

REVIEW ARTICLE

Top 10 acral skin manifestations associated with COVID-19: A scoping review

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Abstract

COVID-19-associated cutaneous manifestations are one of the most important and relatively common extra-respiratory presentations of SARS-CoV-2 infection. The exact identification and classification of these lesions can facilitate the accurate diagnosis and treatment. There are several case reports and small case series which describe cutaneous lesions in hands and feet. Currently, there is no scoping review about acral skin manifestations associated with COVID-19. This paper covers the COVID-related acral skin manifestations in 10 entities including acral papulo-vesicular eruption, acral urticarial lesion, acral non-inflammatory purpura and necrosis, acro-ischemia associated COVID-19, acral vasculitis, chilblain-like lesion (COVID Toe), acral erythema multiform (EM) like lesion, hand and foot skin lesions associated with multisystem inflammatory syndrome in children (MISC), acral peeling conditions and red half-moon nail sign. Future studies should focus on exact investigation of etiologies of these lesions including role of immune senescence, environment, gender, immunogenetics and relation of these lesion with major organ involvements.

KEYWORDS

Acral, COVID-19, cutaneous manifestations, SARS-CoV-2, skin

1 | INTRODUCTION

Cutaneous manifestations associated with COVID-19 are one of the extra-respiratory manifestations of SARS-CoV-2 infection. These manifestations are important and relatively common presentations of SARS-CoV-2 infection.¹⁻⁴

Among cutaneous manifestations, acral skin manifestations of COVID-19 can be divided into at least 10 discrete categories based on their clinicopathological presentations.

Occasionally, acral skin lesions may represent the initial presentation of SARS-CoV-2 infection prior to fever or respiratory manifestations. Moreover, several acral cutaneous manifestations could be associated with poor prognosis or additional medical conditions.⁵

Thus, recognition of covid-19 related acral signs and symptoms can help clinicians to consider COVID-19 in the differential diagnoses of acral skin lesions.

Some of the most common acral skin presentations of COVID-19 include: acral papulo-vesicular eruption, acral urticarial lesion, acral non-inflammatory purpura and necrosis, acro-ischemia associated COVID-19, acral vasculitis, chilblain-like lesion (COVID Toe), acral erythema multiform (EM) like lesion, hand and foot skin lesions associated with multisystem inflammatory syndrome in children (MISC), acral peeling conditions and red half-moon nail sign.

As explained above, we conducted a scoping review to summarize the different acral skin lesions associated with COVID-19 in children and adults as to recognize distinct cutaneous signs in COVID-19

patients for accurate use of each entity and to prevent confusion among clinicians in similar entities. We also provided a table to categorize these findings more (Table 1).

2 | CUTANEOUS MANIFESTATIONS

2.1 | Acral papulo-vesicular eruption

2.1.1 | Clinical presentation

COVID-19-associated papulo-vesicular lesions have two distinct clinical patterns; a widespread chickenpox-like polymorphic pattern and monomorphic acral papulo-vesicular variant.⁶⁻⁸ Papulo-vesicular lesions are associated with intermediate severity of COVID-19.⁶ (Figure 1).

2.1.2 | Etiopathogenesis

The possible explanation for development of acral papulo-vesicular lesions is immune system hyperactivity and direct cytopathic effect of SARS-CoV-2 on endothelial dermal vessels.⁹

2.1.3 | Histopathological findings

Histological features include prominent acantholysis and dyskeratosis associated with intraepidermal vesicles in supra-basal location. In some cases, epidermal necrosis, swelling of keratinocytes, ballooning degeneration of keratinocytes and endotheliitis may be present.^{10,11}

2.1.4 | Clinical management

There is no standard treatment for COVID-19-associated papulo-vesicular lesions. A “watchful waiting” strategy and symptomatic therapy is recommended.¹²

2.2 | Acral urticarial lesion

2.2.1 | Clinical presentation

Urticarial lesions typically present as an erythematous papule or plaque with or without angioedema and intense pruritus. Among the most common sites of involvement are extremities including acral sites.^{13,14} (Figure 2).

