathy in inguinal and cervical regions before rash onset is a key distinguishing feature between monkeypox and smallpox (Tabel 2).^{6,19}

Illness typically begins with fever and prominent lymphadenopathy, followed by the development of lesion multiple papular, vesiculopustular, and ulcerative lesions on the face and body centrifugally in (Figure 8).²⁰ The rash lesions progress through same stages as macular (1–2 d), papular (1–2 d), vesicular (1–2 d), and pustular (5 d) before scabbing (7–14 d) and healing. Lesions are generally deep-seated, circumscribed, vary in size, may be umbilicated, and cause itch or pain. The entire process can last 2–4 weeks or longer.¹⁹

In the 2022 monkeypox outbreak, the rash atypically initiates in the groin and later may follow the classic pattern (Figure 9).⁶ Atypical features also including (a) only a few or even single lesions or the absence of skin lesions in some cases; (b) lesions mostly located in genital and perianal sites and presenting with anal pain and bleeding; (c) skin lesions restricted to genital, perineal or perianal areas; (d) asynchronous lesions, ranging from single or clustered spots to umbilicated

papules with progressive central ulceration, and, finally, to scabs; (E) absence of prodromal symptoms, such as fever, malaise, and headache before the development of a rash; (F) presence of herald skin lesions at the point of sexual contact in some patients.¹⁹

Table 2. Clinical manifestation of typical monkeypox, chickenpox and smallpox.¹⁹

Characteristic	Monkeypox	Chickenpox	Smallpox
Causative virus	Monkeypox virus	Varicella-zoster virus	Variola virus
Fever before rashes	1–3 days	1–2 days	2–4 days
Dermatologic presentation	One stage in slow development	Multiple stages in rapid development	Multiple stages in rapid development
Initial site(s)	Face	Chest, back, and face	Tongue and mouth
Involvement of palms and soles	Yes	No	Yes
Lymphadenopathy	Yes	No	No
Appearance of symptoms post-exposure	5–21 days	10–21 days	7–19 days
Duration of illness	2–4 weeks	4–7 days	Up to 5 weeks
Vaccination	Smallpox vaccine	Chickenpox vaccine	Smallpox vaccine

In collaborative international 528 cases confirmed human monkeypox by clinician accros 16 countries from April-Juli 2022, most common systemic features preceding the rash included fever (62%), followed lymphadenopathy (reported in 56%), lethargy (41%), myalgia (31%), and headache (27%). Allmost all (95%) having a rash (with 64% having ≤ 10 lesions), 73% had anogenital lesions, and 41% had mucosal lesions.⁵



Right arm and torso showing monkeypox skin lesions.
CDC PHIL ID#12779



Rash on hands during recuperative stage.
CDC PHIL ID#12763

Figure 7. Typical cutaneous manifestation.⁶

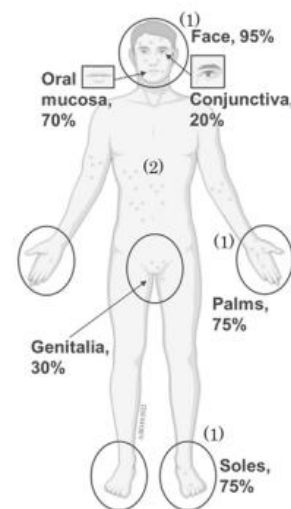


Figure 8. Anatomical distribution of the rash in monkeypox.²⁰



Figure 9. Development of Monkeypox lesion.⁶

Treatment and Prevention

Majority of monkeypox virus patients have mild symptoms, but some patients could need hospitalization and supportive care due to nausea, vomiting, the potential for dehydration, or pain management. Antiviral medication is advised for those people who, are at high risk of contracting a severe illness. Multiple antiviral medications can be used for the treatment of monkeypox such as tecovirimat, cidofovir, brincidofovir and topical trifluridine.²¹

Prevention should be made by promptly treat those infected and provide post-exposure management to minimize the onset of illness. Increased community awareness and wider surveillance of current cases and exposure is the first step toward preventing the spread. Key preventive measure is related to minimizing contact with the lesions, as close and prolonged contact appears to be the primary mode of transmission. Social distancing from those with infection or post-exposure can also be considered useful, thereby minimizing possible respiratory transmission. Avoiding sharing of beddings, towels, and clothes is needed.²¹

CONCLUSION

Monkeypox manifested with a variety of dermatologic and systemic clinical findings. The identification of typical and atypical manifestation cases outside areas where monkeypox has traditionally been endemic highlights the need for rapid identification and diagnosis of cases to contain further community spread.