2.2.2 | Etiopathogenesis

Possible explanations for urticaria associated with COVID-19 are direct cutaneous effect by SARS-CoV-2 virus, drug-induced exanthema and over activity of the immune system.¹³

2.2.3 | Histopathological findings

Pathological findings of urticarial lesions in COVID-19 patients consist of superficial perivascular infiltration of lymphocytes with few eosinophilic infiltrations associated with marked dermal edema in upper dermis.⁶

2.2.4 | Clinical management

Urticarial lesions are usually associated with moderate to severe COVID-19. Non-sedating antihistamines can be used for treatment of COVID-19-associated urticarial lesions. In more severe cases, a short course of low-dose systemic corticosteroids can be used.¹³

2.3 | Acral non-inflammatory purpura and skin necrosis

2.3.1 | Clinical presentation

Most cases of purpura associated with COVID-19 are non-inflammatory retiform purpura presented as a lace-like reddish-blue to purple mottled discolorations on extremities and acral sites. These purpuric lesions may evolve into hemorrhagic blisters or necrotic-ulcerative lesions and dry gangrene.^{15,16} (Figure 3).

2.3.2 | Etiopathogenesis

Hypercoagulable state associated with COVID-19 and pauci-inflammatory micro thrombotic vasculopathy are proposed as the underlying mechanisms for purpuric lesions.¹² In addition, the cutaneous side effects of anti-COVID-19 agents like high-dose intravenous immunoglobulin (IVIg) should be considered as skin manifestations of microvascular occlusion syndrome.¹⁷

2.3.3 | Histopathological findings

Pauci-inflammatory thrombogenic vasculopathy with extensive deposition of complement components within the cutaneous microvasculature are dominant histopathological features of non-inflammatory petechial and purpuric lesions.¹⁸

2.3.4 | Clinical management

Petechia, purpura and acral necrotic lesions are usually associated with greater severity of COVID-19.¹⁸ Since acral non-inflammatory purpura and skin necrosis are cutaneous signs of thrombotic microangiopathy, therapeutic-dose of anticoagulants is appropriate for documented evidence of thrombosis or ongoing thrombosis formation.¹⁹

TABLE 1 Summary of clinical manifestations, etiopathogenesis, histopathological findings and clinical management of 10 acral skin manifestations in COVID-19

No.	Lesion	Clinical presentation	Etiopathogenesis	Histopathological findings	Clinical management
1	Acral papulo-vesicular eruption	Widespread chickenpox-like polymorphic pattern/ Monomorphic acral papulo-vesicular variant	Immune system hyperactivity/direct cytopathic effect of virus on endothelial dermal vessels	Prominent acantholysis/supra-basal dyskeratosis with intraepidermal vesicles	Watchful waiting/symptomatic therapy
2	Acral urticarial lesion	Erythematous papule or plaque ± Angioedema and intense pruritus	Direct cutaneous effect of virus/drug-induced exanthema/immune system over activity	Superficial perivascular infiltration of lymphocytes/few eosinophilic infiltration/marked dermal edema in upper dermis	Non-sedating antihistamines/short course of low-dose systemic corticosteroids in severe cases
3	Acral Non-inflammatory purpura and skin necrosis	Lace-like reddish-blue to purple mottled discolorations/ Hemorrhagic blisters/ Necrotic-ulcerative lesion/ Dry gangrene	Hypercoagulative state/pauci-inflammatory micro thrombotic vasculopathy/drug-induced	Pauci-inflammatory thrombogenic vasculopathy/extensive deposition of complement components in cutaneous microvasculature	Therapeutic-dose of anticoagulation
4	Acro-ischemia	Blue to gray discoloration without relation to the cold	Cytokine storm/hypercoagulative state/thrombotic events/ DIC	Microthrombosis in dermal vessels/endothelial cell damage/extravasation of RBCs/superficial and deep perivascular lymphocytic infiltration/vacuolar degeneration in basal layer	Therapeutic anticoagulation + Intravenous unfractionated heparin
5	Acral vasculitis	Symmetric palpable inflammatory purpura with necrotic center/ Blisters formation	Direct damage of endothelial cells by the virus/indirect damage of endothelial cells by immune dysregulation	Perivascular neutrophilic infiltration/fibrin deposition/fibrinoid necrosis/leucocytoclasia/endothelial swelling	Topical or systemic corticosteroids
6	Chilblain-Like Lesion ("COVID Toe")	Erythematous edematous painful pruritic skin resembling pernio/ Blister formation/ Digital swelling	Damage of skin capillaries/immune dysregulation/immunologic response to cutaneous vessels/drug-induced	Diffuse dense lymphoid infiltration in the dermis and hypodermis/perivascular pattern/endothelial activation	Following public health guidelines for COVID-19 testing and isolation
7	Acral EM-like lesion	Targetoid lesions/ Two or three concentric circles with a small necrotic/ Hemorrhagic area	Immune response to virus/hypersensitivity/potential delayed immune response to the virus	Mild superficial perivascular infiltration /microthrombi formation/Granular positivity in endothelial and epithelial cells of eccrine glands in Immunohistochemistry	Spontaneous improvement in 1-3 weeks
8	Acral lesions associated with MISC in children	Acral erythema and edema	Macrophage activation and T-helper stimulation/cytokine release/overproduction of antibodies/hyper immune response	Perivascular cuffing with cytotoxic CD8+ lymphocytes and eosinophil that can be seen in Kawasaki syndrome	Single dose of 2 g/kg of IVIG over 8-12 h ± Systemic corticosteroids
9	Acral peeling lesions	Superficial desquamation of the distal phalanges of hands and feet	Alteration in regulation of expression of acral keratins	Skin biopsy is usually not performed.	Spontaneous improvement in 1-4 weeks
10	Red half-moon nail sign	Half-moon-shaped transversal red band at the distal margin of the lunula as single crescent erythronychia on the nail bed	Complement-mediated microvascular injury of the nail bed/capillary network damage of the distal subungual arcade/subsequent thrombus formation in small vessels	No histopathological data	Treatment is unnecessary.

Abbreviations: EM, erythema multiform; MISC, multisystem inflammatory syndrome in children.



FIGURE 1 Acral papulovesicular and large blister formation associated with COVID-19

2.4 | Acro-ischemia associated with COVID-19

2.4.1 | Clinical presentation

Distal acute ischemia presents with blue to gray discoloration without relation to the cold. Acro-ischemic lesions usually have been reported in ICU-admitted patients.^{8,20,21} (Figure 4).

2.4.2 | Etiopathogenesis

Acro-ischemic lesions are attributed to the cytokine storm when innate and adaptive immunity fails to get rid of the virus. Compensatory mechanism in COVID-19 patients can be associated with hypercoagulable state, thrombotic events and disseminated intravascular coagulation.^{8,20,21}

2.4.3 | Histopathological findings

Histological features of acro-ischemic lesions are compatible with microthrombosis formation in dermal vessels, endothelial cell damage and extravasation of red blood cells. Superficial and deep perivascular lymphocytic infiltration with vacuolar degeneration in the basal layer can be seen.²²



FIGURE 2 Acral urticarial lesion



FIGURE 3 Acral non-inflammatory purpura associated with COVID-19



FIGURE 4 Acro-cyanosis associated with COVID-19

2.4.4 | Clinical management

Therapeutic anticoagulation combined with intravenous unfractionated heparin should be provided for patients with diagnosis of acro-ischemia. Option for vascular intervention and revascularization depends on the extension of lesion and general condition of patients.²³

2.5 | Acral vasculitis

2.5.1 | Clinical presentation

Cutaneous small vessel vasculitis (CSVV), also known as Leucocytoclastic vasculitis, is characterized by symmetrically distributed palpable inflammatory purpura usually in the lower extremities. In addition to palpable papules, inflammatory purpuric lesions with necrotic center and blisters formation can be seen.^{13,24,25} (Figure 5).