REFERENCES

1. Lovato A., de Filippis C. Clinical presentation of COVID-19: a systematic review focusing on upper airway symptoms. *Ear Nose Throat J.* 2020;99.
2. Genovese G, Moltrasio C, Berti E, Marzano A, V: Skin Manifestations Associated with COVID-19: Current Knowledge and Future Perspectives. *Dermatology* 2021;237:1-12.
3. Samantha Polly S, Fernandez AP. Common skin signs of COVID-19 in adults: An update *Cleveland Clinic Journal of Medicine* March 2022, 89 (3) 161-167



4. Fernández-Lázaro D, Garrosa M. Identification, Mechanism, and Treatment of Skin Lesions in COVID-19: A Review. *Viruses*. 2021 Sep 24;13(10):1916
5. Tornhill J.P. Barkati TS, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox Virus Infection in Humans across 16 Countries — April–June 2022. *N Engl J Med* 2022; 387:8
6. Koenig KL, Beÿ CK, Marty AM, Monkeypox 2022 Identify-Isolate-Inform: A 3I Tool for frontline clinicians for a zoonosis with escalating human community transmission, *One Health*, Volume 15, 2022, 100410,
7. Farahat, R.A., Abdelaal, A., Shah, J. *et al.* Monkeypox outbreaks during COVID-19 pandemic: are we looking at an independent phenomenon or an overlapping pandemic?. *Ann Clin Microbiol Antimicrob* 21, 26 (2022)
8. Potekaev N.N., Zhukova O.V., Protsenko D.N., Khlystova E.A., Bogin V. Clinical characteristics of dermatologic manifestations of COVID-19 infection: Case series of 15 patients, review of literature, and proposed etiological classification. *Int. J. Dermatol.* 2020;59:1000–1009
9. Kaya G., Kaya A., Saurat J.-H. Clinical and histopathological features and potential pathological mechanisms of skin lesions in COVID-19: Review of the literature. *Dermatopathology*. 2020;7:3–16
10. Sameni F., Hajikhani B., Yaslianifard S., Goudarzi M., Owlia P., Nasiri M.J., Shokouhi S., Bakhtiyari M., Dadashi M. COVID-19 and skin manifestations: An overview of case reports/case series and meta-analysis of prevalence studies. *Front. Med.* 2020;7:573188.
11. Tan SW, Yew Chong Tam YC, Choon Chiat Oh CC. Skin manifestationns of COVID-19: A worldwide review *JAAD Int.* 2021 Mar; 2: 119–133.
12. Fernandez-Nieto D., Ortega-Quijano D., Jimenez-Cauhe J., Burgos-Blasco P., De Perosanz-Lobo D., Suarez-Valle A., Cortes-Cuevas J.L., Carretero-Barrio I., Del Real C.G., Fernandez-Guarino M. Clinical and histological characterization of vesicular COVID-19 rashes: A prospective study in a tertiary care hospital. *Clin. Exp. Dermatol.* 2020;45:872–875.
13. Carrascosa J., Morillas V., Bielsa I., Munera-Campos M. Cutaneous manifestations in the context of SARS-CoV-2 Infection (COVID-19) *Actas Dermosifiliogr.* 2020;111:734–742
14. Marzano AV, Genovese G, Fabbrocini G, et al. Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients. *J Am Acad Dermatol* 2020; 83(1):280



15. Najarian DJ. Morbilliform exanthem associated with COVID-19. *JAAD Case Rep.* 2020 Apr;6(6):493–4.
16. Gisoni P, Di Leo S, Bellinato F, Cazzaniga S, Piaserico S, Naldi L. Time of onset of selected skin lesions associated with COVID-19: a systematic review. *Dermatol Ther (Heidelb)* 2021; 11(3):695–705
17. Shanshal M. Low-dose systemic steroids, an emerging therapeutic option for COVID-19-related urticaria. *J Dermatolog Treat.* 2020 Jul;16:1–2.
18. Galván Casas C, Català A, Carretero Hernández G, 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):71–77
19. Lai CC, Hsu CK, Yen MY, Lee PI, Ko WC, Hsueh PR. Monkeypox: An emerging global threat during the COVID-19 pandemic. *J Microbiol Immunol Infect.* 2022 Aug 5:S1684-1182(22)00102-5.
20. Rodriguez-Morales A.J. Monkeypox and the importance of cutaneous manifestations for disease suspicion. *Microbes Infect Chemother.* 2022; 2: e1450
21. Goyal L, Ajmera K, Pandit R, et al. (August 21, 2022) Prevention and Treatment of Monkeypox: A Step-by-Step Guide for Healthcare Professionals and General Population. *Cureus* 14(8): e28230
22. World Health Organization. Accessed on Sept 24, 2022, <https://www.who.int/emergencies/outbreak-toolkit/diseaseoutbreak-toolboxes/monkeypox-outbreak-toolbox>
23. Di Giulio DB, Eckburg PB. Human Monkeypox: an emerging zoonosis. *Lancet Infect Dis* 2004; 4: 15–25