2.5.2 | Etiopathogenesis

Possible mechanisms of CSVV associated with COVID-19 include direct damage of endothelial cells by the virus and indirect damage of endothelial cells by immune dysregulation induced by SARS-COV2^{13,25}.

2.5.3 | Histopathological findings

Histopathological findings of CSVV in COVID-19 patients consists of perivascular neutrophilic infiltration, fibrin deposition, fibrinoid necrosis, leucocytoclasia and endothelial swelling.^{13,25,26}

2.5.4 | Clinical management

CSVV usually occurs in severe cases of COVID-19 and is associated with higher mortality rate. Topical corticosteroids can be used for



FIGURE 5 Cutaneous small vessels cellulitis associated with COVID-19

treating mild cases. Patients with generalized necrotic/ulcerative lesions may be treated with systemic corticosteroids.²⁷

2.6 | Chilblain-like lesion (“COVID Toe”)

2.6.1 | Clinical presentation

Patients present with erythematous edematous painful pruritic skin resembling perniosis on the extremities occasionally associated with blister formation and digital swelling. They are considered as “COVID toes.” These lesions are a common feature in children with positive nasopharyngeal and rectal swabs for COVID-19 with mild symptomatic or asymptomatic conditions.^{8,28,29} These perniosis-like lesions differ from acro-ischemic lesions associated with severe COVID-19 conditions.²⁹ (Figure 6).

2.6.2 | Etiopathogenesis

Chilblain-like lesions are caused by skin capillaries damage. Possible mechanisms for the damage are immune dysregulation and an immunologic response targeting cutaneous vessels.^{8,16} Chilblain-like lesions can also be cutaneous manifestation of strong type I interferon (IFN-I) response in the setting of an effective immune response.³⁰⁻³²

2.6.3 | Histopathological findings

Histology of these acral lesions shows diffuse dense lymphoid infiltration in dermis and hypodermis, with a prevalent perivascular pattern and signs of endothelial activation.⁸

2.6.4 | Clinical management

Although most patients with COVID-19-associated chilblain-like lesions have none or mild symptoms, they should follow public health guidelines for COVID-19 testing and isolation.³³

2.7 | Acral EM-like lesion

2.7.1 | Clinical presentation

Acral EM-like lesions associated with COVID-19 usually present as a conventional EM associated with other causes. This finding presents with targetoid acral lesions with two or three concentric circles with a small necrotic/hemorrhagic area. Lesions may be observed on extremities, dorsal of hands and feet.³⁴ (Figure 7).



FIGURE 6 Chilblain-like lesion on the finger (A) and foot (B)



FIGURE 7 Erythema multiform-like lesion associated with COVID-19. In addition to the acral site, similar bulous lesions were seen on knees and elbows

2.7.2 | Etiopathogenesis

Although the exact mechanism of EM-like lesions in COVID-19 is uncertain, immune response to the SARS-COV-2, hypersensitivity by

cytokines cascade triggered by SARS-COV-2 infection and a potential delayed immune response to the virus can be proposed as possible etiopathogenesis of COVID-associated EM-like lesion.^{17,35}

2.7.3 | Histopathological findings

Mild superficial perivascular infiltration and microthrombi formation are common features of these lesions.³⁴ In some cases, immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein shows granular positivity in endothelial and epithelial cells of eccrine glands.³⁴

2.7.4 | Clinical management

Skin lesions usually improve spontaneously in 1–3 weeks.³⁴

2.8 | Acral lesions associated with multisystem inflammatory syndrome in children (MISC)

2.8.1 | Clinical presentation

Muco-cutaneous manifestations are common in MISC. One of the most important features of MISC which is considered as a sign of organ involvement, is involvement of hands and/or feet. Acral involvement in the setting of MISC presents with acral erythema and edema.^{36,37} (Figure 8).

2.8.2 | Etiopathogenesis

The early infection of SARS-COV2 triggers macrophage activation and T-helper stimulation. These events lead to cytokine release,



FIGURE 8 Acral edema associated with multisystem inflammatory syndrome in children

stimulation of leucocytes (including B-cells) and plasma cells which lead to overproduction of antibodies and induction of hyper immune response which is characteristic for MIS-C.³⁸

2.8.3 | Histopathological findings

Perivascular cuffing with cytotoxic CD8+ lymphocytes and eosinophils that can be seen in Kawasaki syndrome, has also been reported in MIS-C.^{39–41}

2.8.4 | Clinical management

Although MIS-C can be a potentially serious condition with significant complications and organ involvements, most children will survive from acute phase with prompt diagnosis and treatment. Single dose of 2 g/kg IVIG administered over 8–12 h with or without systemic corticosteroids according to the severity of condition and organ failure, should be used for all patients who meet diagnostic criteria for MIS-C.⁴²

2.9 | Acral peeling lesions

2.9.1 | Clinical presentation

Superficial desquamation of distal phalanges of hands and feet can occur in association with COVID-19. The lesions are asymptomatic or slightly symptomatic without preceding edema, in contrast to MIS-C-associated acral edema, erythema and subsequent desquamation.^{43–45} (Figure 9).

2.9.2 | Etiopathogenesis

The exact mechanism of acral peeling lesions in association with COVID-19 is unclear. Similar to other post infections with significant inflammatory response, alternation in regulation of expression of acral keratins can be considered as possible mechanism.⁴⁶



FIGURE 9 Acral peeling syndrome associated with COVID-19

2.9.3 | Histopathological findings

Due to mild and self-limiting nature of these lesions, skin biopsy is usually not performed.

2.9.4 | Clinical management

Treatment is usually not necessary as lesions spontaneously resolve within 1–4 weeks.⁴⁶

2.10 | Red half-moon nail sign associated with COVID-19

2.10.1 | Clinical presentation

Half-moon-shaped transversal red band at the distal margin of the lunula as single crescent erythronychia on the nail bed is considered as a pathognomonic nail finding in COVID-19 infection.^{47,48}

2.10.2 | Etiopathogenesis

The exact pathogenesis of the red half-moon nail sign associated with COVID-19 is unknown. Complement-mediated microvascular injury of the nail bed, distal sub ungual arcade capillary network damage and subsequent thrombus formation in small vessels have been proposed as possible mechanisms.^{47,48}

2.10.3 | Histopathological findings

There is no histopathological data up to date about histology of red half-moon nail sign associated with COVID-19.

2.10.4 | Clinical management

Since the lesions are asymptomatic, treatment is unnecessary.

3 | CONCLUSION

Acral skin changes associated COVID-19 may provide valuable insight into underlying systemic manifestations of SARS-CoV-2. Clinicians should continue to document these changes since they may become important diagnostic clues and help clinicians better understand the pathophysiologic basis for this viral illness. Future studies are needed to investigate etiopathogenesis and management of these skin lesions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Saeedeh Farajzadeh, Maryam Khalili, Shakiba Dehghani and Bahareh Abtahi-Naeini contributed in study conception and design. Data collection was done by Sharareh Babaie and Bahareh Abtahi-Naeini. Analysis and interpretation of results was carried out by Mahdi Fattah and Bahareh Abtahi-Naeini. Shakiba Dehghani and Bahareh Abtahi-Naeini prepared the manuscript draft and Saeedeh Farajzadeh, Maryam Khalili, Sharareh Babaie and Mahdi Fattah did the manuscript revision. All authors reviewed and approved the final version of manuscript and agreed with all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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